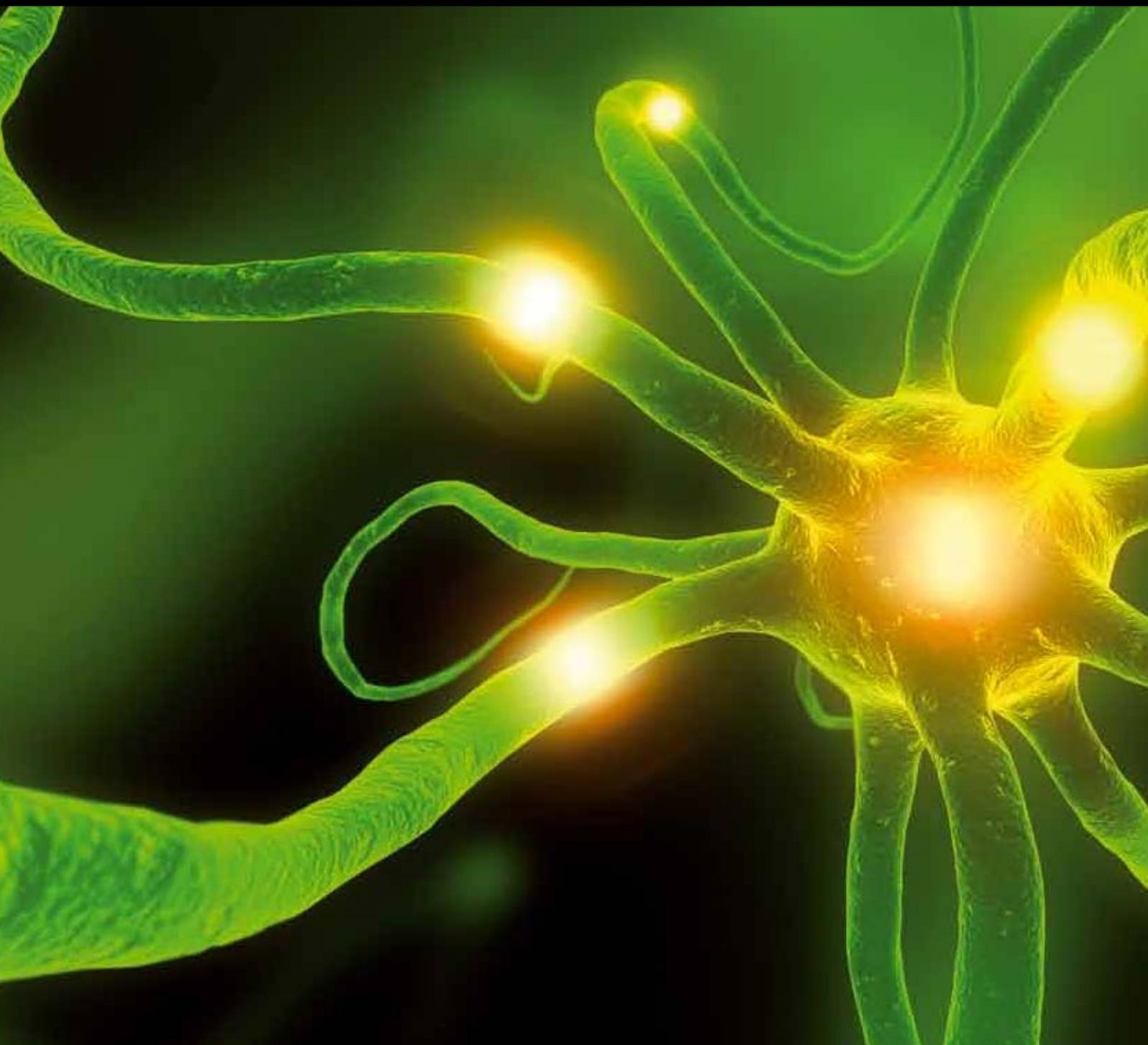


Epilepsy Research and Treatment

# Update on Temporal Lobe Epilepsy

Guest Editors: Seyed M. Mirsattari, Jerome Engel, Warren T. Blume,  
and Dennis Spencer





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## Editorial

# Update on Temporal Lobe Epilepsy

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Received 24 December 2012; Accepted 24 December 2012

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Although the most common and best studied of focal epilepsies, a substantial proportion of patients with temporal lobe epilepsy (TLE) continue to have seizures despite medical therapy. Of these, surgery cannot be offered for most with bitemporal TLE while its effectiveness is limited in these and others because of memory and/or language concerns [1]. This up-to-date special edition contains a variety of valuable topics relative to TLE with the expectation that clues to unraveling this intractability will be found herein.

Focal epilepsy occurs in 60% of patients with epilepsy and TLE is the most common of these (J. F. Téllez-Zenteno and L. Hernández-Ronquillo). These authors describe difficulties encountered by epidemiologists in identifying patients with TLE leading to a possible underestimation of this significant health care issue.

The description of TLE ictal semiology by Blair constitutes a useful introduction to this set of articles and may aid in distinguishing between mesial and neocortical temporal seizures. However, the several clinical features common to both mesial and neocortical TLE create a need for tests to distinguish these entities. As described by E. Bercovici et al., EEG and fMRI may aid in making this therapeutically important differentiation. Moreover, ictal semiology may vary considerably by age as documented for children by E. C. Wirrell et al. group and S. de Ribaupierre et al. and among the elderly by L. E. Morillo.

S. Raghavendra et al. provide comprehensive evidence that interictal and ictal EEG remain essential contributors to localization of epileptogenesis. The thorough review of scalp and invasive EEG with a section on its automated analysis by M. Javidan helpfully complements the aforementioned review, providing the reader with an up-to-date picture of this topic. Early identification of interictal-to-ictal transition may

be assisted by the measure of desynchronisation described by J. Pastor et al.; high desynchronisation levels were found in MRI-normal mesial temporal epilepsy patients. That simultaneous EEG-fMRI recording may facilitate disclosure of the neurobiology of ictal and interictal epileptiform discharges, which is described by S. M. Mirsattari's group (Z. Wang).

Neuropsychologists play major roles in assessment of patients with temporal lobe epilepsy: (1) in localisation of dysfunction, thus aiding epileptogenesis localisation and (2) prediction of any postsurgical impairment of function in memory or language as reviewed by M. P. McAndrews and M. Cohn.

Since the era of Wilder Penfield, a detailed pre- and post-operative memory evaluation has been considered requisite for temporal lobectomy consideration, especially when the left (language "dominant") side is involved in epileptogenesis. The noninvasive fMRI, here described by C. Limotai and S. M. Mirsattari, may ultimately replace the Wada test to prognosticate the risk of significant postoperative memory decline. Fortunately, S. Oddo et al. found improvement in visual memory and executive function after temporal lobectomy among Argentinian patients.

A. Wang et al. describe the ability of functional MRI (fMRI) to map language networks in patients with intractable temporal lobe epilepsy and compares its capability in this assessment with more traditional tests such as Wada and cortical stimulation. The particular "challenges and solutions" of language mapping in children undergoing temporal lobectomy are described by S. de Ribaupierre et al.

Temporal lobe neuroanatomy is a complex subject that perhaps is best comprehended by two approaches as presented in this volume. J. A. Kiernan, the anatomist,

thoroughly depicts its multiple components, their terminology, and their many connections.

As the neurosurgeon needs a complete and confident knowledge of the complex anatomy of the temporal lobe to perform an adequate resection with minimal to no neurological complications, the paper by B. Kucukyuruk et al. represents a “must read” for epilepsy surgeons in training. Knowledge of such intricate neuroanatomy and related physiology form the bases of the several resection approaches available to neurosurgeons as presented by F. Al-Otaibi et al. As described by D. Spencer and K. Burchiel, selective amygdalohippocampectomy is an alternative to the time-honoured standard temporal lobectomy. Reports of its effectiveness, covered by these authors, require scrutiny as it may be less so than its predecessor.

A variety of mental health abnormalities may be associated with or resemble epilepsy including: mood disorders, anxiety, and psychotic states (V. Beletsky and S. M. Mirsattari). Their symptoms, occasionally overlapping with those of epilepsy, may complicate both diagnosis and management. These authors cite Freud (1928) as questioning the accuracy of Dostoyevsky’s self-diagnosis of a seizure disorder! Indicating the frequent cooccurrence of depression in patients with epilepsy, C. S. Garcia describes recent efforts in diagnosis and management of depression in those with epilepsy.

Integration of clinical findings of the patient with the several tests that may help to identify seizure origin determines surgical candidature; this process is well described by T. A. Valiante et al.

F. Al Sufiani and L. C. Ang have reviewed the several pathological abnormalities found in human temporal lobe resection specimens, including some newly recognised tumours; presumably, each contributes to epileptogenesis. The pathogenesis of mesial temporal sclerosis (MTS), the most common lesion found with temporal lobe seizures is more complex than first realised. Closely associated with a history of febrile seizures, the relationship may involve another temporal lobe lesion thus “dual pathology.” The illustrative case of cryptogenic status epilepticus leading to MTS presented by J. G. Boyd et al. further implicates prolonged seizures as a MTS aetiology. L. Carmant et al. comprehensively describe experimental models that may unravel the physiology of these associations. The natural history of TLE, reviewed by G. A. Shukla and N. Prasad, will likely provide further pathophysiological insights—particularly by scrutinising the latency period between an initial precipitating event and refractory TLE. This topic is further illustrated through an evidence-based approach as described by C. B. Josephson and B. Pohlmann-Eden. Although linkage analyses have thus far failed to disclose a gene related to TLE (A. Salzmann and A. Malafosse), the rapidly evolving field of human genetics may generate some future revelations in this regard.

As an estimated 80% of epilepsy patients live in underdeveloped countries (M. Z. Tahir et al.), the methods by which these authors established an epilepsy centre in Pakistan hold considerable interest. These include teleconferences, interactive teaching sessions, a nationwide workshop, public

awareness events, and a visit to the proposed site by participating experts.

Seyed M. Mirsattari  
Warren T. Blume

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## Review Article

# Slowly Evolving Trends in Temporal Lobe Epilepsy Management at London Health Sciences Centre

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Received 19 January 2012; Accepted 15 June 2012

Academic Editor: Seyed M. Mirsattari

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Although the advent of MRI impacted significantly our presurgical investigation, ictal semiology with interictal and ictal EEG has clearly retained its roles in localizing epileptogenesis. MRI-identified lesions considered epileptogenic on semiological and electroencephalographic grounds have increased the likelihood of resective surgery effectiveness whereas a nonlesional MRI would diminish this probability. Ictal propagation and the interplay between its source and destination have emerged as a significant component of seizure evaluation over the past 30 years.

## 1. Seizure Semiology and Epilepsy Evaluation before and Since MRI

Ictal semiology and EEG dominated our localization of intractable epileptogenesis prior to the introduction of MRI. Dr. John Girvin and I each attempted to outdo the other in obtaining patient and observer descriptions of the patients' seizures, guided by the most comprehensive observations and perceptions documented by Wilder Penfield and Herbert Jasper in *Epilepsy and Functional Anatomy of the Human Brain* [1]. Seizures of the first 3 medically intractable patients operated upon at University Hospital, London originated in the frontal, occipital, and anterior parietal lobes. Similar extratemporal experiences in Montreal and Glasgow (Dr. Girvin) and the Mayo Clinic (WTB) paradoxically sharpened our clinical definition of temporal/limbic epilepsy.

In addition to Penfield's identification for a semiological pattern as representing temporal lobe epilepsy and subsequent description of mesial temporal ictal semiology [2], subsequent studies disclosed that some features such as version and dysphasia could lateralise epileptogenesis within the temporal lobe, enhancing further the semiological role in this evaluation [3, 4].

The works of International League against Epilepsy Commissions on Epileptic Seizure Classification and Terminology have, in sequential fashion, clarified our clinical analyses.

The 1981 ILAE Commission classified partial (focal) seizures into simple partial (consciousness preserved) and complex partial (consciousness impaired). This division has encountered clinical and heuristic limitations as it depends upon evaluating an entity—consciousness—that can neither be defined nor assessed.

Gloor [5] discusses the several aspects of consciousness presented by philosophers (1713), neuropsychologists, and other neuroscientists and since Hebb [6]. "As none of the attempts at arriving at a scientifically satisfactory concept of consciousness have been successful" [5], neuroscientists have turned to the more tractable aspects of "consciousness" such as perception, memory, affect, and voluntary movements [6]. Continuing in this direction, the ILAE replaced consciousness and "complex partial" with "cognition" as the pivotal defining concept of focal seizures by creating as "dyscognitive" a focal or generalised seizure type that impairs two or more aspects of cognitive function. Thus "dyscognitive" refers to a seizure in which a disturbance of cognition is the predominant or most apparent feature. Components of cognition are all assessable and include: perception, attention, emotion, memory, and executive function [7]. Guided by neuropsychologists, clinicians, health care staff, relatives, or other observers could intraictally administer specific tests for each of these possible components and thus, over several attacks, fully characterize a dyscognitive seizure disorder. For example, unresponsiveness could represent ictal dysphasia or

dyspraxia. No recall of an ictus with intact responses may be a “pure amnesic seizure” [8].

## 2. Electroencephalography (EEG)

Combined with ictal semiology, ictal and interictal EEG were the principal tools before the mid-1980s to localize epileptogenesis in virtually all patients whose intractable focal epilepsies required resective surgery for alleviation. Focal temporal interictal spikes, if predominant over one temporal lobe, lateralised temporal lobe seizure origin in over 90% of patients [9]. As the ictal scalp EEG is often marred by scalp muscle, movement, and electrode artifact, such high correlation of interictal EEG epileptiform abnormalities with temporal seizure origin degraded the long-held ictal EEG as the “gold standard” of identifying seizure origin.

For many years, nasopharyngeal or sphenoidal EEG leads supplemented the Ten Twenty EEG electrode system to better record anterior-mesial temporal EEG activity, especially spikes. As illustrated by F. A. Gibbs and E. L. Gibbs [10], the anterior temporal spike field was usually centred below the Ten Twenty Electrodes [11]. When Sadler and Goodwin [12] demonstrated convincingly that mandibular notch electrodes recorded anterior temporal spikes just as well as sphenoidal leads, we abandoned the latter for reasons of ease of application and patient comfort.

Our group at Western/University Hospital was the first to formally study and describe the morphology of scalp-recorded focal seizures-temporal and extratemporal [13]. Recognition of such features sharpened our visual assessment of clinical seizures.

## 3. Subdural EEG

In 1979, Dr. John Girvin and Mr. Dan Jones, EEG technologist, designed *subdural electrodes*. Inserted as imbedded in silicon strips through burr holes to avoid a craniotomy during the patient’s evaluation, these electrodes record directly from the cortical surface. Moreover, they may extend to mesial and inferior cortical surfaces, areas remote from scalp electrodes. For patients with temporal lobe epilepsy, SDE provides more precise and sensitive ictal and interictal recording from the mesial temporal regions.

Commercially manufactured subdural electrodes were not available in the early 1980s, resulting in some other epilepsy centres purchasing our in-house-manufactured electrodes. Design and manufacture of SDE at UH without any complication continued by Dan Jones and Frank Bihari for over 20 years. Figures 1 and 2 depict Mr. Jones and Mr. Bihari designing and inspecting our subdural electrodes.

However, in 2004 London Health Sciences Centre chose to make use of commercially produced electrodes, though at a significantly greater cost.

Our centre was the first to routinely employ subdural electrodes (SDE), and they continue today as a major part of evaluation of about 50% of our patients ultimately operated upon.



FIGURE 1



FIGURE 2

We studied 27 consecutive patients whose temporal lobe epilepsy clinically implicated both temporal lobes from ictal semiology, scalp EEG, and imaging features. We found that the side of SDE-recorded seizures correlated with that containing most scalp spikes and most scalp-recorded seizures in most but not all patients, confirming the value of both EEG and SDE [14].

## 4. Pre-MRI Imaging

Although unable to detect small cortical epileptogenic lesions, plain skull X-rays had disclosed several cranial and intracranial abnormalities of lateralising value. Cranial erosion on skull roentgenography could have resulted from a previous wide fracture or from a subdural or subarachnoid cyst; one or more asymmetrical cranial features may have indicated cerebral hemiatrophy, compatible with accompanying epileptogenesis; intracerebral calcification may have represented tumours or congenital lesions. Pneumoencephalography disclosed displaced or deformed ventricles from tumours, abscesses, hematoma, and other lesions. Cerebral arteriography helped localize expanding lesions but proved less helpful in the study of atrophic lesions [1].

## 5. Magnetic Resonance Imaging (MRI)

A major advance in evaluating patients for temporal lobe surgery was the advent of MRI. Imaging afforded by MRI discloses focal structural abnormalities underlying intractable epilepsy that may remain undetected by earlier neuroimaging methods [15]. Subsequently, Lee et al. [16] demonstrated both

high sensitivity and specificity for MRI in detecting pathologically verified hippocampal/amygdala and other temporal lobe epileptogenic lesions.

Three common epileptogenic lesions are particularly well displayed by MRI: mesial temporal sclerosis, cortical dysplasia (CD), and benign tumours such as dysembryoplastic neuroepithelial tumours (DNETs) and gangliogliomas (GGL). Rhythmic epileptiform discharges (REDs) may characterize the scalp EEGs of those with focal CD [17]; abundant focal spikes appear on scalp EEGs of DNET and GGL patients.

The presence or absence of mesial temporal sclerosis (MTS) became far better displayed by MRI than any previous imaging modality. This greatly facilitated, with EEG, an assessment as to whether one or both temporal lobes are epileptogenic. In the latter instance, assessment of their relative epileptogenicities may influence a surgical decision.

In some patients, MRI and EEG (via REDs) have demonstrated both MTS and CD with comparable epileptogenicity in each, termed “dual pathology” [18, 19]. Originally we opted for temporal lobectomy as the mesial temporal epilepsy is the region most likely to resist AED therapy [20]. However subsequent experience has suggested that a cortical CD or similar lesion should be resected first.

The appearance of dual pathology in some patients augmented our awareness of seizure propagation and its influence on semiology. Thus, ictal symptoms and signs may signify the site of seizure spread rather than origin. Both normal cerebral connectivity and neuronal pathways developed in the process of epileptogenesis likely participate in seizure spread. For example, occipital seizures may propagate to the mesial temporal region via the “ventral stream,” a multisynaptic pathway that terminates primarily in the amygdala but also in the parahippocampal area [21]. Munari and Bancaud [22] described ictal fear, epigastric and olfactory sensations, and orolimentary automatisms consequent to seizure spread from the orbital frontal cortex to the amygdala and insula. Suspect this situation in any patient with: (1) intractable limbic-like seizures and no anterior-mesial temporal EEG spikes, (2) no temporal MRI pathology, and (3) frontal lobe semiology in some seizures.

## 6. Neurosurgical Approach and Technique

Three approaches to the mesial temporal region have been described: sylvian fissure, middle temporal gyrus, and inferior temporal pole [23]. Our surgeons have accessed the mesial temporal structures via the middle temporal gyrus (Steven DA, *personal communication*). However, often a full temporal lobectomy has been performed (Parrent A, *personal communication*). Surgical approach and technique have not measurably changed over the years.

## 7. Outcome: Neuropsychological Effects

That a substantial left temporal lobectomy will significantly impair verbal memory has become increasingly realized over the past decades creating a distinction between left and right temporal epilepsy in terms of surgical candidacy [24, 25].

Concern about verbal memory and other verbal functions has raised considerably our threshold for left temporal lobectomy over the past several years.

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## Review Article

# Role of Electroencephalography in Presurgical Evaluation of Temporal Lobe Epilepsy

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Received 5 September 2011; Revised 18 January 2012; Accepted 28 June 2012

Academic Editor: Warren T. Blume

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Surgery remains a therapeutic option for patients with medically refractory epilepsy. Comprehensive presurgical evaluation includes electroencephalography (EEG) and video EEG in identifying patients who are likely to benefit from surgery. Here, we discuss in detail the utility of EEG in presurgical evaluation of patients with temporal lobe epilepsy along with illustrative cases.

## 1. Introduction

Temporal lobe epilepsy (TLE) is the most common form of epilepsy worldwide. Anterior temporal lobectomy (ATL) for medically refractory TLE secondary to mesial temporal sclerosis (MTS) is the most commonly performed surgical procedure in many of the comprehensive epilepsy management centres. Surgery is ideally directed towards complete seizure freedom without or with very minimal cognitive or functional deficits. Wiebe et al. in 2001 published the only randomised control study demonstrating the effectiveness of surgery in adults with medically refractory TLE [1]. Here, we would like to emphasise that the art of presurgical workup is to effectively use all the clinical, imaging, and electrophysiological information to localize the seizure onset zone (SOZ) and the epileptic network. In this paper, the electroencephalography (EEG) aspects of TLE with relevance to surgery are discussed with illustrative cases (see Table 1).

## 2. Surface EEG

Electrophysiological assessment remains the cornerstone for patients with TLE [10]. Standard EEG with 10–20 system provides limited coverage of the temporal regions detecting only about 58% of temporal spikes or interictal epileptiform

discharges (IEDs). Additional electrodes help in increasing this yield [11, 12]. Silverman's electrodes (T1 and T2, placed at posterior one-third and anterior two-thirds of a line connecting the outer canthus of the eye and the tragus) are often used to record from the anterior-basal areas of the temporal lobes [13–16]. Mandibular notch, nasopharyngeal (NP), sphenoidal (SP), and foramen ovale (FO) electrodes also help similarly.

NP recordings are cumbersome and provide little information over the well-tolerated routine anterior temporal and ear recordings especially with regard to anterior temporal IEDs [17, 18]. However, NP recordings have increased sensitivity for IEDs arising from mesiobasal temporal regions (increasing IEDs identification by 25%) [19]. FO electrodes offer a unique opportunity for simultaneous intracranial and surface EEG recording without breach of the skull. They may lateralize seizures in adults and children with mesial TLE when scalp ictal EEG fails [20–22]. It serves as intermediary between surface and invasive recordings.

The utility of SP electrodes remains debated. In TLE, fluoroscopic placement of SP electrodes below foramen ovale increases the sensitivity and interrater agreement for recognizing IEDs and ictal rhythms [18, 23]. In asymmetric onset ictal scalp EEG recordings, ictal changes may be

TABLE 1: Clinical details of the illustrative cases.

Case Figure	Age/sex/age at seizure onset	Seizure type	Intrictal EEG (VVEG)	Ictal EEG (VVEG)	MRI brain	Neuropsychology	FDG-PET/SPECT	Surgical procedure/histopathology	Outcome (Engel score)	Comments
1	4	CPS with epigastric aura Febrile seizures in childhood	Right anterior temporal IEDS, moderate right temporal theta-delta Right temporal TIRDA	Type I rhythm over right temporal/temporal-polar regions	Right MTS	Mild nonverbal dysfunction	None	Right TLY Severe HS with a small area of cortical dysplasia in temporal neocortex	Grade I	Typical MTLTLE Type I IEDS Focal slowing Type 1 ictal rhythm. Associated cortical dysplasia with MTS [2, 3]
2	5, 6	CPS	Right temporal IEDS Occasional right temporal theta	Type II ictal rhythm	Cavernous hemangioma in the right temporal neocortex	Normal	None	Limited corticectomy	Grade I	Late-onset epilepsy Oligospikes Type 2 ictal pattern
3	7, 8, 9, 10	CPS with unclear aura	Rare right anterior temporal IEDS Mild right temporal theta	Right temporal type I ictal rhythm <i>Subdurals</i> covering right temporal and the lesion Spikes (often periodical) and slowing over temporal pole, HC, and PHC areas Electrographic seizures over PHC area <i>Clinical seizures</i> : ictal onset over anterior mesial temporal structures with rapid posterior temporal lesion area with a faster frequency	Right posterior temporal enhancing lesion (fusiform gyrus) Normal mesial temporal structures	Mild nonverbal dysfunction	PET—mild hypometabolism right mesial temporal structures	TLY with lesionectomy DNET Mild neuronal loss and abnormal neurons in the HC	Grade I	Oligospikes Spikes and seizures are not always congruent Dual pathology occurs. Importance of dealing with both pathologies to achieve better seizure outcome [4, 5]
4	11	CPS	Occasional mild right temporal slowing No spikes	Initially, no clear changes. Late right temporal theta delta lateralization	Right posterior temporal enhancing lesion (fusiform gyrus)	Very mild nonverbal dysfunction	SPECT (<4 seconds)—no areas of increased perfusion other than lesion	Lesionectomy Pilocytic astrocytoma	Grade I	Late lateralization in temporal lobe epilepsy [6]
5	12, 13, 14	CPS, no clear aura Febrile seizures in childhood	Essentially normal	<i>Scalp</i> : right temporal type I rhythm with onset of clinical semiology <i>Subdurals</i> with bitemporal lines: left temporal ictal onset spreading to right temporal at onset of clinical semiology without involving the left neocortical temporal areas.	Severe left MTS	Moderate verbal dysfunction	None	Selective AH Severe HS	Grade I	Seizure pattern spread and surface expression need inferior and lateral temporal cortex involvement for surface expression Wasted hippocampal syndrome Ictal SPECT of limited use here as seizures remained subclinical when localised to the left temporal lobe In this case, interictal PET might be valuable if it shows left mesial temporal hypometabolism and normal right temporal metabolism

TABLE 1: Continued.

Case Figure	Age/sex/age at seizure onset	Seizure type	Interictal EEG (VEEG)	Ictal EEG (VEEG)	MRI brain	Neuropsychology	FDG-PET/SPECT	Surgical procedure/histopathology	Outcome (Engel score)	Comments
6	15	38/F/13 CPS	Bitemporal theta Bilateral anterior temporal IEDS (Right > left (70:30))	Left temporal type 2 rhythm No right temporal seizure onset (16 seizures)	severe left MTS and subtle right HC signal changes	Moderately severe verbal and mild nonverbal dysfunction	PET—left temporal hypometabolism	Left temporal polar selective AH	Grade I	Bitemporal IEDs in TLE, seizure onset zone, neuropsychology, MRI, and PET help ascertain degree of laterality and predict outcome
7	16	42/F/32 CPS with left upper limb paraesthesia at onset, hypersalivation, and hypomotor	Left temporal theta-delta Left temporal-frontal IEDS	Type 1 left temporal rhythm after few seconds of attenuation	Left MTS, subtle signal changes in right HC	Moderate verbal > mild nonverbal dysfunction	PET—left mesial temporal and left insular hypometabolism	Medical management	None	EEG alone does not distinguish temporal from temporal plus epilepsies

CPS: complex partial seizures, IEDS: interictal epileptiform discharge, MTS: mesial temporal sclerosis, HC: hippocampus, PHC: parahippocampus, HS: hippocampal sclerosis, TLY: temporal lobectomy, AH: Amygdalo-hippocampectomy.

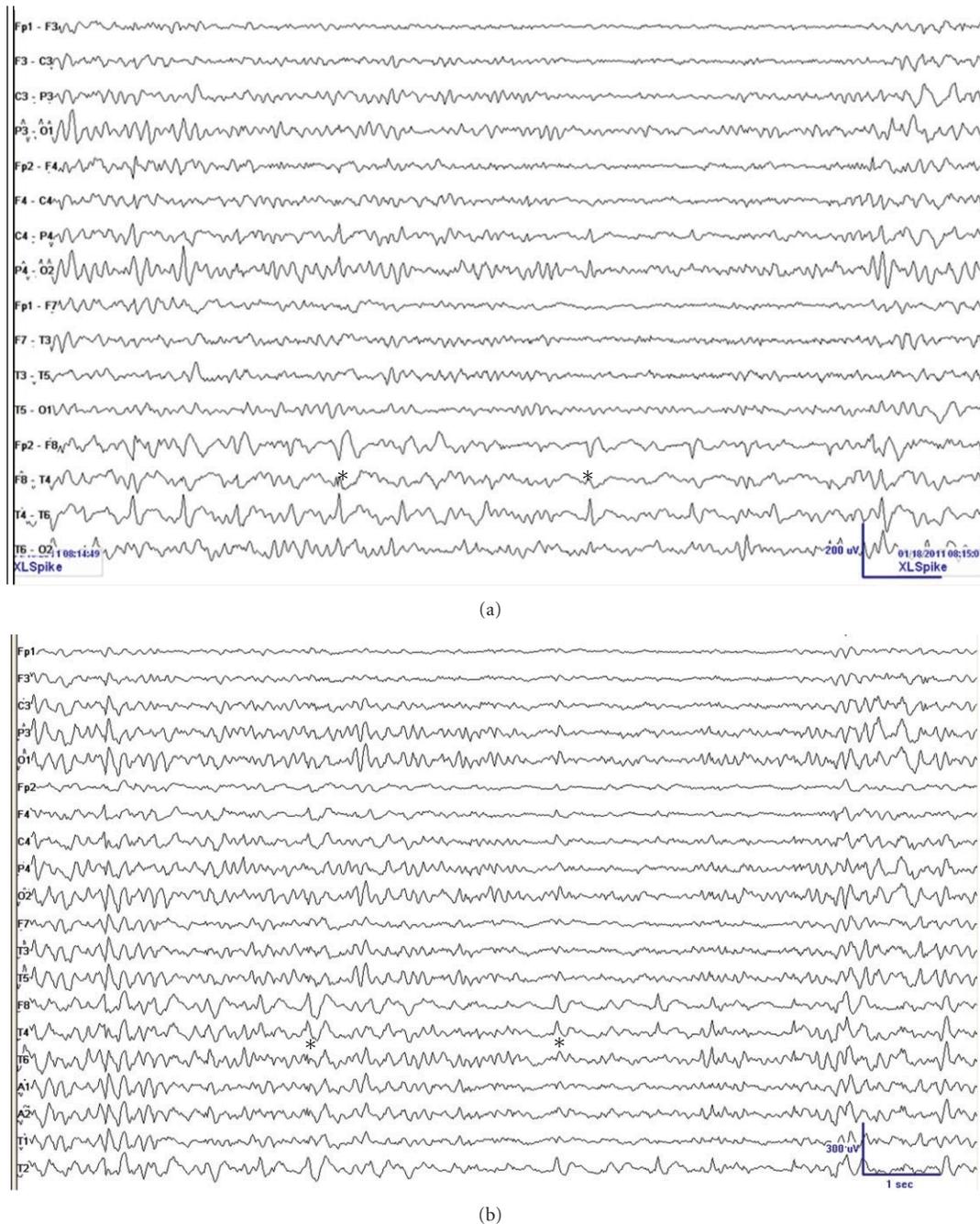


FIGURE 1: Typical EEG in a patient with right mTLE showing theta-delta activity over the right temporal region and right temporal spikes (\*) with phase reversal across F8 and T4 electrodes (The same epoch reformatted (a) bipolar montage and (b) common average referential montage; LFF = 1 Hz; HFF = 70 Hz).

earlier discernible on SP than scalp thus increasing seizure lateralization (5.4–7% increased yield) [24, 25]. Dipole localization techniques with SP electrodes also help with accurate source localization [26]. Blindly placed sphenoidal electrodes often do not lie below anatomical foramen ovale and may account for reduced efficiency [27]. Significant anatomical migration of the SP electrodes is also inevitable with prolonged recordings [28].

### 3. Interictal EEG Findings in TLE

Preoperative interictal EEG abnormalities commonly observed in TLE are focal arrhythmic slowing (either theta or delta) and focal IEDs that are often restricted to the anterior temporal areas (Figures 1(a) and 1(b)). In majority, these abnormalities correlate well with SOZ and the structural abnormalities seen on magnetic resonance imaging (MRI) (illustrative case 1). In TLE, single or

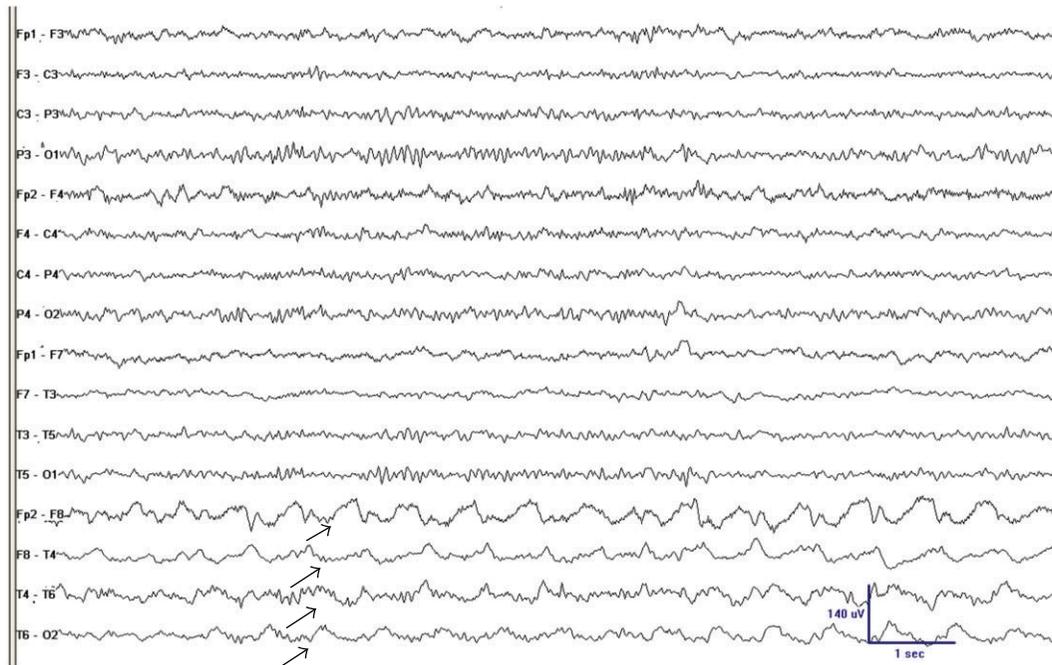


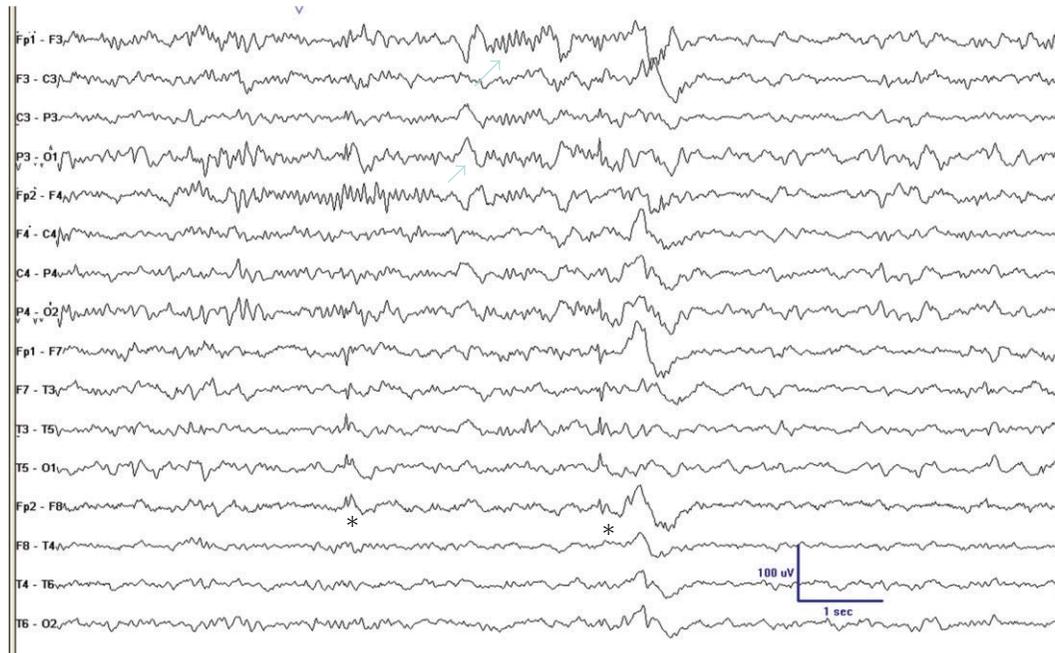
FIGURE 2: Bipolar anterior to posterior montage with 10–20 system showing 1–1.5 Hz temporal intermittent rhythmic delta activity (TIRDA) over the right temporal region (arrows) with maximal amplitude over anterior temporal region. Patient was a 42-year-old man with refractory CPS, right MTS, right temporal IEDs, and right temporal CPS (VEEG recordings). He was rendered seizure-free with right TLJ and remained seizure-free at 2-year followup (LFF 1 Hz—HFF 70 Hz).

serial outpatient EEGs demonstrate strong correlation of interictal abnormalities with areas of surgical resection and postoperative seizure outcomes (90% for IEDs and 82% for focal slowing) [29, 30]. Such strong correlations may obviate the need for mandatory ictal recordings during presurgical workup in patients with unilateral hippocampal atrophy (HA) and congruent clinical and neuropsychological data [31]. However, ictal recording becomes essential to rule out the possibility of concurrent psychogenic nonepileptic seizures (PNESs) [32]. Moreover, bilateral TLE, coexisting extratemporal epilepsy, or generalized epilepsy may not be appreciated in routine outpatient scalp EEGs.

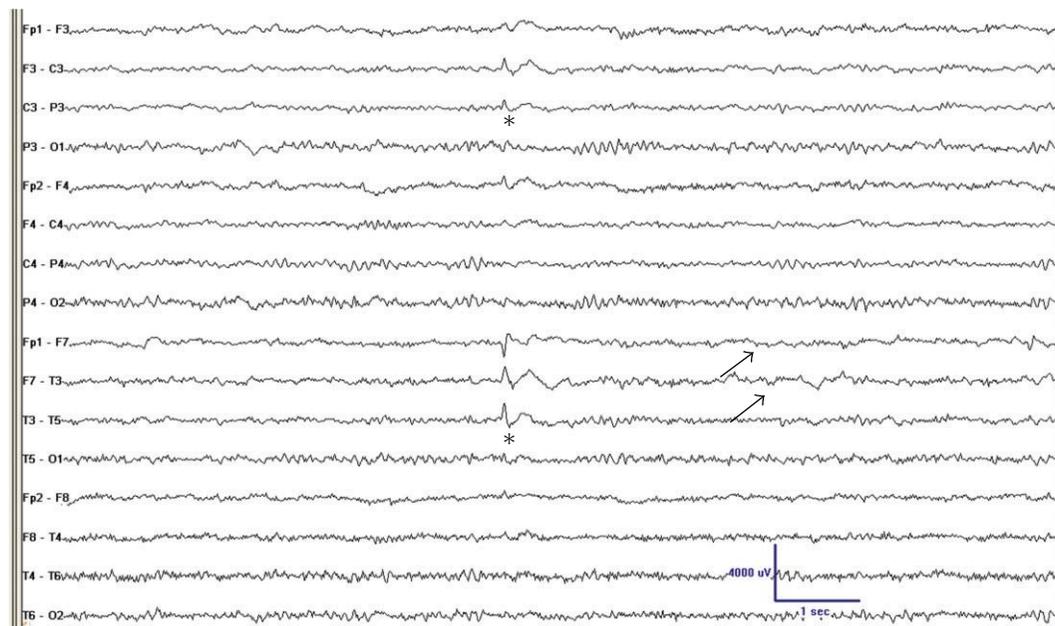
IEDs and clinical semiology aid to differentiate between mesial TLE (mTLE) and lateral or neocortical TLE (nTLE) [33]. The IEDs remain lateralized to the temporal regions in both syndromes (illustrative cases 1 and 2). In mTLE, IEDs are dominant over the anterior mesial temporal areas (T1/2, A1/2, F7/8, and T3/4), while patients with nTLE tend to have more lateral and posterior temporal IEDs (T5/6). While mesial temporal IEDs can infrequently occur in nTLE, converse is unlikely, that is, mTLE patients usually do not have neocortical IEDs. In TLE associated with MTS, IEDs tend to be more localized to the anterior temporal regions, while in the TLE associated with tumors, there is an increased tendency for bilateral expression of IEDs [34]. Typical anterior temporal spikes can also be seen in extratemporal epilepsy (a.k.a. temporal plus syndrome) [35, 36] (illustrative cases 7, 8).

Approximately 30 percent patients with unilateral TLE on other evaluation parameters show bitemporal IEDs [37,

38]. Many of these patients with refractory epilepsy do well with epilepsy surgery. However, greater degree of bilateral IEDs trends towards lesser postoperative seizure outcomes [39]. Chung et al. [40] in an invasive depth study of patients with unilateral SOZ demonstrated that greater than 90 percent lateralization of IEDs resulted in good surgical outcome in more than 90 percent of patients. Less than 90 percent laterality of IEDs resulted only in 50 percent of patients having good surgical outcome. Additionally, SOZ also predicts surgical outcomes in patients with bilateral temporal IEDs. Bilateral SOZ and bilateral IEDs have very poor outcome with surgery (only 12% seizure-free), while those with bilateral IEDs but unilateral SOZ have favorable outcome (40 to 56 percent) [41]. Repeated video EEG recordings may be at times necessary to demonstrate consistency of ictal laterality in TLE with bilateral IEDs [42]. Other findings such as MRI abnormality, hippocampal sclerosis (HS), neuropsychology, and clinical details help to determine the degree of laterality and the surgical outcome [42, 43]. Interestingly, in many with bilateral IEDs and good postoperative outcome followup, EEGs may show reduction or disappearance of contralateral spikes thus supporting the “seizure-induced epileptogenesis” hypotheses for contralateral IEDs [44] (case 6). Temporal IEDs also predict ictal scalp pattern. Lateralized ictal patterns are more common with unilateral temporal IEDs than bilateral [45]. The presence of bisynchronous IEDs in unilateral TLE is predictive of higher incidence for generalized seizures, but such patients still have favorable surgical outcome [46].



(a)



(b)

FIGURE 3: EEG in a 21-year-old man with complex partial seizures and normal MRI showing small sharp spikes (a) in sleep (\*) and left temporal spike (\*) and slowing (arrows) during wakefulness (b). Note the very frequent occurrence of small sharp spikes and its localization to the left temporal lobe where IEDs and slowing occurred (LFF = 1 Hz; HFF = 70 Hz).

Temporal “plus” epilepsies are characterized by seizures involving a complex epileptogenic network of the temporal lobe and the neighboring structures such as the orbitofrontal cortex, the insula, the frontal and parietal operculum, and the temporo-parieto-occipital junction [47–49]. Neither temporal IEDs nor temporal SOZ effectively rules out “temporal

lobe plus” epilepsies (Figure 17). These patients are often recognized by a combination of clinical, imaging, and EEG findings. The IEDs are often precentral and bilateral in these patients. They often need invasive monitoring to localize the SOZ. Insular seizures due to dense temporolimbic connections have clinical manifestations very similar to TLE

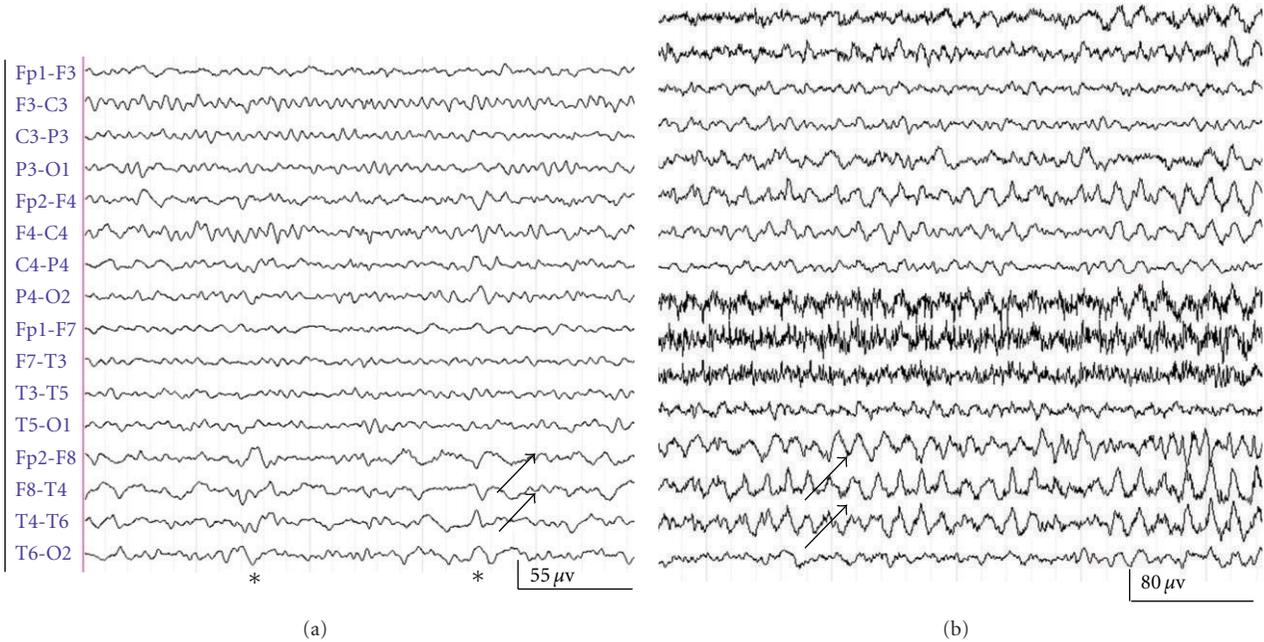


FIGURE 4: (Case 1) (a) Theta-delta slowing (arrows) and sharp waves (\*) over the right temporal region (phase reversal across T4) in anterior-posterior bipolar montage in right MTL. (b) Ebersole ictal pattern type I involving the right temporal region (arrows) in one of the complex partial seizures recorded during continuous video (LFF = 1 Hz; HFF = 70 Hz).

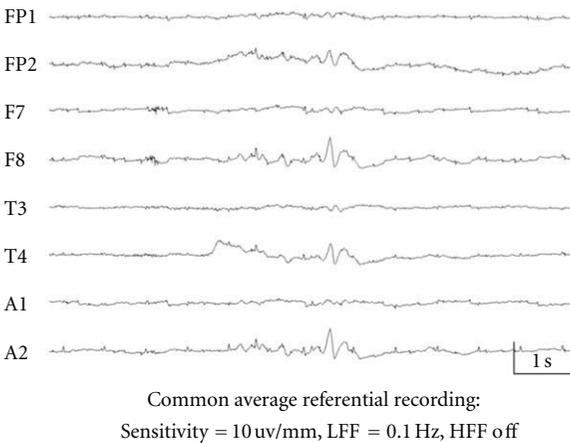


FIGURE 5: (Case 2) A typical right temporal IED involving F8, A2, and T4 during sleep (LFF = 0.1 Hz; HFF = 70 Hz) in a patient with refractory CPS secondary to right temporal neocortical cavernous hemangioma.

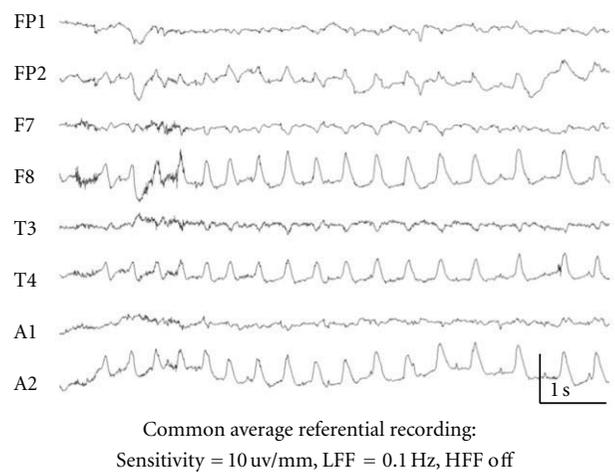


FIGURE 6: (Case 2) Ictal changes as right temporal seizure onset (F8, A2, and T4) with minimal involvement of the right frontopolar (FP2) region (type 2 ictal rhythm).

[50–53]. Such seizures are characterized by a sensation of constriction in the throat, paresthesias, or warmth feeling over the perioral region or large body territories, followed by focal sensory-motor manifestations. Positron emission tomography (PET) and ictal single-photon emission computed tomography (SPECT) studies may help identify few of these patients with nonlesional insular seizures [54] (illustrative case 7).

The electrical dipole nature of the IEDs has a prognostic value. A relatively localized negativity with steep

voltage gradient at the anterior temporal electrodes or sphenoidal electrodes with widespread vertex positivity termed as “Ebersole type 1 source” localizes the abnormality to mesiobasal temporal lobe (illustrative case 1). These patients are likely to have a very good surgical outcome. IEDs with relatively broad frontal-basal negativity that may cross the midline, gradual voltage gradient, and poor electropositivity (“Ebersole type 2 source”) indicate either nTLE or frontal originating spikes [55, 56] (illustrative case 2).

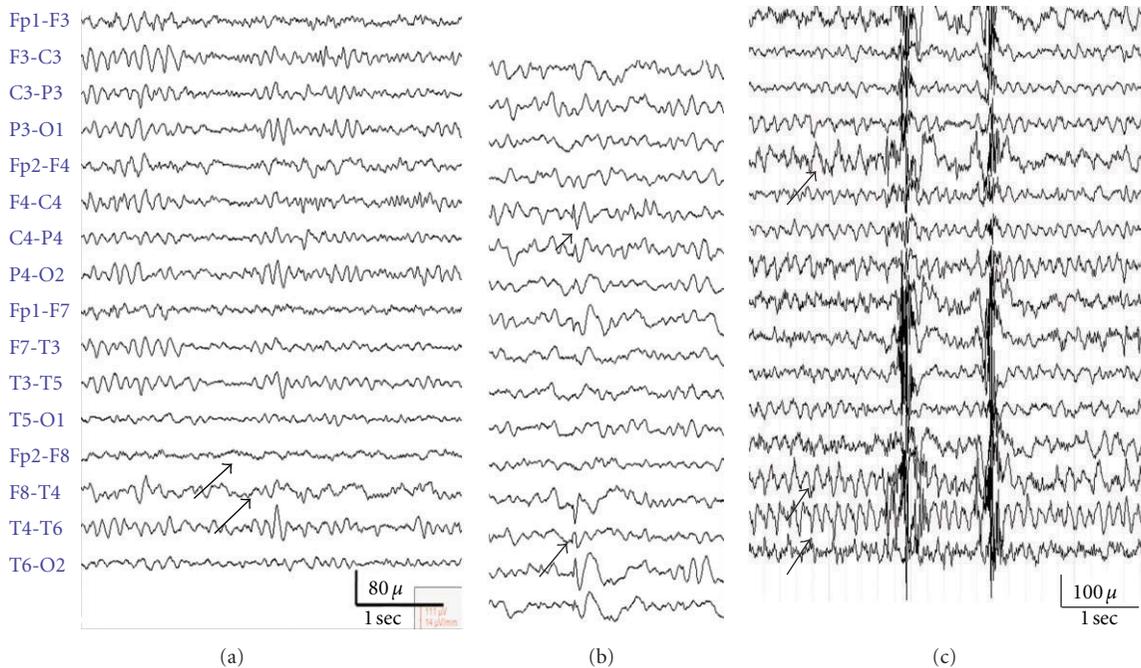


FIGURE 7: (Case 3) Interictal EEG in a patient with medically refractory complex partial seizures and right posterior temporal lesion on MRI (Figure 8) shows mild right anterior temporal slowing ((a) arrows) and rare right anterior temporal spikes with minimal spread to the frontopolar region ((b) arrows). Ictal rhythm during a complex partial seizure shows right temporal regionalized semirhythmic theta activity ((c) arrows).

Frequent IEDs (i.e., 60 spikes/hour in one EEG recording) are associated with less than desirable outcome after temporal lobectomy (TLY) [57]. This supports the “mouse model hypothesis” that IEDs are inhibitory phenomena, and they help to control seizures [58]. A small subset of patients with TLE have infrequent or absent IEDs (cases 2, 3). Such “oligospickers” (i.e., IEDs < one in an hour on several scalp EEG recordings) tend to have a good ictal localization and excellent surgical outcomes similar to other TLE patients. Oligospikes in TLE often correlate with later age of seizure onset, low seizure frequency, lesser tendency for status epilepticus (SE), or hippocampal atrophy (HA). This subset likely represents milder degree of MTS without differences in etiological factors [59]. Absence of IEDs may suggest extratemporal seizures, and such patients may need extra care during presurgical workup [60].

*Small sharp spikes (SSS) or benign epileptiform transients of sleep (BETS)* are benign epileptiform variants common in adolescents and young adults. These are typically monophasic or diphasic discharges, without aftercoming slow wave, having widespread distribution and are often most prominent over the anterior temporal and frontal regions. They occur sporadically and independently over both hemispheres and are often seen during stages 1 or 2 of NREM sleep. Pathological SSS or unilateral SSS (often with theta) may be linked to complex partial seizures tend to occur in deeper stages of sleep, wakefulness, in couplets and often localize to one of the anterior temporal lobes from where the seizure arises [61] (Figure 3).

#### 4. Temporal Intermittent Rhythmic Delta Activity (TIRDA)

In TLE, interictal EEG (often in drowsiness or light sleep) shows a rhythmic sinusoidal 1–4 Hz delta activity that remains localized to the temporal lobes (Figure 2). TIRDA has high correlation with anterior temporal IEDs, SOZ, mesial, and mesiolateral TLE, particularly in patients with MTS. Lateralized TIPDA is more common in patients with extratemporal epilepsy (about 20%) [62, 63].

#### 5. Ictal Rhythms in TLE

In majority (approximately 90%) with unilateral TLE (unilateral MRI abnormality and IEDs), the ictal lateralization corresponds to interictal IEDs and slowing. Ictal rhythms can be variable even within the same patient. Lateralization at onset can be observed in only a third of unilateral TLE [30, 64]. Ictal EEG may not aid in differentiating the anterior from posterior lateral TLE [65]. Ebersole et al. classified the ictal rhythms in TLE into three types [66]. Typical ictal surface EEG with high interrater concordance consists of a rhythmic 5 to 9 Hz theta activity that slowly evolves and remains localized to the temporal or subtemporal regions which is termed type 1 ictal rhythm (illustrative case 1). This pattern is most specific for hippocampal seizures. A lower frequency of 2 to 5 Hz irregular ictal rhythm with widespread temporal distribution is termed as “type 2 rhythm” and is

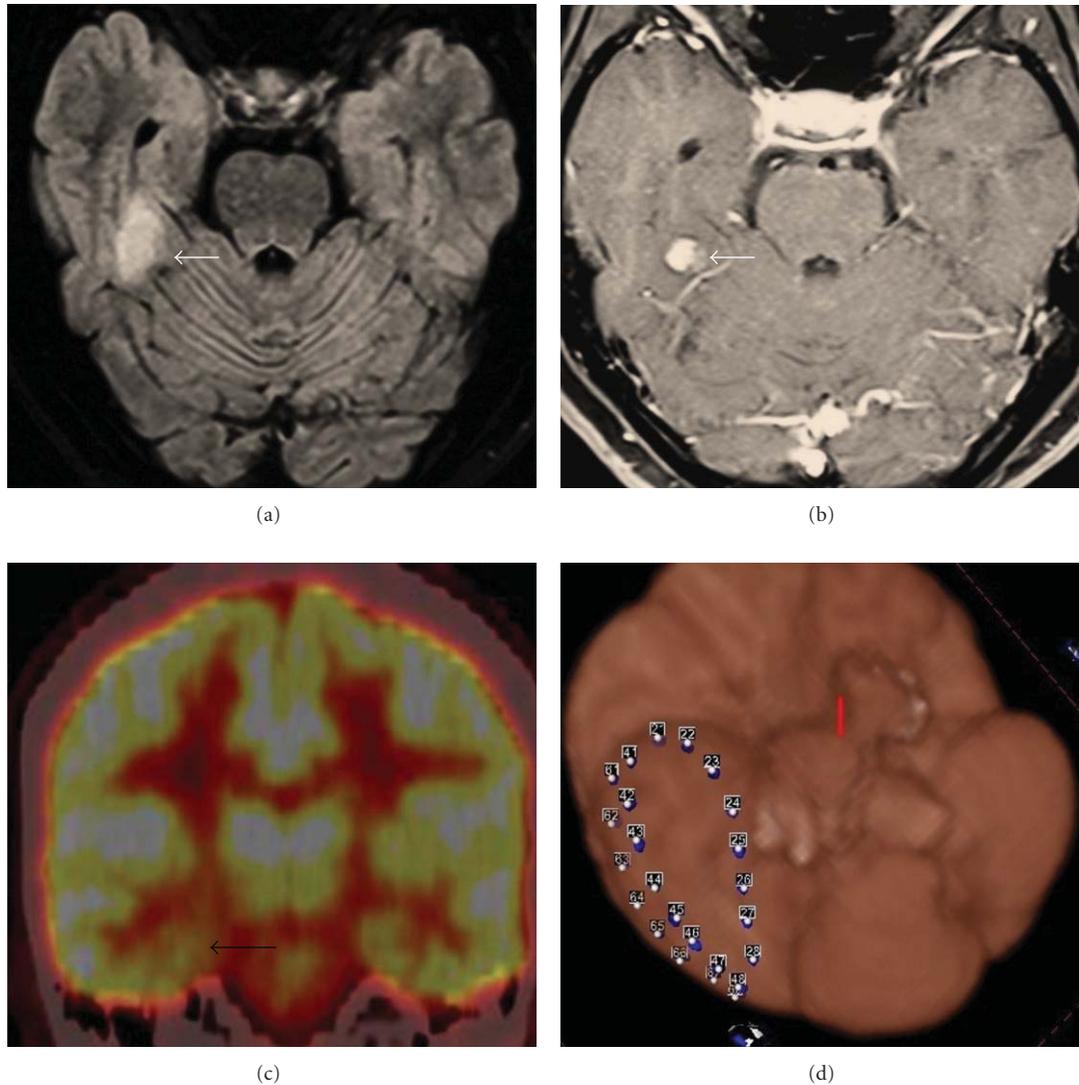


FIGURE 8: (Case 3) MRI of the brain ((a) FLAIR and (b) contrast) shows a right posterior temporal lesion that is enhanced with contrast injection. FDG-PET (c) scan shows mild right temporal hypometabolism. (d) Coregistered image of the location of the subdural lines during invasive monitoring (8 contacts and three strips; the image was obtained with Atamai Epilepsy Viewer software [6]).

often associated with neocortical seizures [67] (illustrative case 2). Diffuse ictal EEG changes or attenuation without clear lateralization (type 3 rhythm) can be seen both in hippocampal and temporal neocortical seizures.

## 6. Comparison of Surface EEG with Invasive Recordings

Correlating studies comparing surface EEG with simultaneous subdural electrodes (SEs) and depth electrodes (DEs) demonstrate that most subclinical electrical seizures confined to the hippocampus do not result in surface EEG changes (illustrative case 5: subdural recordings). When the seizure spreads from mesial temporal to the inferolateral temporal structures, type I surface rhythm is observed.

Type 2 rhythms are often neocortical seizures starting as fast activity of 20 to 40 Hz on subdural electrodes that are either not detectable on surface EEG or are seen as “attenuation patterns” followed by asynchronous theta-delta activity over the temporal regions. Type 3 ictal rhythm occurs when seizures are confined to the hippocampus or spreads rapidly to the contralateral hippocampus, where there is little synchronisation of the electrical activity over the inferior lateral temporal structures for expression on to the surface EEG.

*Start-stop-start* is an ictal phenomenon observed in TLE when initial ictal pattern is followed by complete cessation often reverting back to interictal EEG and then again reappearance of ictal potentials. In about a third, the restart may occur at a different anatomical location than the initial start, thus a potential pit fall of ictal localization [68].

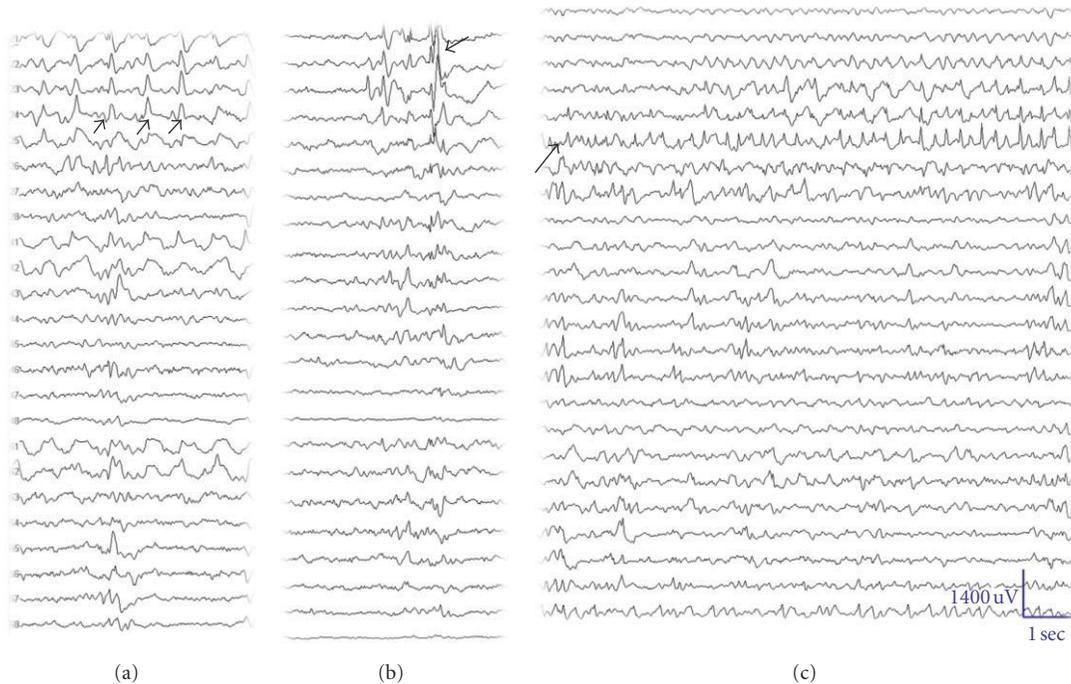


FIGURE 9: (Case 3) ((a) and (b)) Subdural recordings show temporal polar and anterior mesial temporal region IEDs (arrows, (a) rhythmic spikes, (b) sporadic). (c) An electrographic seizure involving the parahippocampal structures (arrow) without clinical manifestations.

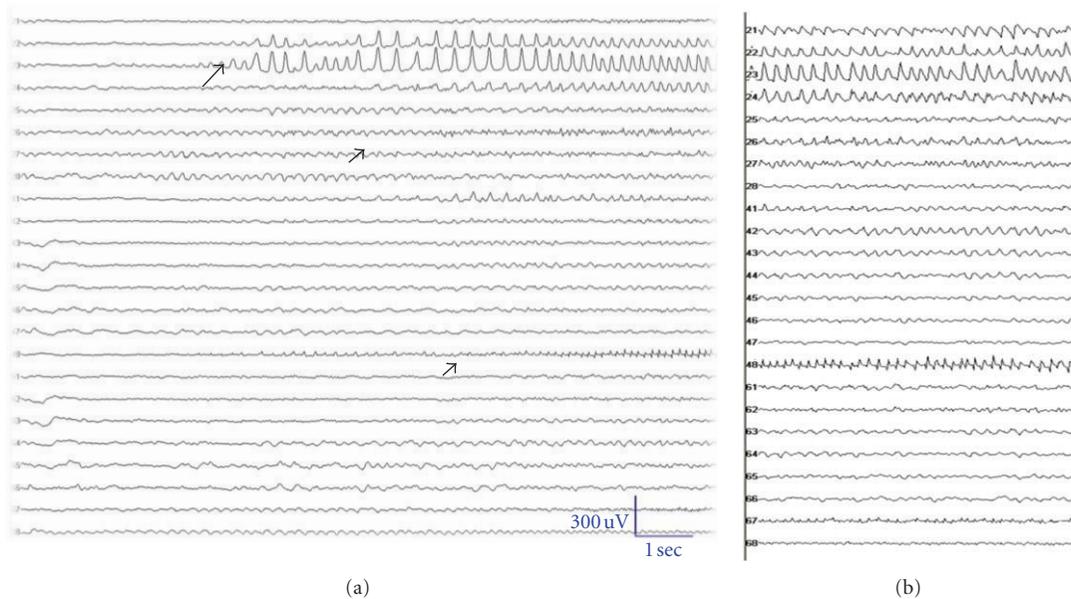


FIGURE 10: (Case 3) Ictal EEG shows 3 Hz evolving rhythm in the temporal polar and mesial temporal regions (long arrow) with faster rhythm posteriorly (short arrows) within 2 to 3 seconds (Note that (a) and (b) are contiguous time frame).

## 7. Ictal Propagation Patterns

Temporal lobe seizures often use indirect pathway for propagation into the contralateral temporal lobe more than direct hippocampal commissures [69]. The orbitofrontal cortex is strongly influenced by mesial temporal ictal activity [70]. In majority, the propagation is to ipsilateral frontal lobe,

the contralateral frontal lobe, and then to the contralateral temporal lobe.

Early propagation of seizures (less than 10 seconds) suggests more widespread hyperexcitability and greater probability of bilateral temporal epileptogenicity and tends to occur in patients other than pure MTS [39, 71, 72]. Best surgical benefits can be expected in those patients with

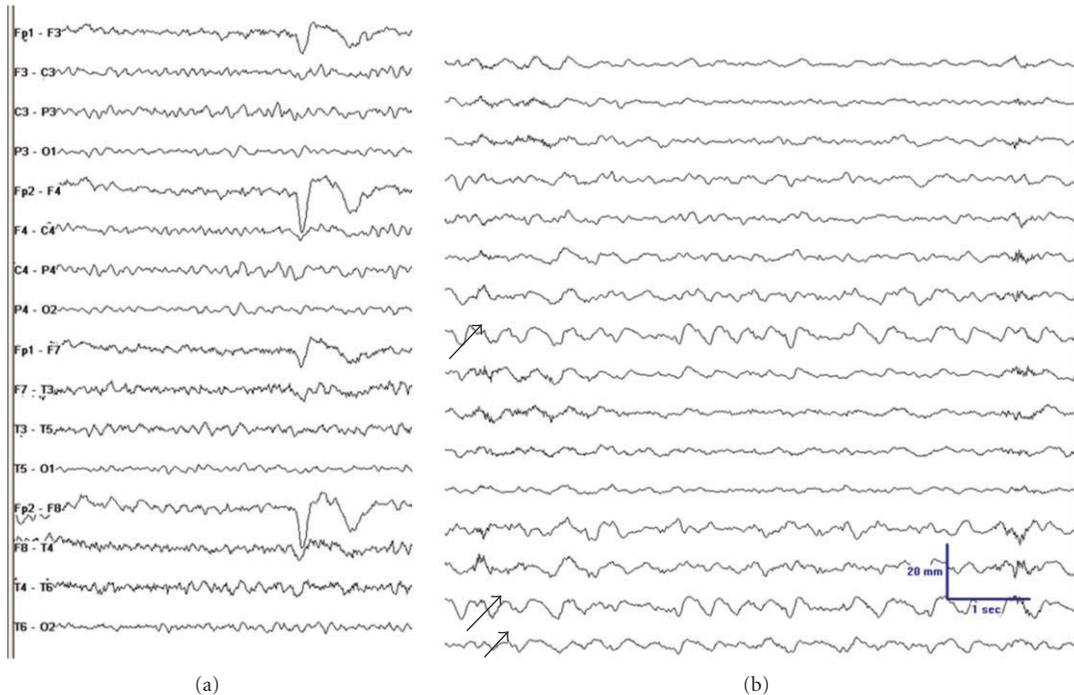


FIGURE 11: (Case 4) (a) Normal EEG in a 20-year-old man with refractory complex partial seizures and right posterior temporal enhancing lesion. (b) Ictal EEG about 30 seconds into one of the typical complex partial seizures shows arrhythmic theta-delta activity over the right temporal-occipital regions. No clear lateralizing ictal EEG changes were discernible early in the seizure (not shown here).

regionalized ictal EEG activity without contralateral spread and ipsilateral interictal abnormalities.

## 8. Invasive Monitoring: Depth, Subdural Lines, or Both

Invasive monitoring can be safely performed either with SE or DE when noninvasive data are discordant [73, 74]. The most important step prior to embarking upon invasive recording is an “unbiased hypothesis.” Indications for invasive recordings in TLE are either bitemporal epilepsy or temporal plus syndromes [75].

Hippocampal DEs (6–8 contacts) are placed stereotactically along the long axis of hippocampus to amygdala through a small occipital burr hole. These are particularly useful in mTLE of uncertain lateralization. However, DE recordings alone do not differentiate mesial from neocortical TLE. DEs are not useful in isolation for “temporal plus” syndromes. A combination of SEs or grids with DEs tailored to an individual patient becomes essential. This is either performed through multiple subdural electrodes (for further details on the placement of invasive EEG electrodes, see Steven et al. [76]) or by a combination of a subdural grid covering the lateral temporal lobe, while the mesial structures are covered by two or three DEs (4 contacts) perpendicular through the middle temporal gyrus and the overlying grid [77, 78]. Both of these techniques are equally effective. In TLE, there is a high degree of concordance between the SE and DE recordings particularly if the electrode placement

is mesial to the collateral sulcus and is recording from the surface of parahippocampal gyrus [79] (illustrative cases 3 and 5). SE/grids also provide an opportunity for functional language localization by stimulation.

In general, most of the seizures recorded by SE arise from the same lobe showing predominant IEDs and seizures on scalp EEGs [80]. On occasions, auras and subclinical seizures detected by DE recordings may not be evident on SE [81]. Presence of periodic IEDs prior to the seizure onset in mesial temporal lobe structures is often specific for hippocampal onset seizures and correlates well to reduced CA1 cell counts. Temporal neocortical seizures at onset have significantly faster frequencies (20 to 40 Hz) in contrast to the hippocampal seizures that have slower frequencies (13 to 20 Hz). TLE associated with MTS is more likely to have higher seizure onset frequency than mTLE not associated with MTS (illustrative cases 3 and 5).

Two common seizure patterns in temporal lobe seizures are hypersynchronous rhythmic high-amplitude activity (HYA) and low-voltage fast activity (LVFA) (illustrative cases 3 and 5). HYA is likely to represent more focal onset and lesser rate of spread to contralateral mesial temporal structures and is associated with more marked neuronal loss in the hippocampi than the LVFA that tends to be more regionalized and neocortical in nature involving both hippocampal and extrahippocampal networks [82–85]. Seizures with LVFA or rhythmic sinusoidal ictal patterns are associated with better outcomes after surgery [86].

Following seizure onset and initial recruitment of the surrounding area, the ictal rhythm propagates variably. The

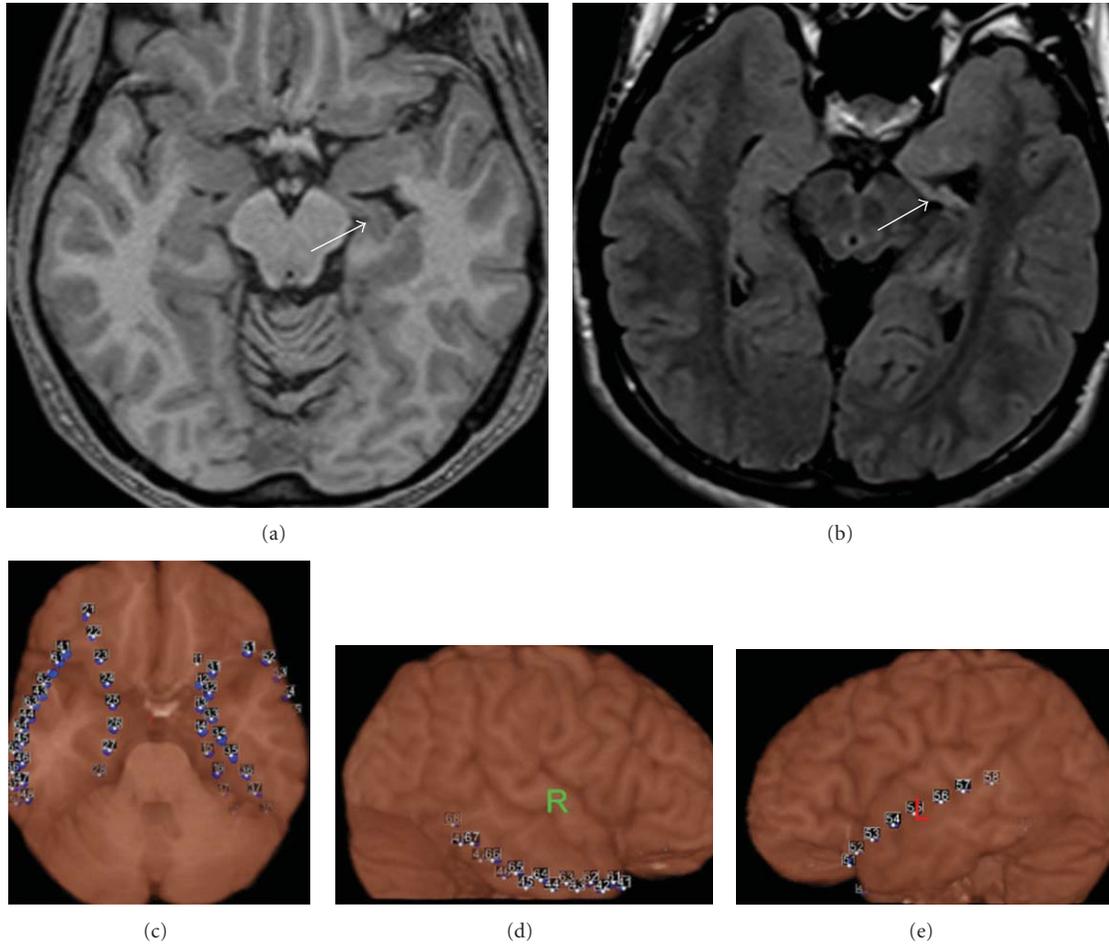


FIGURE 12: (Case 5) MRI of the brain in a patient with refractory complex partial seizures shows severe left MTS (upper). Atami Epilepsy Viewer image of bilateral subdural lines placed for invasive monitoring (lower).

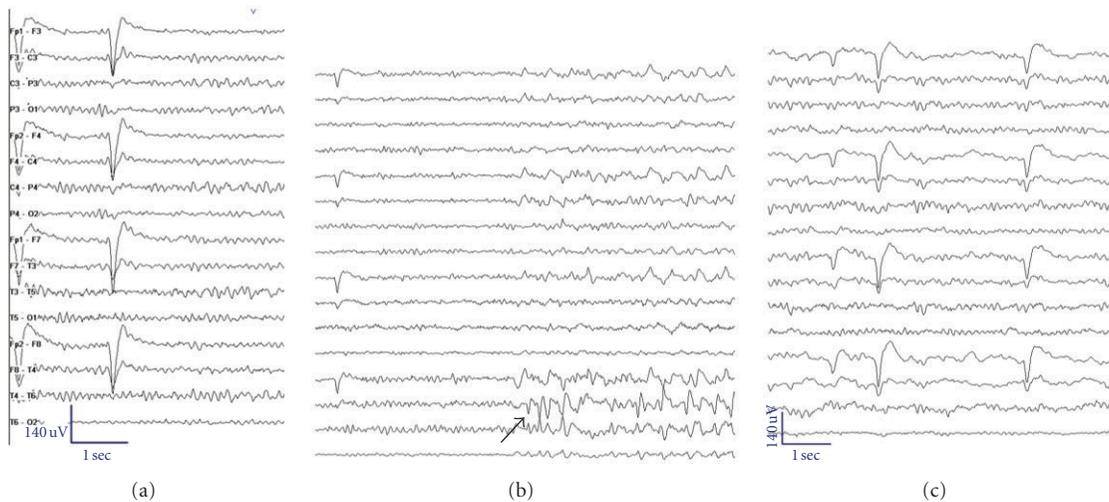


FIGURE 13: (Case 5) Normal EEG (a) in a patient with refractory complex partial seizures and left mesial temporal sclerosis. Ictal EEG at onset during one of the CPSs (b) (arrows) shows semirhythmic theta onset over the right temporal regions (arrow). Postictal EEG (c) shows right temporal rhythmic delta activity (arrow).

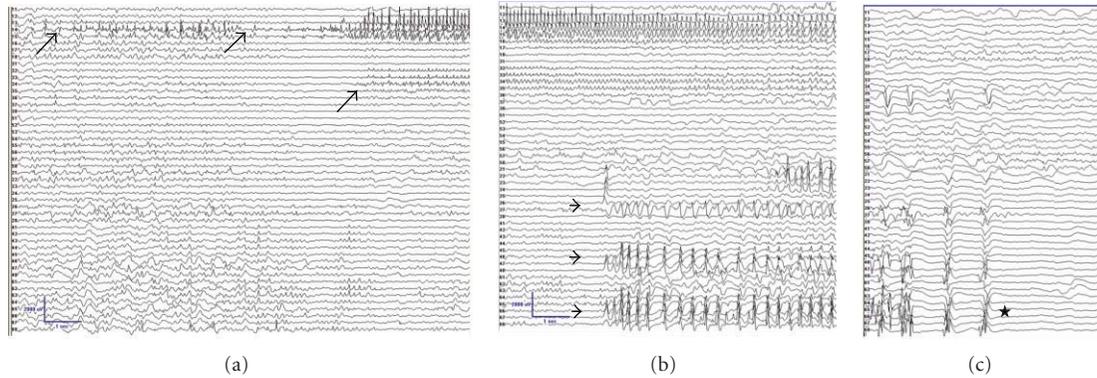


FIGURE 14: Subdural ictal EEG shows rhythmic spikes arising from the left hippocampal area followed by localised low-voltage fast activity and then sequential spikes spreading to the left subtemporal area (a) (arrows) but not to the left temporal neocortex. (b) About 12 seconds into the seizure, it spreads to the right temporal regions (both mesial and neocortical) (arrow heads) with continued activity in the left temporal region with offset in right temporal lobe (c). Prominent postictal slowing over the right temporal region is seen (c).

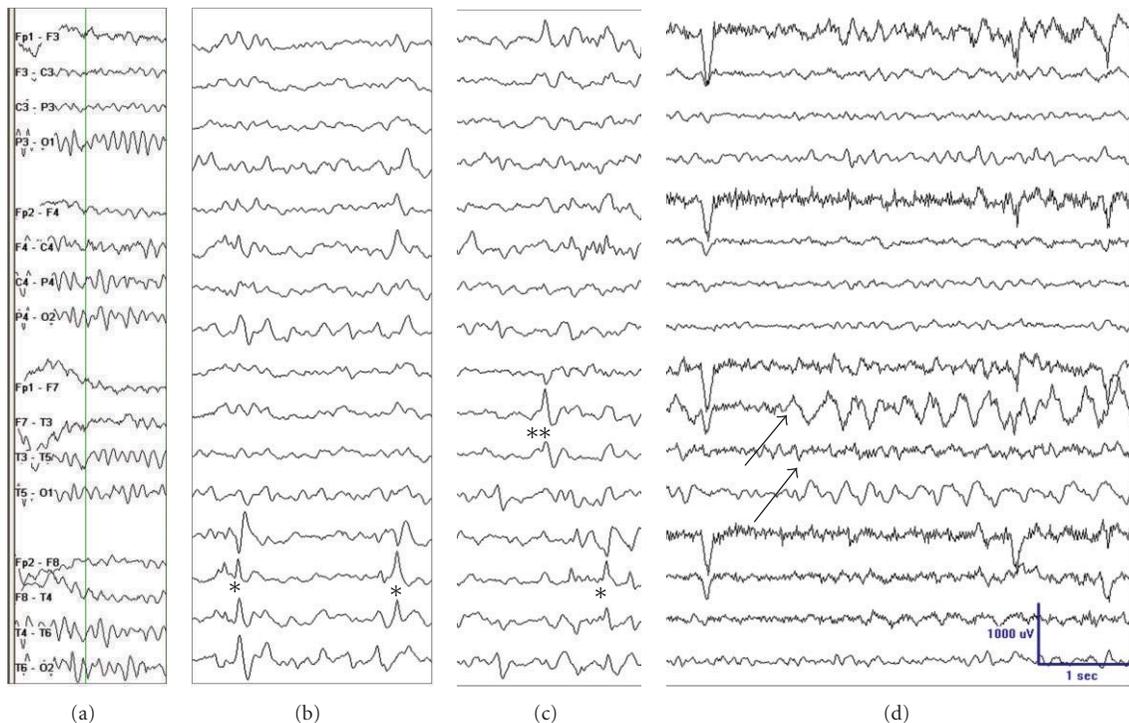


FIGURE 15: (Case 6) EEG in a 38-year-old woman with refractory complex partial seizures and left MTS. (a) Background EEG that showed mild independent bilateral temporal and generalized slowing; (b) right anterior temporal spikes (\*); (c) left anterior temporal spikes (\*\*) (right temporal IEDs to left temporal IEDs 70:30) in sleep; (d) left temporal type 2 ictal rhythm as rhythmic delta activity in the left temporal regions (arrows) during one of her typical complex partial seizures (seizure onset zone). A total of 16 seizures were captured from the left temporal region. She underwent a left ATL and was seizure-free at last followup 12 months and had a marked reduction in the right temporal IEDs.

spread can be to the ipsilateral temporal lobe, contralateral mesial temporal, or temporal neocortex [87]. Long inter-hemispheric propagation times are associated with good surgical outcomes in mTLE. Time to propagation of the seizure to the contralateral hippocampus is directly proportional to cell loss in the Cornu Ammonis (CA) subfield 4 (CA4, also known as the hilar region of the dentate gyrus), suggesting a role for CA4 in this process [88].

## 9. Wasted Hippocampal Syndrome

In rare instances, one may come across patients with severe unilateral HA with contralateral ictal onset of seizures. These patients are often referred to have “wasted hippocampal syndrome” (illustrative case 5) [89]. In vast majority of patients, invasive recordings show seizures arising from the atrophic side, and they have very good seizure outcomes with

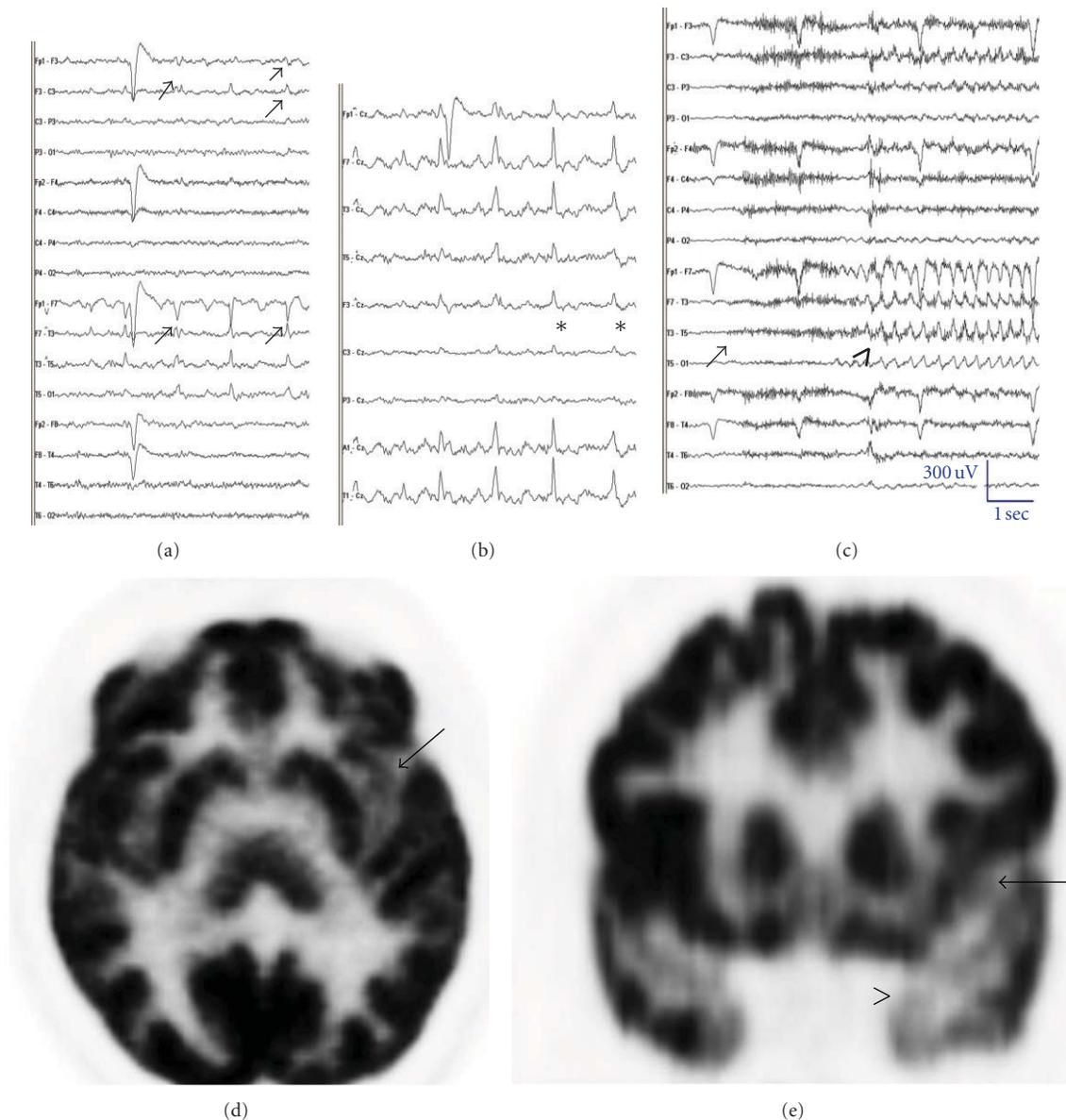


FIGURE 16: (Case 7) A 42-year-old woman with refractory CPS of suspected insular origin from the age of 32 years with left MTS on MRI. Her seizures would start with an aura as upper limb paraesthesia in about 20% of her seizures that would progress to lack of awareness and profound drooling lasting less than 30 seconds. Interictal EEG showing left temporal theta and left temporal-frontal spikes ((a) arrows and (b) \*) ((a) bipolar and (b) referential montage of same epoch). (c) EEG during her recorded seizures showing left temporal rhythmic theta after a brief attenuation for few seconds (c). FDG PET (d) and (e) demonstrate left insular (long arrow) and left mesial temporal (arrow head) hypometabolism ((c) and (d) arrows).

surgery. IEDs on surface EEG are more likely to correlate with the lateralization of the seizures in this situation. It is debatable if these subsets of patients need invasive study. In selected patients, noninvasive tests such as SPECT or PET may aid resective surgery without invasive monitoring.

## 10. Postictal EEG

Postictal EEG adds critical information particularly when seizure onset is unclear, or ictal changes are marred by muscle

artifacts. The accuracy of postictal findings for lateralization has a higher degree of interrater reliability particularly in TLE than extratemporal seizures [90]. Postictal EEG findings include polymorphic lateralized delta activity [91], background suppression, and postictal spikes (57%, 29%, and 25%, resp.) [92]. Postictal spikes are most sensitive for lateralization but may be affected by seizures spreading to the contralateral temporal lobe. In about a third, there may be no distinctive postictal change. These findings are affected by intensity of seizures, degree of HA, contralateral spread, and secondary generalization [93, 94]. A combination of

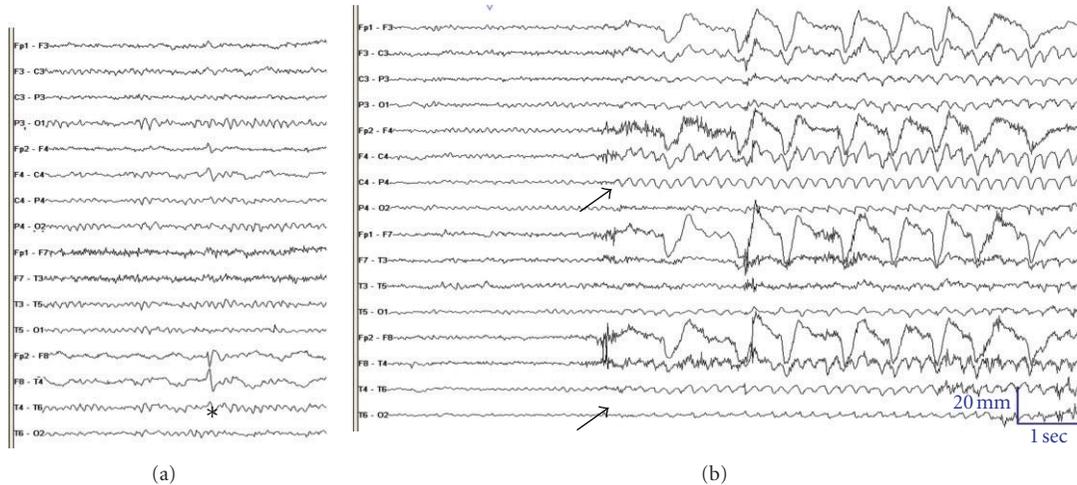


FIGURE 17: EEG in a young 25-year-old adult with right mesial occipital dysplasia who became seizure-free after lesionectomy. (a) Interictal EEG shows slowing over the right anterior temporal region and anterior temporal spikes (\*). (b) Ictal changes (arrow) were dominant over the right occipital region during one of his typical complex partial seizures. *Comments:* this case illustrates the presence of temporal spikes and slowing in a patient with occipital epilepsy due to a lesion (i.e., temporal lobe plus syndrome) [7–9].

postictal changes that persist longer is likely with widespread or secondary generalized seizure.

## 11. High-Frequency Oscillations (HFOs)

HFOs or ripples are electrical potentials in 80–600 Hz range recorded from the normal hippocampus and parahippocampal structures of humans with intracranial macroelectrodes. They may reflect normal inhibitory field potentials needed for neuronal synchronization. HFOs in the range of 250–600 Hz (fast ripples, FRs) are often recorded from the pathologic hippocampus and parahippocampal structures of patients with mTLE [95]. They are prominent in the SOZ, and they provide independent additional information on epileptogenicity of IEDs [96]. HFOs have high specificity for SOZ even with very short recordings of only 10 minutes. Total resection of HFOs containing tissues results in good surgical outcomes [97, 98].

## 12. Conclusions

EEG remains the most important investigation in appropriately subclassifying patients with TLE along with other clinical and noninvasive data. Clinical history, physical findings, neuropsychological testing, MRI, and at times PET and SPECT, fMRI, or MEG data need to be integrated with EEG to select the ideal patients who would benefit from surgery. Most patients with TLE can be selected for surgery based on surface recordings alone. With discordant data, invasive monitoring helps to aid this decision.

## Acknowledgment

The authors wish to acknowledge the Human Brain Tissue Repository (Brain Bank), Department of Neuropathology,

National Institute of Mental Health and Neurosciences, Bangalore for histological evaluation.

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## Review Article

# Functional Magnetic Resonance Imaging for Language Mapping in Temporal Lobe Epilepsy

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Received 2 February 2012; Accepted 28 June 2012

Academic Editor: Warren T. Blume

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Functional magnetic resonance imaging (fMRI) is a noninvasive technique that is increasingly used to understand the cerebral cortical networks and organizations. In this paper, we describe the role of fMRI for mapping language networks in the presurgical workup of patients with medically intractable temporal lobe epilepsy (TLE). Studies comparing fMRI with the intracarotid sodium amobarbital (Wada) test and fMRI with intraoperative cortical stimulation mapping for language lateralization and/or localization in medically intractable TLE are discussed.

## 1. Introduction

Epilepsy is a common neurological disorder that affects about 0.5%–1% of the general population. Temporal lobe epilepsy (TLE) is the most common form of partial epilepsy [1]. About 20%–30% of the patients with TLE develop medication resistance and may benefit from a surgical treatment. For patients with medically refractory TLE, surgical excision of the affected temporal lobe is an alternative approach to the treatment of this disorder [2]. While anterior temporal lobectomy (ATL) has proven to be effective in the treatment of TLE patients resistant to medical therapy [3], successful surgical outcome depends not only on an accurate localization of the epileptogenic focus, but also on the ability to map and preserve the “eloquent cortex.” In particular, the lateralization and localization of language cortex are of paramount importance for ATL in the dominant hemisphere. As demonstrated by Haglund et al. [4], the distance from the language cortex to the resection boundary is the most important predictor of developing postoperative language deficits.

Currently, invasive tests such as the intracarotid amobarbital procedure (IAP, also called the Wada test) [5] and electrocortical stimulation mapping (ESM) [6], both of which present the patient with additional risks, are the common means for lateralization and localization of the functional regions in brain. Noninvasive imaging techniques may reduce the need for such procedures, and, in particular, functional magnetic resonance imaging (fMRI) is an alternative to replace these invasive procedures for surgical planning of the patients with TLE.

In the following section, we review the basics of fMRI, while Sections 3 and 4 review previous studies comparing fMRI to the Wada test for language lateralization and fMRI to ESM for language localization. In Section 5, we discuss the role of fMRI in studying brain plasticity for language function after temporal lobectomy (TLY).

## 2. Basics of fMRI

fMRI employs the blood-oxygenation-level-dependent (BOLD) [7] contrast mechanism as an indirect measure of

underlying neuronal activity. When certain functional areas in brain are activated, there is an increase in local metabolism and oxygen consumption. Because of the neurovascular coupling between regional changes in brain metabolism and cerebral blood flow (CBF), the activated local areas in the brain experience a decrease in oxyhemoglobin and an increase in deoxyhemoglobin in the postcapillary vascular bed. Since hemoglobin has different magnetic properties depending on its state of oxygenation, being diamagnetic when oxygenated and paramagnetic when deoxygenated, these oxygen-related changes to the blood lead to local magnetic field inhomogeneities, which in turn result in detectable changes in the magnetic resonance signal measurable by MRI.

To elicit the activated functional areas in brain using the BOLD signal effectively and robustly, most fMRI studies employ a block design, in which tasks are alternated to generate brain response in different states (in the simplest form, two states: rest versus activation). Event-related designs have also been employed in the last few years to examine language function and lateralization. In contrast to a block design, in which the conditions are alternated within a block (resting, task1, resting, task2) with each block having a fixed duration, in an event-related design, events of different types are randomly intermixed. Some studies have shown a more robust activation of language areas in event-related than in block design paradigms [8].

Because the magnetic signal changes caused by the hemodynamic behaviour are usually very small, the selection and design of the experimental paradigm is of utmost importance. Various auditory and visual stimulation paradigms have been developed to examine the language functions, and since language tasks are most likely to activate not only language areas but also other functional regions, the experimental paradigm requires controlled tasks that activate non-language cortex equally. A common example used for language study that can be performed easily in patients for lateralization purposes is the “verb generation” and “verbal fluency” task. In this type of design, participants are instructed to covertly generate action verbs for each noun (e.g., for the word “knife” one can think “to cut,” “to slice,” “to throw”). The resting phase involves participants looking at a cross in the center of the screen while not actively engaging in any language function. Alternatively, subjects may be presented with nonsense collections of letters to “washout” the nonlinguistic aspects of the task. This task provides relatively consistent activation of the anterior language areas (Figure 1). Another commonly used language task employed at our institution is a “sentence completion paradigm” (also called “sentence comprehension”). Participants are informed they will see a sentence on the screen, which they must covertly complete, such as “I CALLED THE ...”, “WOMEN WEAR ...”, “WE CLEANED ...”, “I LOVED ...” The resting phase task involves participants looking at the instructional word “RELAX” projected onto the screen. Compared to the “verb generation” task, the “semantic decision-making” task demonstrates more widely distributed networks, including the anterior and posterior language areas. In this type of design, for example, the subjects are instructed to compare

the samples in terms of their meaning and to select two out of three words that are “most alike.”

The most commonly used imaging sequence in fMRI studies is echo planar imaging (EPI), due to its fast acquisition time. However, the temporal resolution of such a sequence is in the order of several seconds, as it requires some time to produce detectable hemodynamic changes after stimulus onset and the spatial resolution is usually significantly lower than that of anatomical MRI. Another drawback is that EPI is sensitive to field inhomogeneities, leading to geometric distortion of the images in certain brain regions.

Since the BOLD signal is extremely sensitive to motion, one of the common problems during any fMRI experiment is subject motion, which can compromise the entire experiment. Motion can range from gross head movement to the minimal brain motion associated with cardiac or respiratory cycles, a.k.a. the cardioballistic effect. Before any subsequent analysis can be performed, the individual images are commonly realigned and coregistered to minimize the motion effect. Next, the signal time course in each voxel of the images and the time course of different tasks are correlated using statistical modeling. Various statistical tests (e.g., “Student’s *t*-test”) can then be applied on a voxel-by-voxel basis to examine the probability that a particular voxel with an increased signal is associated with a particular functional state of the brain. The result of this process is a map of the voxels that show statistically significant changes associated with the brain function under investigation. This step is critical since the fMRI signal changes are usually very small (in the order of 0.5%–5%), leading to a high probability of false negative results. To better appreciate the anatomical location of the origin of the signal, these statistical maps are usually registered and fused to a high-resolution anatomical image (Figure 2).

As described above, fMRI analysis requires considerable mathematical, statistical, and image processing that is provided by a variety of free or commercial software packages, such as statistical parametric mapping (SPM) (<http://www.fil.ion.ucl.ac.uk/>), FSL (<http://www.fmrib.ox.ac.uk/fsl/>), AFNI (<http://afni.nimh.nih.gov/afni>), and Brain Voyager (<http://www.brainvoyager.com/>).

### 3. Role of fMRI in Lateralization of Language Functions

*3.1. Language Lateralization Using the Wada Test.* The Wada test consists of unilateral injection of sodium amobarbital into the internal carotid artery (ICA), which temporarily anaesthetizes the hemisphere ipsilateral to the injection site. While one hemisphere is anaesthetized, language and memory functions of the hemisphere contralateral to the injection site can be tested. To test cerebral dominance for language, the patient is asked to perform a number of tasks involving expressive and receptive language. For example, tasks involving counting numbers, naming the months of the year, or naming objects are often used to examine frontal language areas, while repetition, responding to verbal commands, and reading are employed to explore language

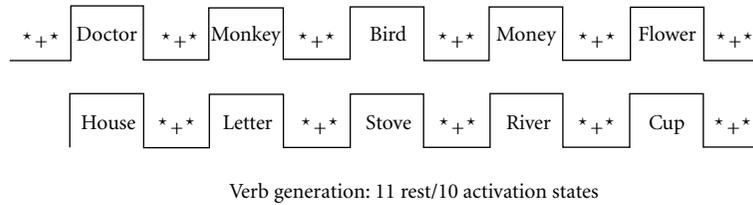


FIGURE 1: Schematic diagram of a verb generation task used at our centre.

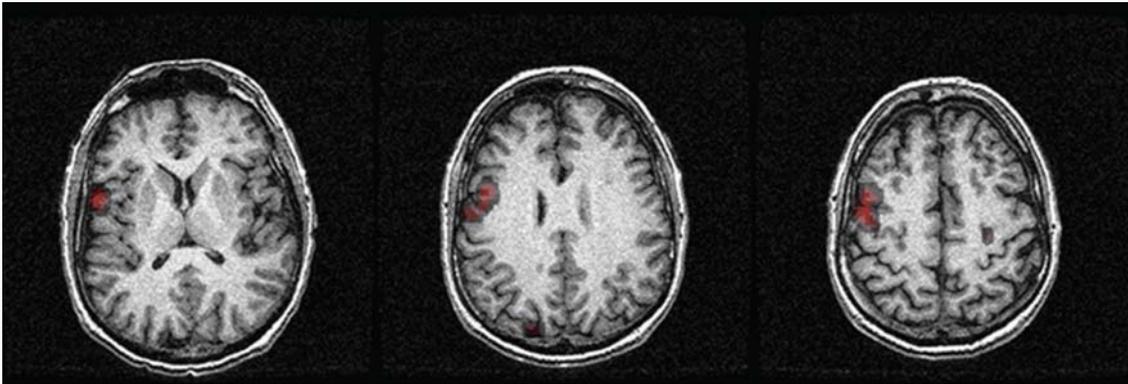


FIGURE 2: fMRI activation map overlaid on anatomical images.

functions served by the posterior brain regions. These protocols can be adapted or simplified for children or mentally challenged individuals, as long as they possess expressive language and are able to understand the instructions. The test is administered before the injection to provide a baseline measure and is repeated after the anaesthesia has taken effect. If the hemisphere dominant for speech is anaesthetized, the patient is temporarily rendered mute, which is not the case when the nondominant hemisphere is deactivated. When each hemisphere retains some language functions following unilateral injection, bilateral representation is confirmed.

Although the Wada test has long been considered as the gold standard for preoperative language and memory testing, the method has several drawbacks, since it is highly invasive and quite uncomfortable for most patients, and there is a small risk of morbidity. Figure 3 shows axial T<sub>2</sub> (a) and axial diffusion-weighted (b) images of a patient with medically intractable TLE of left temporal lobe origin who had experienced a right middle cerebral artery stroke secondary to a traumatic dissection of the right ICA during the Wada test. Another major drawback for the Wada test is that the procedure requires the patient to respond verbally, making it difficult to obtain reliable results from young children and mentally challenged patients. Finally, the Wada test only provides information about lateralization, but not localization of cognitive functions. These important limitations have led many epilepsy centers to seek alternative means to probe language and memory functions in patients prior to epilepsy surgery.

*3.2. Concordance of Language Lateralization Using fMRI with the Wada Test.* A number of studies have examined the utility

of fMRI as compared to the Wada test for language lateralization in patients with various neurological conditions, with reports being related specifically to epilepsy and TLE. One of the first published studies to compare fMRI with the Wada test in patients with TLE was described by Desmond et al. [9], where the authors employed a semantic task during which the patients pressed a button when they recognised a word as being abstract as distinct from being concrete. The hemispheric language lateralization index was calculated using the formula

$$LI = \frac{(V_L - V_R)}{(V_L + V_R)} \times 100, \quad (1)$$

where  $V_L$  and  $V_R$  are activation volumes for the left and right hemispheres, respectively. Desmond et al. found that the fMRI laterality indices were in agreement with the Wada test in all of their seven patients. Binder et al. [10] used a semantic decision task, in which the patients pressed a button if they heard a word that was both “animal native to the US” and “commonly used by humans.” The laterality indices were in concordance with the Wada test for all of their 22 patients with epilepsy. Following these two studies, Bahn et al. [11] studied four epilepsy patients with two relatively simple covert word generation tasks and found 100% concordance between fMRI and the Wada test in all their four patients with epilepsy. In a study conducted by Yetkin et al. [12], a group of 13 patients with medically intractable epilepsy were tested with a verbal fluency task. Good concordance between fMRI and the Wada test with the laterality correlation coefficient of 0.96 between the two techniques was reported except for one patient. Lehericy et al. [13] studied ten patients with TLE using a panel of language

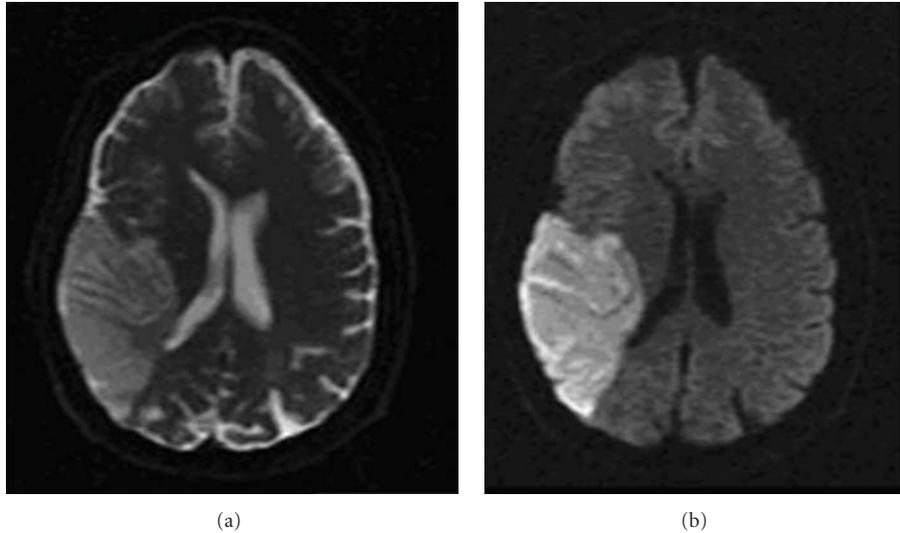


FIGURE 3: Axial  $T_2$  (a) and axial diffusion-weighted (b) images of a TLE patient who experienced a stroke in the right middle cerebral artery territory secondary to a traumatic dissection of the right internal carotid artery during the sodium amobarbital testing.

paradigms including verbal fluency, story-listening, and sentence repetition tasks. They found that fMRI laterality indices were highly concordant with the Wada test in the frontal lobe, although this was not the case in the temporal lobe. Moreover, they found that a verbal fluency task was more effective than other tasks in achieving better correlation with the Wada test.

While the previous studies have shown promising concordance between fMRI and the Wada test, the patients in these studies had mainly unilateral dominant epilepsy. Rutten et al. [14] enrolled seven patients with unilateral and six with bilateral TLE to investigate the predictive power of fMRI for language lateralization. They concluded that using a combination of language tasks that included verb generation, verb fluency, picture naming, and sentence comprehension, they were able to better predict the lateralization of these patients. Another study by Sabbah et al. [15] also tried to investigate the effectiveness of fMRI in lateralization of atypical language in patients with epilepsy. By using two different semantic fluency paradigms, they reported that 19 out of 20 patients had concordant lateralization result from both fMRI and the Wada test. Comparing fMRI-based and Wada-based laterality quotients for speech in TLE patients, Benke et al. [16] found agreement in 89.3% of right TLE patients and in 72.5% of left TLE patients. However, while fMRI correctly detected atypical right hemisphere speech in all cases, it missed left hemispheric dominance of speech in 17.2% of patients with TLE. Furthermore, the method was less sensitive to bilateral speech representation.

While higher magnetic field strength is desirable for fMRI studies, this may not be necessary for language lateralization. For instance, Deblaere et al. [17] used a simple word generation paradigm in an 1.0 T MR scanner and showed that fMRI reliably lateralized the language function in a clinical setting. Although most of the previous studies focused on expressive speech, Gaillard et al. [18] conducted an fMRI

study in which a combination of expressive and receptive language paradigms was employed. They reported that there was a complete agreement between the Wada and fMRI in 21 of 25 patients and that the use of multiple tasks increased the accuracy in determining hemispheric dominance for language function.

To date, the largest study on comparison between fMRI and the Wada test was conducted by Woermann et al. [19], who enrolled 100 patients with epilepsy, of whom 69 had TLE. They employed a single covert word generation language paradigm and derived the laterality based on visual inspection of fMRI statistical maps. Concordance of 91% was observed, and the discordance may have been the result of visually assessing often bilateral, although mainly asymmetric fMRI activations.

Generally, fMRI and the Wada test agree very well with each other. Because of the relative advantages of fMRI, more and more epilepsy centers are replacing the Wada test with fMRI for presurgical language mapping. However, we also note some divergent results from the previous studies, which can be attributed to several factors. First of all, the fMRI paradigms used to evaluate language lateralization vary considerably between studies. Most of the paradigms are capable of activating the left frontal lobe in healthy control subjects and patients with typical representations for language functions. In patients with atypical representations for language, the use of multiple language tasks increases the likelihood of accurate lateralization of the cerebral hemispheres for language functions. Other limitations of fMRI for language mapping include the variability in statistical thresholds employed to calculate the activated volumes, difficulties in determining the extent to which the right hemisphere participates in language processing in patients with bilateral representations for language networks, and because not all areas involved in a task may be activated by a particular fMRI paradigm. Another disadvantage is that the patients must lie

motionless in the scanner during image acquisition, making this technique less suitable for children and other special populations.

One of the limitations of the previous fMRI studies in language mapping of patients with epilepsy has been their small sample sizes, resulting in low statistical power. While the largest study enrolled over 100 patients with epilepsy [19], even for a study with this size, it is difficult to distribute the subjects uniformly over the different subgroups of epilepsy. For example, some studies may have more patients with typical dominance for language than patients with atypical dominance for language. Systematic review with meta-analysis is one statistical technique that may overcome the small sample size problem faced by many clinical studies. Meta-analysis combines the results of several studies that address a set of related research hypotheses, with the general aim being to more powerfully estimate the true “effect size” as opposed to a smaller “effect size” derived in a single study under a given single set of assumptions and conditions. One example is a meta-analysis of English speaking healthy adult subjects performed by Vigneau et al. [20], who selected 126 studies among 260 published articles from 1992 to 2004. They separated the contrasts into three groups phonology, semantics, and sentence processing, and were able to find the relative clusters associated with each group. A similar study was performed by Medina et al. [21] who combined several related studies to investigate the role of fMRI to replace the Wada and ESM tests for epilepsy surgery using the Bayesian analysis approach. They concluded that the use of fMRI increased the final posttest probabilities of hemispheric dominance for language in patients with epilepsy.

#### 4. Role of fMRI in Localization of Language Function

*4.1. Intraoperative Localization of Language Functions by Electroconvulsive Stimulation (ESM) Technique.* ESM is a common routine clinical tool to localized language functions. This procedure involves direct application of electrical currents to the cerebral cortex of the awake patient, which either produces a response (e.g., movement) or disrupts function (e.g., speech arrest). ESM is believed to directly identify cortex essential for a specific task and can be performed extraoperatively in patients with implanted electrodes or intraoperatively with the cerebral cortex exposed at surgery. ESM is the “gold standard” tool for localization of language function during TLY. Figure 4 demonstrates the ESM stimulation sites from 13 TLE patients who underwent surgery, normalized to MNI space [22], and fused with the MNI “Colin 27” single subject brain. The red and green dots represent the critical language and somatosensory sites, respectively. The red dots concentrated around the inferior frontal gyrus in the frontal lobe represent Broca’s areas, while the cluster of red dots situated near the superior temporal gyrus represent Wernike’s area.

Although it is widely accepted as the most reliable method of localizing language functions in the brain, ESM has several major drawbacks, including invasiveness, low

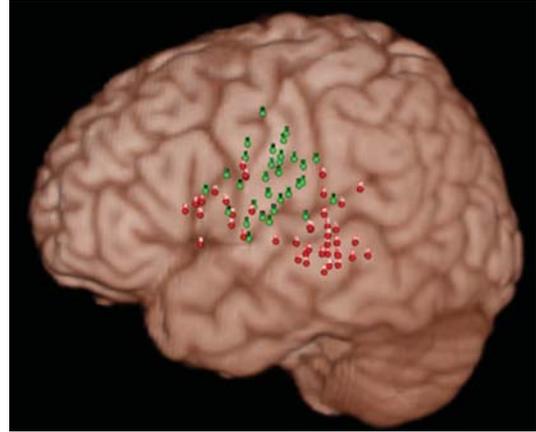


FIGURE 4: Electrocortical stimulation (ESM) sites from 13 patients with TLE of the left temporal lobe origin that are spatially normalized to MNI space and fused with MNI single subject brain.

spatial resolution due to limited sampling of the exposed cortex intraoperatively, the potential to induce epileptic after-discharges, as well as prolonging the operating time. Moreover, this technique is not always feasible in clinical practice, since it requires full collaboration of the patient as well as the clinical expertise of the surgical team [23]. In contrast to ESM, fMRI offers several appealing features for language localization, including noninvasiveness, pre-operative data that can be employed to guide surgery and lead to reduced operating time, and superior spatial and temporal resolution for whole brain analysis. Accordingly, some studies have investigated the utility of fMRI to replace ESM for preoperative function localization in TLE surgical planning [24–29].

*4.2. Comparison of fMRI to ESM for Localization of Language Functions.* One of the first studies that compared fMRI and ESM included 28 patients, of whom 22 had epilepsy [24]. Two language tasks, number counting and word generation, which consistently activated mostly the inferior frontal lobe, were employed in this study, with results indicating a correspondence within 2 cm between fMRI and ESM using the word generation task. Another early investigation to compare fMRI and ESM was performed by FitzGerald et al. [25], who employed an array of five fMRI language tasks using both auditory and visual input to probe the language areas of 13 patients (one with epilepsy and eight with brain tumors). The sensitivity and specificity of fMRI for identifying language regions were calculated based on the ESM results. FitzGerald et al. concluded that the combination of language tasks was more effective than any single task and that fMRI was sufficiently sensitive to localize the language areas in these patients. Schlosser et al. [26] studied 33 patients with TLE, brain tumour, and AVM, using a single auditory comprehension task during the course of the study. They showed in 23 patients a consistent fMRI activation that was similar to that observed in healthy control subjects. Because in some patients the lesions were remote

from the language areas, only 16 received intraoperative ESM for language localization. While four of their five TLE patients had a successful matching between fMRI and ESM, their correlation studies were rather qualitative and not discussed in detail.

Although some fMRI language paradigms have been developed and shown to activate language networks consistently in the normal population, it is expected that neurological disorders could affect the organization of the network and make these paradigms less effective in this population. Carpentier et al. [27] conducted a study in which a control group was compared with the diseased cohort to determine how the neurologically impaired group performed relative to the normals. While they found that their language tasks (visual and auditory comprehension) were able to successfully activate both Broca's and Wernicke's areas in the healthy control group, the same array of language tasks resulted in lower activation and greater bilateral representations in the diseased group. Nevertheless, the concordance between fMRI and ESM was 100% (15 positive language sites identified by ESM matched with fMRI activation within a 1 cm range).

While a single language task activated some aspects of language network to achieve a good correlation with ESM in some of the previous studies, it is unlikely that this limited approach could fully explore the complete language networks. Therefore, several studies have been conducted to investigate the utility of multiple tasks to increase the likelihood of concordance between ESM and fMRI. Pouratian et al. [28] employed a battery of linguistic tasks, including visual object naming, word generation, auditory responsive naming, visual responsive naming, and sentence comprehension to identify language areas of 10 patients with vascular malformation. They found fMRI to be very sensitive, but rather unspecific, in identifying which cortical areas are essential for language. Rutten et al. [23] employed a battery of language tasks (i.e., verb generation, picture naming, verb fluency, and sentence comprehension) in their study and found that a single task could not elicit all the critical language areas that are elicited by ESM. They demonstrated that despite high sensitivity, on average only 51% of fMRI sites were confirmed by ESM. In contrast, in 10 out of 11 patients, the absence of fMRI activity was 100% concordant with the absence of critical language areas in ESM. Roux et al. [29] performed a study in which naming and verb generation tasks were administered to a group of 14 brain tumour patients. They also found that by combining the two language tasks they were able to increase sensitivity to 59% and specificity to 97%. Eight of their patients underwent postoperative fMRI, but only three of them showed an agreement between preoperative fMRI, postoperative fMRI, and ESM.

In general, good but not complete agreement between fMRI and ESM can be achieved when using a combination of carefully designed language paradigms. The inconsistency between the two techniques can be due to several factors. First of all, while the choice of language paradigm is of outmost importance to effectively activate the language network, there is still no consensus as to what combination

of language paradigms is the most suitable for language mapping in an fMRI study, and this topic remains an active area of research. Furthermore, the classical human language system model consists of two primary regions: the expressive Broca's area in the posterior inferior frontal lobe, and the receptive Wernicke's area in the posterior superior temporal lobe. It has been shown that certain language tasks can activate Broca's area more effectively than Wernicke's region. Therefore, it is expected that the sensitivity of fMRI to map language areas, and the concordance between fMRI and ESM may be task and lobe dependent. However, most studies performed so far have not examined the concordance at the lobe level.

The choice of the significance threshold used in statistical analysis for fMRI is important. The significance threshold is used to define the extent of language activation from the fMRI studies. A very strict threshold would result in very poor correlation (high Type II error) while a relaxed threshold would produce false positive correlations (high Type I error). The selection of threshold has usually been subjective and based on the previous experiences in these studies, and this variation may be partially responsible for the different results obtained. In addition, using a single fixed threshold across multiple subjects does not take into account the variability of activated language areas among individuals [25, 30]. An alternative approach to this problem is to apply an adaptive threshold that, based on the physiological observation of the extent of the language area, confines the area to be around 1 to 2 cm<sup>2</sup> on the cortical surface. While this approach makes the comparison more consistent for all patients, in practice this can be very laborious.

Finally, different registration approaches are used to align ESM and fMRI maps for comparison purpose. In several studies [23, 27], 2D ESM maps captured intraoperatively using a camera were manually correlated to the 2D fMRI maps and visually inspected, an approach that is considered to be subjective and qualitative. In contrast, other studies employed a relatively simple 2D-2D automatic rigid registration [24, 25, 28]. However, since 2D-2D registration does not account for the perspective effect in the 2D camera images, errors of several mm can remain in the registration. A third approach is to use a neuronavigation system [29]. However, such devices are not always available in many procedures, while simply imaging exposed cortical surface with a digital camera is a very common practice and requires less time to perform. An additional complicating effect is that the brain can deform up to 10 mm after opening the dura matter [31]. Without correction for this deformation, the accuracy of the reconstruction of the 3D coordinates of the stimulation sites is compromised by using the current navigation systems. This in turn degrades the fidelity of registration between ESM and fMRI. Figure 5 demonstrates our approach, which employs automatic 2D to 3D projective registration to fuse an interoperative cortical photographic image onto an MR brain image that incorporates a preoperative fMRI activation map [32]. In, Figure 5(a) the label "F" is a speech arrest site elicited by ESM that corresponds well to the peak of fMRI activation in the frontal lobe as shown in Figure 5(b).

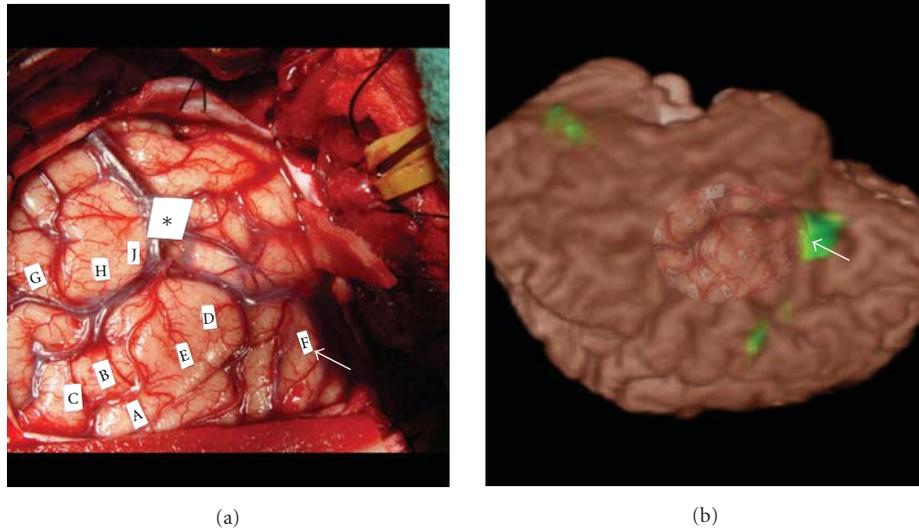


FIGURE 5: Overlay of intraoperative cortical images with fMRI for comparison. (a) Shows the intraoperative cortical photograph acquired just after ESM on the left temporal lobe. (b) Shows the overlay of this photograph onto volume-rendered anatomical MRI and fMRI. Arrows indicate where the label “F” is in the two images.

## 5. Role of fMRI to Study Brain Plasticity for Language after TLY

Another area in which fMRI can play a role in the treatment of TLE is to study the language plasticity and reorganization before and after surgery. Previous fMRI studies have shown that ATL had a differential impact on the language functions of the left and right TLE patients [33]. Wong et al. [34] studied a group of 24 TLE patients who underwent ATL procedures to examine the impact of ATL on the cortical organization of language processing, using a verb generation task on both left and right TLE patients to compare their preoperative and postoperative fMRI response. After the surgery, the right TLE patients activated the same cortical network as before the surgery, while the left TLE patients elicited less activation. A subtraction analysis between the preoperative and postoperative BOLD response showed that the right inferior frontal gyri (IFG) and the left middle frontal gyri (MFG) were less activated after the surgery in the left TLE patients. The attenuated correlation between the language scores and the postoperative BOLD response within the IFG and MFG in both patient groups indicated cortical reorganization after the ATL. These findings suggest that the cortical organization of language processing is affected differently by the left and right TLE and is subsequently reorganized after ATL. Another finding of this study is that the right TLE patients shifted the correlation between their language scores and BOLD signals from the typical language areas (i.e., IFG and MFG) to the anterior cingulate cortex (ACC) after ATL.

## 6. Conclusions

fMRI is a noninvasive technique that has replaced the invasive tests for presurgical assessment of the language network

in some epilepsy centers. Generally, good concordance exists between fMRI and Wada or fMRI and ESM. However, there are still some requirements that fMRI must meet to enable its wider utility in the clinical practice for language mapping. First, a highly effective language paradigm or a battery of paradigms needs to be developed that can be administered to the patients in a clinically feasible time. Second, a robust statistical analysis methodology that removes individual biases (in selecting threshold levels, e.g.) must be developed. Finally, because the population being studied is, in general, atypical with respect to language localization, a high predictive power is required for critical language areas in the brain. These issues are currently being addressed one by one. With the availability of higher field strength MRIs, faster imaging sequences, better study paradigms, and improved postprocessing tools, the clinical applications of fMRI in epilepsy will only grow.

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## Review Article

# Neocortical Temporal Lobe Epilepsy

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Received 20 May 2011; Revised 4 January 2012; Accepted 22 May 2012

Academic Editor: Warren T. Blume

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Complex partial seizures (CPSs) can present with various semiologies, while mesial temporal lobe epilepsy (mTLE) is a well-recognized cause of CPS, neocortical temporal lobe epilepsy (nTLE) albeit being less common is increasingly recognized as separate disease entity. Differentiating the two remains a challenge for epileptologists as many symptoms overlap due to reciprocal connections between the neocortical and the mesial temporal regions. Various studies have attempted to correctly localize the seizure focus in nTLE as patients with this disorder may benefit from surgery. While earlier work predicted poor outcomes in this population, recent work challenges those ideas yielding good outcomes in part due to better localization using improved anatomical and functional techniques. This paper provides a comprehensive review of the diagnostic workup, particularly the application of recent advances in electroencephalography and functional brain imaging, in neocortical temporal lobe epilepsy.

## 1. Introduction

Neocortical temporal lobe epilepsy (nTLE) is a rather newly recognized entity that is different than the well-known entity of mesial temporal lobe epilepsy (mTLE) although not as well characterized [1]. The documented cases of patients with nonlesional neocortical temporal lobe seizure origin are not as rare as previously reported. In one study, out of 31 patients seizure-free more than 18 months after temporal lobectomy, only 3 patients (9.6%) were found to have nTLE [2]. More recently, Schramm et al. [1] demonstrated 62/581 of the temporal lobe epilepsy (TLE) cases as being neocortical. With better structural-functional imaging modalities as well as invasive monitoring, more of these cases are being described. Unfortunately, the nomenclature is inconsistent in the literature, often being dubbed as nonlesional, extrahippocampal, or lateral neocortical. For the purpose of this review, we will use the term nTLE. Recognition of nTLE is important because these patients may either be considered non surgical candidates or

undergo extensive surgeries due to the poor localization of their seizure focus.

Lesional nTLE cases are often not reported in the literature as compared to the nonlesional cases because they may be less likely to be admitted to an epilepsy monitoring unit (EMU) for video-electroencephalography (EEG) telemetry unless the lesion is closely associated with eloquent cortex, thereby limiting surgical resection or may be unamenable to surgery. Thus, the reported prevalence of nTLE is low. Therefore, it is difficult to know the prognosis of nTLE because lesional nTLE cases typically have better outcomes than nonlesional nTLE cases [2] although classically they were dubbed as having poorer outcomes compared to mTLE [3–9].

## 2. Historical Background

Although nonconvulsive seizures and seizures manifesting with complex behaviours have been recognized since antiquity [10], their relationship to temporal lobe origin was first

described in the late 1800s by Jackson [11]. The psychic and motor characteristics of these seizures prompted the term of psychomotor seizures [12]. With the first application of EEG to human by Berger in 1929 [13] and the increased interest in surgical treatment of epilepsy, the anatomical significance of these seizures led them to be labeled temporal lobe seizures [14]. The prominent role of mesial temporal structures in the genesis of temporal lobe seizures was first suspected by Falconer et al. [15] and was confirmed and widely recognized thereafter [15–17]. The majority of temporal lobe seizures originate in the mesial structures, primarily in the hippocampus, with the rest beginning in temporal neocortical regions. Mesial temporal lobe seizures are far more common than lateral neocortical seizures [18]. Wieser [19] was the first to propose 5 subtypes of temporal lobe seizures depending on electroclinical features. They included temporal-basal limbic, temporal polar, posterior temporal neocortical, opercular, and frontobasal cingulate. The classification was revised to simplify the nomenclature in 1989, and only 2 of the subtypes remained. Thus temporal lobe epilepsy is now categorized into mesial and lateral [20]. Whether or not these 2 types can reliably be separated based on noninvasive evaluation was disputed [1, 21, 22]. Differentiation between mTLE and nTLE remains a challenge even for epileptologists, as many symptoms overlap. This may be due to extensive reciprocal connections between the mesial and lateral temporal structures, allowing spread of ictal discharge in either direction [23–25].

The clinical profile of patients with nTLE is different from mTLE. The average age of onset in nTLE is approximately 5–10 years more than in mTLE [6, 26]. There is no known gender, cultural, or racial risk factors for nTLE. Patients with nTLE usually do not have a history of the typical risk factors associated with mTLE such as febrile seizures, head injury, perinatal insults, or previous central nervous system (CNS) infections as compared to mTLE [3, 7, 26, 27].

Many of the clinical characteristics of the seizures described in autosomal dominant lateral temporal lobe epilepsy (ADLTE) are similar to those seen in patients with nTLE. ADLTE is a well-defined, albeit rare, condition characterized by onset in adolescence or early adulthood of lateral temporal seizures with prominent auditory auras sometimes triggered by external noises, normal conventional magnetic resonance imaging (MRI), good response to antiepileptic treatment, and overall benign outcome. The same phenotype is shared by sporadic and familial cases with complex inheritance. Mutations in the LGI1 gene in the 10-cM region on chromosome 10 q24 are found in about 50% of ADLTE families and 2% of sporadic cases. LGI1 shows no homology with known ion channel genes. Recent findings suggest that LGI1 may exert multiple functions, but it is not known which of them is actually related to lateral temporal epilepsy [28–30].

### 3. Clinical Semiology

Ictal manifestations common in mTLE (ipsilateral limb automatisms, contralateral dystonic posturing, and oroalimentary automatisms) are significantly less frequent in nTLE [1, 5, 31]. These differences are summarized in Table 1. Dupont et al. [32] compared the ictal semiology of 45 mTLE patients with 13 nTLE patients and found that contralateral dystonic posturing with ipsilateral automatisms occurred in a third of the mTLE group but was never seen in those with nTLE. Auditory and vertiginous auras have been associated with the temporal neocortex, and visceral sensations and fear with the mesial temporal lobe [23, 33]. One study analyzing ictal semiology between nTLE and mTLE reported that seizures in the nTLE group were of shorter duration (46 seconds) as compared to the mesial group (67.5 seconds) [8]. Patients with mTLE were more likely to display manual or oroalimentary automatisms, dystonic posturing, hyperventilation, or postictal cough [7, 34]. nTLE patients had experienced only experiential auras, whereas mTLE patients had epigastric or olfactory/gustatory sensations or fear as their auras. Comparison of clinical semiology of 28 mTLE patients and 12 nTLE patients [35] showed that epigastric sensations, fear, olfactory auras, and dystonic posturing were typical of mTLE, whereas auditory auras, cephalic/indescribable sensations, vocalizations, ictal speech, whole-body movements, rapid onset of version, and secondary generalization were significantly more common in patients with nTLE.

A recent study [26] where 55 patients with TLE (same as above) were classified into 3 distinct groups (mTLE, nTLE, and mixed and characterized them based on semiology and spatiotemporal pattern of discharges. At seizure onset, patients with nTLE were less likely to describe rising epigastric sensation, fear) or dreamy state but more likely to describe any type of hallucination or illusion. As the seizures progressed, mesial seizures produced oroalimentary, verbal and upper limb automatisms. In general, nTLE were shorter but more frequently generalized. In another study of 21 patients with nTLE, 71% of them had auras, with the experiential auras being the most common [4]. The most common initial behavioural change was motionless stare in 48% of patients. Only 2/21 patients had hippocampal atrophy (HA). A lateralized memory deficit was observed in 62% [4].

### 4. Ictal Semiology in nTLE

Several studies have attempted to localize the semiology based on the anterior-posterior axis of the neocortical temporal lobe. One study in particular separated the groups based on interictal temporal lobe discharges (anterior, posterior, or diffuse) and correlated those to subjective ictal phenomena [36]. Olfactory and gustatory phenomena and déjà vu were present exclusively in patients with anterior foci, whereas visual auras were more common in the posterior temporal group. Complex automatisms were more common in the anterior group, and neurological abnormalities were more common in the posterior group.

Studying patients with posterior TLE ( $n = 14$ ), the authors found that behavioural arrest was the first manifestation and was followed by motor signs as the seizure activity spread to the frontoparietal convexity. They also observed that behavioural automatisms (oro-alimentary and gestural), although present in half the patients, were never the first or most prominent ictal manifestations [37]. Another study attempted to analyze semiologic differences between mTLE and different anatomic subgroups of nTLE included 1-year postsurgical followup. Total of 107 seizures in 13 patients with anterior TLE, 8 patients with posterior TLE, and 21 patients with mTLE were reviewed. Frequent behavioural arrest, absence of initial oroalimentary automatisms, and early generalization were characteristic findings of posterior TLE, although they were insufficient to differentiate from anterior TLE or mTLE.

## 5. Diagnostic Workup

As described in other articles of this special issue of the journal, patients with mTLE have typical characteristic seizure semiology and may demonstrate MTS on MRI. Their prognosis after surgical resection is said to be good if the lesion is definable. However, occasionally HS is not evident as in the nonlesional cases (i.e., symptomatic epilepsy) or the semiology and EEG findings do not fully localize to the mesial temporal lobes. Some of these patients undergo more invasive monitoring to consider the possibility of nTLE. The following includes a summary of literature depicting how EEG, structural and functional imaging can help to differentiate nTLE. Later, other advanced techniques are discussed for their putative roles.

### 5.1. Electroencephalography

**5.1.1. Interictal Scalp EEG.** A prospective study [38] on 132 consecutive patients (mTLE = 86 and nTLE = 36) with epilepsy showed that a history of febrile seizures, abdominal auras, contralateral dystonic posturing, and predominance of mesial temporal spikes point to mTLE (positive predictive value 81% and negative predictive value 70%). They concluded that analysing the clinical and EEG features, particularly the distribution of interictal epileptiform discharges (IEDs), helps to differentiate between mTLE and nTLE.

There is little evidence to support the use of interictal scalp EEG in differentiating nTLE from mTLE. In one study [2], the utility of the interictal EEG was examined in patients with neocortical symptomatic epilepsies. It was useful in 9/17 of patients (52%) with nTLE. In another study, 22 patients admitted to an EMU were enrolled, and the findings were correlated the results from PET scans [39]. They found that the interictal rhythmic slow activity was highly correlated to nTLE. In contrast, no significant difference was found among 14 patients with nTLE and those with mTLE in another study when using standard intracranial EEG as comparison [40].

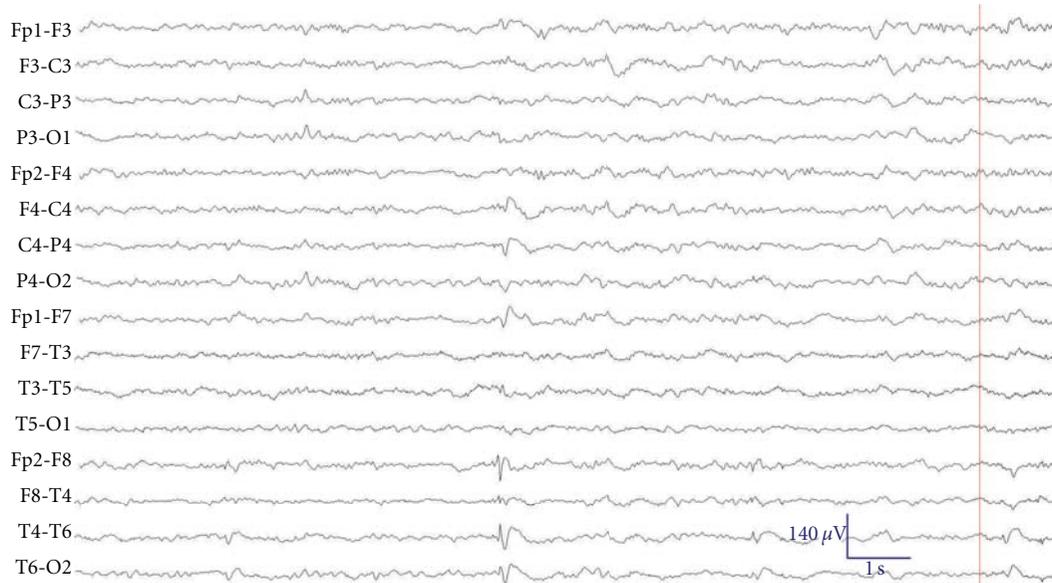
**5.1.2. Ictal Scalp EEG.** Ictal scalp EEG has the potential to localize seizures better than interictal especially in a long-term video-EEG monitoring unit. Recording a unilateral IED cannot always distinguish between mesial or lateral temporal or extratemporal foci [41]. In one case series, the sensitivity of localizing IEDs to the temporal neocortex increased from 52% (interictal) to 76% (ictal) [2]. The most commonly observed scalp ictal pattern is ipsilateral temporal rhythmic theta activity, seen in both nTLE and mTLE [8] although slower in frequency in nTLE. In nTLE, it may be preceded by an irregular 2 to 5 Hz polymorphic slowing that may or may not be lateralized [8, 42]. The characteristic ictal EEG in patients with mTLE is rhythmic theta activity of 5 to 7 Hz [43, 44]. In a clinicopathologic study comparing 46 patients with MTS or neocortical lesions by EEG, those with mTLE had significantly more fast rhythmic activity (>4 Hz). Patients with nTLE tended to develop bilateral ictal EEG changes, occurring significantly more often and faster onset of bilaterality [27]. Similar results were obtained studying ictal scalp EEG in 93 patients with seizure origin verified by intracranial EEG, showing an association between irregular polymorphic, slow (2 to 5 Hz) seizure onsets and nTLE, and regular (5 to 9 Hz) ictal onsets in mTLE patients [44]. The nTLE pattern was either preceded by periodic sharp waves or followed by theta rhythms. Unfortunately, a subsequent study by the same authors using simultaneous scalp and intracranial EEG study revealed that these associated patterns were not established on the scalp at seizure onset but resulted from differences in the development, propagation, and synchrony of cortical discharges as seizures progressed in mTLE and nTLE patients [45]. While some studies have demonstrated good localization, others have not been able to differentiate mTLE from nTLE based on ictal EEG [7].

A relatively novel and underrecognized EEG analysis involves transitional sharp waves. In one study involving 52 ictal discharges from 13 patients, the authors were able to determine with certainty that the pattern localized to the nTLE, versus mTLE. Interestingly, none of the 61 discharges in 15 patients with mTLE had the transitional sharp waves [46]. Further studies are warranted to determine if this is an easily demonstrable and reproducible scalp EEG finding

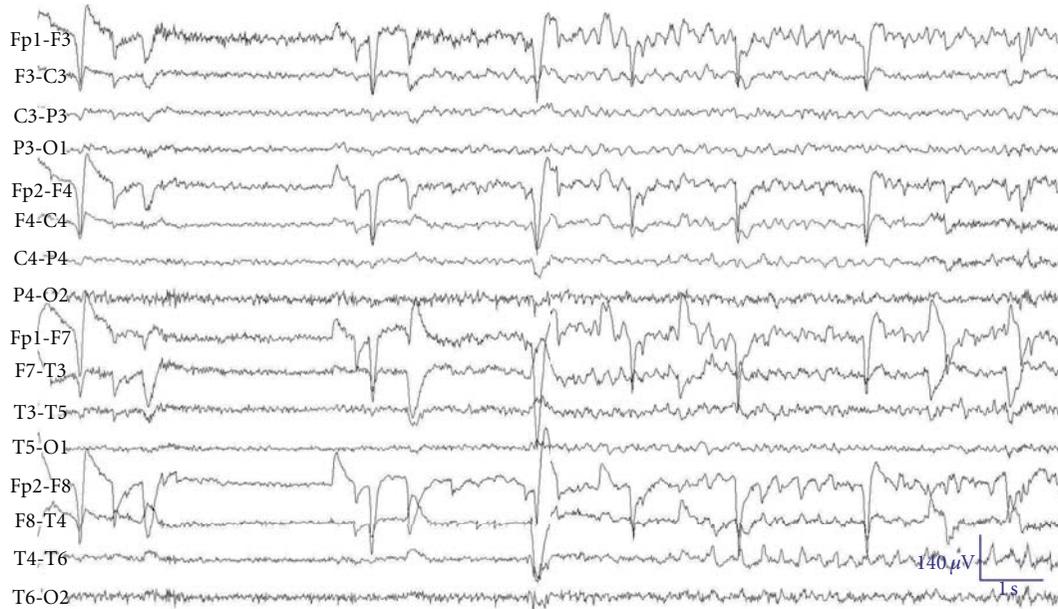
Although at this time scalp EEG is not highly sensitive or specific to differentiate mTLE from nTLE practically, it has been used to assess outcomes in patients with known nTLE. In a study of 29 patients with nTLE a localized or even lateralized EEG pattern was associated with good outcomes [47]. Similarly, in larger study comparing 80 patients with nTLE to other neocortical epilepsies localized EEG rhythms highly predicted seizure freedom after resection [48].

Therefore, ictal rhythm cannot be used in isolation to definite localization (Figures 1(a)–1(f)). However, even among patients whose scalp data are complex to require invasive recording, lateralization of temporal scalp IEDs, and ictal activity should be included when assessing the side of temporal epileptogenesis [49].

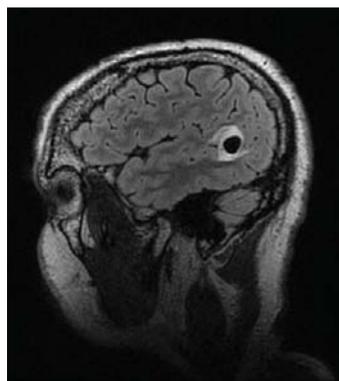
**5.1.3. Intracranial EEG.** Neocortical foci are seen in up to 65% of patients with TLE in some series [5, 50]. Differentiating nTLE from mTLE often requires intracranial EEG



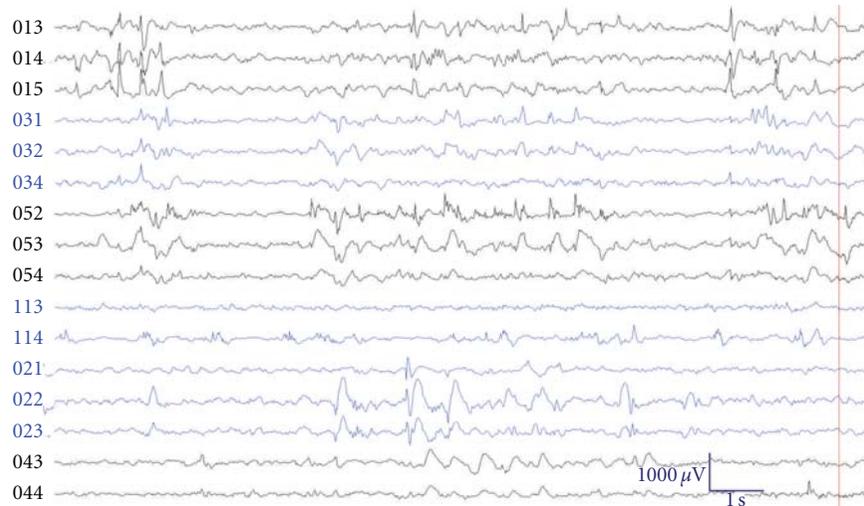
(a) Interictal scalp showing right anterior temporal spikes during sleep



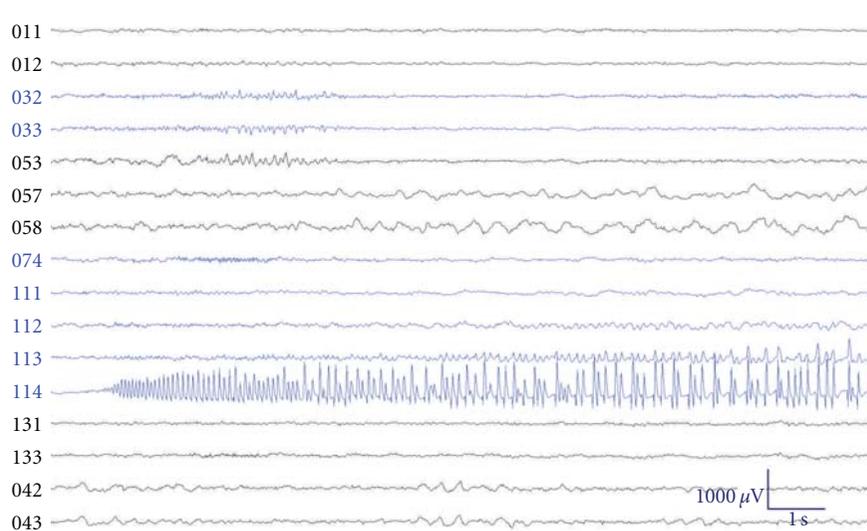
(b) Ictal scalp EEG in the same patient showing possible bitemporal onset of seizure



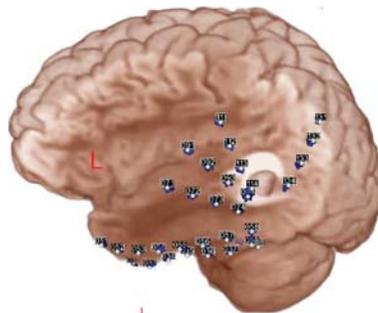
(c) Sagittal T2 FLAIR MRI brain showing left posterior temporal neoplasm (pathologically proven ganglioglioma)



(d) Interictal subdural EEG showing spikes arising independently from left mesial and neocortical temporal lobe (electrodes 10s, 30s, and 50s) as well as right anterior mesial and neocortical regions (electrodes 20s and 40s)



(e) Ictal subdural EEG showing seizure onset at electrode 114 (left posterior temporal region, coinciding with the lesion)



(f) Subdural electrode insertion with MRI coregistration. Cortical stimulation produced speech arrest over left anterior inferolateral temporal region (electrode 52), anterior to the lesion (electrode 114). fMRI

FIGURE 1: EEG of a 37-year-old right-handed male with complex partial seizures since 16 years of age characterized by speech arrest, transient impaired consciousness, automatisms with right hand, and secondary generalization, with no contributory antecedent history.

TABLE 1: Comparison of ictal semiology between mTLE and nTLE based on data from references (see text). If <5% of group were reported to have symptom then it would be designated yes/no. Otherwise it would be described based on likelihood (more or less likely).

Sign/symptom	mTLE	nTLE
Seizure duration	>1 minute	<1 minute
Ambiguous onset/offset	No	Yes
Visceral/epigastric sensation	More likely	Less likely
Nonspecific auras	Less likely	More likely
Auditory hallucination	Less likely	More likely
Oral automatism	More likely	Less likely
Manual automatism	More likely	Less likely
Leg movements	Yes	No
Dystonic posturing	Yes	No
Clonic movement	Less likely	More likely
Body shifting	More likely	Less likely
Hyperventilation	Yes	No
“Dreamy state”	Yes	No
Fear	Yes	No
Searching	More likely	Less likely
Postictal cough/sigh	More likely	Yes

recordings because ictal manifestations of nTLE and mTLE may be similar [40], and imaging studies may be inconclusive or misleading. IEDs recorded on EEG are known to be highly correlated with the presence of epilepsy [49, 51]. Although seizures and IEDs are not always colocalized, there may be valuable localizing information in the spatial distribution of IEDs. Intracranial EEG offers an opportunity to understand IEDs recorded closer to the source of their generation. Challenges to the study of IEDs with intracranial EEG are both the limited spatial sampling provided by intracranial electrodes and the considerable number of IEDs that can be observed with intracranial electrodes. Studying the spatial distribution of intracranially recorded IEDs in mTLE ( $n = 12$ ) and nTLE ( $n = 9$ ), the authors found a higher IED rate in the mesial temporal region in the mTLE group and higher IED rates in the frontal and parietal regions in the nTLE group [52]. This may indicate that frequent IEDs in extratemporal cortex may be a sign of nTLE, suggesting value for analysis of IEDs during the presurgical evaluation of patients. While some researchers conclude that the process of IED and seizure generation are independent [53] or have a common generator [54], this study shows that the spatial distribution of IED and seizure onset location are not independent, but rather related, and that the spatial distribution of IEDs can differentiate mTLE from nTLE. Some studies reported a less favourable surgical outcome for nTLE patients [9] because the lateral temporal neocortex mediates language and other cognitive functions (visual and auditory association cortex), thereby limiting the extent of resection for some patients [22, 55].

While intracranial electrodes are sensitive to localize IEDs due to little interference from underlying tissue, they have also been used to detect rhythmic slow activity. In

one study, interictal rhythmic delta slow wave activity was correlated to IEDs and ictal discharges in 18 presurgical TLE patients. The rhythmic delta activity was highly correlated within nTLE patients [56].

Intracranial EEG studies have shown an association between favourable outcome and ictal changes such as onset EEG frequency of more than 13 Hz [57], long propagation time [57–59], and focal onset [3, 60]. A systematic analysis of intracranial ictal EEG done in 31 consecutive patients with medically intractable nTLE to predict surgical outcome showed good seizure outcome in patients with focal or sublobar onset, anterior temporal onset, and slow propagation time. In this study, 66.7% were seizure-free, and 96.7% achieved Engel class I or II outcomes showing that selected features of intracranially recorded seizures predict good seizure outcome [61].

## 5.2. Neuroimaging

**5.2.1. Structural MRI.** A high-resolution anatomical MRI is one of the most critical diagnostic tests in the workup of a patient with CPSs of possible temporal lobe origin. Using dedicated sequences (e.g., coronal T2, coronal FLAIR, or short T1 inversion recovery (STIR)) can significantly increase the ability to detect abnormalities within the mesial temporal structures with high sensitivity (93%) and specificity (83%) [62]. In patients where nTLE is more likely, a high-resolution anatomical MRI is very important to exclude HS and demonstrate other pathologies because these can alter surgical approach and outcome. The potential etiologies that could cause nTLE include, but are not limited to tumours (astrocytomas, gangliogliomas, meningioma, and dysembryonic neuroepithelial tumour (DNET)), vascular malformations (AVM and cavernous hemangioma, and meningioangiomas), malformation of cortical development (MCD), stroke, trauma, or infections [63]. Occasionally, patients can have MTS or HA in addition to a “primary” pathology in the neocortex. These cases are referred to as dual pathology which occur with great variability (9–30%). In a recent pathological study of 243 patients with TLE, dual pathology was found in 34% of the cases, and surprisingly only 14% had isolated HS [64]. This complicates the diagnostic workup because it suggests that the presumed TLE patients require dedicated high-resolution anatomical MRI at 3T or higher magnetic field strength [65], that should be read by a neuroradiologist well familiar with epileptology. Voxel-based analysis of MRI scans can identify subtle structural changes that are not evident on visual inspection [66]. For example, in one study using this analysis method 14% of the nonlesional cases revealed to have abnormalities [67].

## 5.2.2. Functional Imaging

**(a) Positron Emission Tomography (PET).** PET utilizes tracers labeled with positron-emitting isotopes (e.g.,  $^{18}\text{F}$ fluorodeoxyglucose (FDG)) to visualize and quantify cerebral metabolism and specific neurochemical fluxes in the brain. FDG-PET scans are usually obtained in the

interictal state, and areas of hypometabolism are considered to be regions of interest. FDG PET is useful in patients with nonlesional mTLE. These “MRI negative PET positive cases” are quite different than nTLE even though they may have a cortical lesion [68]. One group did a quantitative parametric analysis on 133 scans of 35 patients with nTLE with confirmed pathology [69]. They were able to localize the seizure focus and with some certainty determine whether it was mesial or neocortical. Similarly, a different quantitative study was able to find differences in metabolism in mesial versus neocortical temporal cortex. Mesial temporal metabolism was nearly normal in patients with nTLE, but severely depressed in nonlesional mTLE. Neocortical temporal metabolism was mildly decreased in patients with mTLE caused by tumors and severely reduced in both nTLE and mTLE [70]. Based on both of these studies, nTLE is suggested when the mesial metabolism is normal although the neocortical metabolism is not entirely reliable.

(b) *Single-Photon Emission Computerized Tomography (SPECT)*. Ictal SPECT involves intravenous injection of a radiolabeled tracer during the beginning of a seizure and obtaining CT scan of the head short time afterwards. The cerebral uptake of the tracer reflects cerebral blood flow, thus reflecting ictal perfusion. SPECT images can indicate the location of seizure onset zone and are useful in patients with normal MRI scans or who have discordant data [71, 72]. In 7 patients with temporal neocortical tumors, ictal SPECT showed bitemporal hyperperfusion, higher on the side of the lesion but sparing the mesial structures. Newer methods of analysis using statistical parametric (SPM) analysis may prove useful. In a recent study of new method of ictal SPECT, analysis was developed to analyze scans of 87 patients with TLE. They found that this method more correctly lateralized the seizure focus and correctly localized it to the mesial temporal lobe. They found a good correlation of their findings to surgical outcome [73].

(c) *Functional MRI (fMRI)*. Cognitive functions of the brain such as memory and language can be mapped by fMRI using blood oxygenation-level-dependent (BOLD) technique, which in turn reflects local blood delivery to the brain [74, 75]. fMRI is noninvasive, reproducible, and more widely available. The asymmetry of activation can be calculated, thereby enabling to determine the cerebral dominance for language [76]. The results of language fMRI and the intracarotid amytal test have been concordant in many individuals with epilepsy [74, 75].

However, lateralization of language might not be uniform. Functions close to the pathology can relocate contralaterally, whereas functions further away from the abnormalities might remain in the ipsilateral hemisphere [77]. In patients with left TLE with frequent IEDs, right-sided language dominance has been shown [78]. fMRI helps to predict the risk of language dysfunction after anterior temporal lobectomy (ATL) [79]. In contrast to expressive language, laterality of receptive language is, in general, not well defined as it gives rise to bilateral activation [80]. The

role of fMRI in predicting the effects of temporal lobe surgery is being studied through ongoing investigations.

5.2.3. *Simultaneous EEG fMRI*. Simultaneous EEG-fMRI exploits the complementary features of these 2 techniques to overcome the spatial limitations of EEG and the temporal limitations of fMRI [81, 82]. This is especially important in nTLE, where the ictal focus can be colocalized to eloquent cortex. Thus, it may aid in the determination of area of resection and possible deficits. Simultaneous EEG-fMRI can map the BOLD signal changes associated with IEDs and occasionally ictal activity [83]. Fifty percent of patients with medically intractable focal epilepsy and frequent IEDs on scalp EEG will have an IED during EEG-fMRI acquisition, with 50% showing an identifiable BOLD signal change [84, 85]. A report of 48 fMRI studies on 38 patients with focal epilepsy using either spike-triggered or continuous EEG-fMRI showed significant BOLD activations in 22% (2/9) and 45.5% (10/22), respectively. The yield over all studies was 38.7%. Subsequent intracranial recordings in 4 patients further validated the EEG-fMRI results [86]. Negative BOLD responses, called deactivations, are now routinely examined in patients with focal and generalized epilepsy [87, 88]. A large review reported deactivations in 26 out of 34 experiments that showed robust BOLD responses to focal discharges, and noted deactivations were often found with concomitant activations, and several possible mechanisms were suggested [89]. Other studies have shown that deactivations are less concordant with location of IEDs supporting a distinct electrophysiological mechanism from activations [84, 89]. BOLD signal changes can occur at sites distant to the presumed seizure focus in focal epilepsies [89]. A report of 35 EEG-fMRI studies in 27 patients with TLE showed BOLD signal increases at sites distant to the seizure focus in most patients. Eighty-three percent of studies had BOLD responses, which predominated in the spiking temporal lobe (activation or deactivation); however, BOLD responses were often seen in contralateral temporal lobe and extratemporal one [89]. Based on these studies, it is likely that distant cortical and subcortical circuits are involved in the generation of focal discharges [89, 90]. BOLD changes can occur prior to the detection of IEDs on EEG-suggesting that physiological processes underlying spike-associated BOLD signal changes may begin before electrical activity can be detected using scalp EEG [91]. EEG-fMRI integration has considerable clinical relevance in the presurgical evaluation of patients with drug-resistant focal epilepsy [82, 85, 92]. Compared to intracranial EEG, both scalp EEG and fMRI remain less powerful techniques to definitely identify the seizure onset zone. Studies comparing spatial localization of the “irritative zone” using scalp EEG and fMRI to intracranial EEG and to each other have indicated that scalp EEG and fMRI both colocalize more closely with intracranial localization alone than they do with each other. This suggests that scalp EEG and fMRI provide complementary information regarding the intracranial source of epileptiform discharges. In another study, congruence between interictal and intracranial EEG and EEG-fMRI results was found in 3 of 8 patients, in whom

intracranial EEG was available [93]. The colocalization of BOLD changes within the resected volume has been related to a better outcome in a small case series [94, 95]. In another study, 4/29 patients who were rejected for epilepsy surgery due to poorly localized epileptic focus with the use of other diagnostic modalities underwent reevaluation for surgery based on EEG-fMRI findings [92]. Despite practical challenges, ictal EEG-fMRI recordings have been able to provide information about widespread cortical changes associated with seizures.

**5.2.4. High-Frequency Oscillations (HFOs) in Intracranial EEG.** High-frequency oscillations (HFOs) in intracranial EEG have been associated with epileptogenesis in humans and animal epilepsy [96–99]. They have been divided into ripples (80–250 Hz) and fast ripples (FR; 250–500 Hz) [87]. Such high-frequency activity cannot be recorded from the scalp because of the small areas of the brain that generates them and the high-frequency filtration by the extracranial tissue [88]. Although HFOs were first recorded with micro-electrodes, they can be observed by subdural EEG electrodes, with a surface contact of 4 mm<sup>2</sup> [98, 100–103]. Ripples are considered more physiologic in nature because they have been recorded in healthy animal brains, whereas FRs are more frequent with the seizure onset zone [97, 98, 101]. Thus, examining the EEG between 100 and 500 Hz may add clinically useful information to the interpretation of intracranial EEGs.

HFOs remain confined to the same, epileptogenic area during interictal and ictal periods, while IEDs are more widespread during seizures. Ictal and interictal HFOs represent the same epileptogenic area and are probably similar phenomena [104]. HFOs have been detected on top of IEDs, independent of IEDs, and after filtering of sharp waves. Examples of HFOs are shown in Figure 2.

HFOs have been found in the neocortex as well as in mesial temporal structures [98, 100]. They have a tighter relationship than IEDs with the seizure-onset zone [101]. Therefore, they may be a better biomarker of ictogenesis than IEDs. In patients with lesions, HFOs were closely coupled with the region of seizure onset than with the lesion, which may not always be the source of seizures [105]. In one study, the authors found that HFOs often increased in the few seconds immediately preceding a seizure [102]. Contrary to IEDs, HFOs do not increase after seizures, but do so after medication reduction, similar to seizures. This implies that IEDs and HFOs have different pathophysiologic mechanisms and that HFOs are more tightly linked to seizures than IEDs. Thus, they can be a useful marker of disease activity [106, 107]. Neocortical seizures are often poorly localized, explosive, and widespread at onset, making them poorly amenable to epilepsy surgery in the absence of associated focal brain lesions. Using an unselected group of patients with neocortical epilepsy, HFOs were shown to localize to the seizure-onset zone [108]. They were noted in all 6 patients with neocortical epilepsy out of 23 consecutive patients implanted with intracranial electrodes for presurgical evaluation. The majority of seizures (62%) could be anticipated by an increase in high-frequency activity

20 minutes prior to the onset of neocortical seizures. HFOs were maximal during slow-wave sleep, which may explain the propensity for neocortical seizures during sleep. These findings show that HFOs may be clinically useful in localizing the seizure-onset zone in neocortical epilepsy, for identifying periods of increased probability of seizure onset, and in elucidating mechanisms underlying neocortical ictogenesis.

**5.2.5. Validation of HFOs in Focal Epilepsy.** Jacobs et al. [109] studied 20 patients who underwent surgical resection for medically intractable epilepsy most being mTLE but some nTLE. They compared surgical outcomes to extent of HFOs and IEDs in resected versus nonresected areas. The mean followup was 22.7 months. Eight patients had good (e.g., Engel classes I and II) and 12 had poor (e.g., Engel classes III and IV) seizure outcomes. Patients with a good outcome had a significantly larger proportion of HFO-generating areas removed than patients with a poor outcome. No such difference was seen for IED-generating regions of the seizure-onset zone showing that HFOs could be used as a better marker of epileptogenicity and may be more accurate than IED-generating areas or the seizure onset zone.

**5.3. Magnetoencephalography (MEG).** Magnetoencephalography (MEG) is a safe noninvasive method to measure magnetic currents emanated by cortical pyramidal neurons. Since magnetic currents are perpendicular to electric currents, MEG provides complementary information to the EEG and is able to assess the deep sulci that would otherwise be nonlocalizable by the EEG [110]. The magnetic field is not attenuated by the heterogeneous conductivities. However, due to its small magnitude, technically MEG signals are difficult to obtain requiring a magnetic-free surrounding to maximize signal-to-noise ratio [111, 112].

In one study of randomly selected presurgical patients with epilepsy, epileptiform discharges on MEG could be recorded in 73% of cases [113, 114]. Similarly, the diagnostic yield of MEG during a single 2- to 3-hour recording session was 53.1% in patients with TLE [115]. MEG is slightly more sensitive than EEG by 55.8% to 49.7%, and it can map IEDs, particularly if they arise from the neocortical convexity [116]. Thus, the diagnostic yield was 92% for nTLE and 50% for mTLE in one study [113]. In another study, similar results were obtained; the yield was 73.3% for nTLE versus 42.3% for mTLE [115]. MEG and EEG can provide complementary information in detection of IEDs [117]. In this study of 67 patients with intractable epilepsy, the combined MEG-EEG studies increases sensitivity of detecting IED to 75% as opposed to 62% for EEG alone. In 13% of patients with negative EEG, IEDs were detected by MEG. Park et al. [118] compared 12 consecutive patients with neocortical epilepsy with simultaneous MEG and EEG studies. None of the 12 patients had IEDs seen only in one modality. While all patients had IEDs seen by both modalities, MEG was more sensitive than EEG. They found IEDs unique to MEG ranging from 5.9 to 97.9% of the total IEDs per patient, whereas IEDs unique to EEG were seen in 0 to 35% of IEDs.

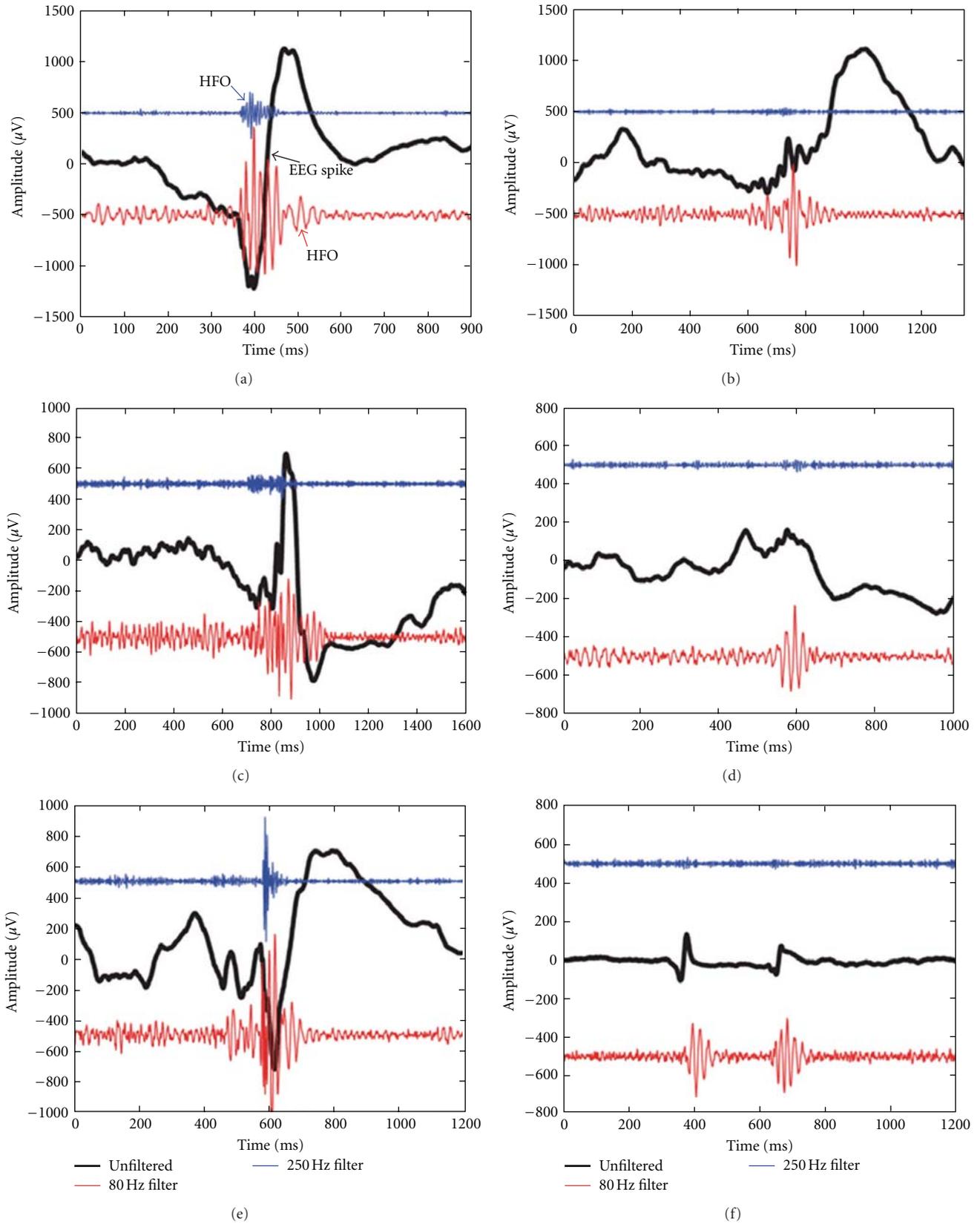


FIGURE 2: High-frequency oscillations (HFOs) occurring at the same time as spikes (a, c, e, and possibly f) and outside of spikes (b and d). The black trace is the original EEG. The red and blue traces result from high-pass filtering at 80 and 250 Hz, respectively. The amplitude of these traces has been multiplied by 10 to facilitate viewing (Source: <http://www.mni.mcgill.ca/>, permission obtained from author).

**5.3.1. Ictal MEG.** Occasionally, MEG can be useful to capture seizures. Thirteen patients who had seizures during MEG recording showed the ictal MEG to be well localizing to the ictal onset in all the 13 patients, using MR-FOCUSS technique of localization [119]. In a study of 20 patients with neocortical epilepsy, ictal MEG recording was made in 6 patients and was able to localize the seizure focus. When the results were compared to invasive EEG recordings, ictal MEG was better at predicting focus location as compared to interictal MEG [120]. These studies tend to be difficult to accomplish because they require patients to have frequent seizures with predictable onset.

**5.3.2. High-Frequency Oscillations and MEG.** Due to the magnetic fields ability to penetrate the underlying tissue unaffected, MEG can also be helpful in recording HFOs (with a frequency greater than 200 Hz). In a recent study of 30 children with epilepsy, the authors found that 26 (86%) patients had HFO activity recorded by MEG, and 21 patients demonstrated concordance between HFO focus and a lesion on MRI. Of those studied, 11 patients underwent epilepsy surgery; the HFO focus obtained from MEG was concordant in 9 out of 11 (82%) of patients during intracranial recording [121]. Further studies are needed to compare the HFOs to MEG-detected HFOs in nTLE and determine its utility in localization of IEDs and ictal foci.

**5.3.3. Functional Mapping Using MEG.** MEG signals can be correlated to MRI to create magnetic source imaging (MSI). MSI is a powerful technique not just for IEDs but also to help map eloquent primary sensory area such as somatosensory cortex [122]. In addition, MEG can be used to lateralize language as a prelude to epilepsy surgery. Both the intracarotid amytal test (a.k.a. Wada test) and the intracranial electrode stimulation are invasive techniques that entail a certain risk of morbidity. The MEG is increasingly being recognized as a tool for non-invasive lateralization as well as localization of language cortex. In a study of 27 patients, who had Wada testing as well as an MEG study for language lateralization, the MEG (at Broca's area latency) and WADA were in agreement in 23 of 24 (96%) patients who had a successful WADA test performed [123]. In addition, the MEG correctly lateralized, as was determined by subsequent electrocorticography, 1 of 3 patients who had an undetermined or bilateral IAP. These results indicate an 89% agreement rate (24 of 27) for magnetoencephalographic determination of the hemisphere of language dominance.

**5.3.4. Use of MEG in Presurgical Evaluation of Focal Epilepsy.** The mapping of MEG IED sources (a.k.a dipoles) are increasingly being used as a tool to help determine the best candidates for epilepsy surgery and help better outline the surgical margins. MEG can help distinguish the irritative zone of seizure onset from the area of seizure propagation. In patients for whom interictal data and long-term scalp EEG recordings were inconclusive (25 of 105 patients), MEG was able to localize the epileptogenic focus, which helped surgical resection in 44%. All these patients had an improvement of

seizure frequency postoperatively (6 patients were seizure-free; 5 had seizure reduction by >50%) [124]. MEG predicted the outcome following surgery for medically intractable epilepsy in children with normal or nonfocal MRI findings [125]. Systematic review on the use of MEG in the presurgical evaluation of localization-related epilepsy (between 1987 and 2006) reported insufficient evidence to support the use of MEG in surgical planning [126]. MEG's effects on outcomes have also been recently examined demonstrating good surgical outcomes in 22 children with intractable seizures and nonlocalizing or normal MRI [125]. Similarly, in the presurgical evaluation of 67 adults using EEG and MEG the authors found almost similar sensitivities between the two in detecting IED but MEG could correctly identify a source in 1/3 of patients that were EEG negative. They predicted that MEG would be useful in patients with neocortical epilepsy or those with focal cortical dysplasia [117].

**5.3.5. Treatment and Outcome.** Pharmacotherapy for focal epilepsy does not depend on anatomical diagnosis, and there is no difference in response to antiepileptic drugs (AEDs) based on anatomical localization of a neocortical epileptogenic region [127]. In patients with medically refractory seizures, surgical treatment depends on precise localization and delineation of the epileptogenic region rather than anatomical diagnosis, and outcome reflects the accuracy of this process and the ability to resect the abnormal tissue. Total resection may be limited by the involvement of the adjacent eloquent areas, or by the failure to correctly map the epileptogenic substrate, as can often occur in nonlesional localization-related epilepsy. If an epileptogenic region involves eloquent cortex, seizures may be relieved by the removal of a structural lesion alone (i.e., lesionectomy) or by multiple subpial transections [128, 129].

There have been many studies reporting less favourable postsurgical outcome in patients with lesional/nonlesional nTLE [3–9]. In one study, improved outcomes were apparent by resecting the combined neocortical and mesial temporal areas [5]. Recent research has challenged this view and suggests the poor outcomes is due to poor patient selection, poor localization, and incomplete resection of the seizure focus. While this current paper highlights the challenges in distinguishing mTLE from nTLE, there have recent studies demonstrating good-to-excellent outcomes in nTLE patients as compared to mTLE [1, 26, 40] or compared to other focal cortical epilepsies [2, 130]. These outcomes are reported using tailored neocortectomy or multiple subpial transections in addition to a standard ATL, after intracranial ictal EEG recording and cortical mapping [4, 131] even in patients with nonlesional nTLE [1, 132].

Factors affecting outcomes have been assessed by several studies. In a study comparing all neocortical focal epilepsies, the authors found that FDG-PET and interictal EEG localization predicted good outcome in nTLE [2]. The extent of neocortical resection is seen as a positive predictor [131], especially when the underlying area demonstrates pathological delta waves on intracranial monitoring [133].

In a large prospective-retrospective series in patients with TLE, 10% of the cases had nTLE. Pathological analysis demonstrated only 5% being nonlesional, whereas 57% were neoplastic (ganglioglioma predominating) and 38% non-neoplastic (e.g., MCD). Outcomes seemed to be best for those with neoplastic lesions [1]. This is echoed by another clinicopathological study showing left hemispheric lesions and focal MCD associated with poor outcomes as compared to tumours [47]. However, it should be noted that dual pathology can exist even in patients with presumed nTLE. In a recent analysis of 243 samples from patients with TLE, 86% had HS in addition to other pathologies (33% having tumours and 45% having MCD). Nonetheless, they still demonstrated excellent surgical outcomes (Engel class I) in 87% of those with tumours and 79% with MCD [64].

## 6. Conclusions

nTLE is less common compared to mTLE and accounts for about 10% of TLE. The risk factors for nTLE are quite different from mTLE. Seizure freedom for lesional nTLE is approximately 70%. During the past decade, additional converging evidence has been provided that there are some clinical and electrophysiological characteristics that can help to differentiate nTLE from mTLE. Advances in brain imaging with currently available high-resolution structural MRI can reveal previously covert epileptic lesions, with quantitative and voxel-based MRI analysis increasing the diagnostic yield. HFOs in intracranial EEGs increase the detection rate of ictal onset zone that further helps surgical planning in nonlesional cases. MEG provides complementary electrophysiological information to the EEG but can also determine epileptogenic focus in EEG negative patients, possibly raising surgery as a viable option in previously nonsurgical candidates. The data from MEG and EEG-fMRI can assist in the placement of intracranial electrodes to further define the seizure onset zone. PET and SPECT have also provided some data in localization of neocortical epileptic focus. Thus, reliable integration of all the structural and functional data will help to establish the neocortical origin of the seizures in patients with nonlesional nTLE which is crucial to achieve a good surgical outcome.

## Acknowledgment

The authors wish to thank Dr. Jean Gotman, Montreal Neurological Institute, Canada, for the illustration on HFOs (Figure 2).

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## Review Article

# Electroencephalography in Mesial Temporal Lobe Epilepsy: A Review

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Received 12 October 2011; Revised 17 January 2012; Accepted 23 February 2012

Academic Editor: Seyed M. Mirsattari

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Electroencephalography (EEG) has an important role in the diagnosis and classification of epilepsy. It can provide information for predicting the response to antiseizure drugs and to identify the surgically remediable epilepsies. In temporal lobe epilepsy (TLE) seizures could originate in the medial or lateral neocortical temporal region, and many of these patients are refractory to medical treatment. However, majority of patients have had excellent results after surgery and this often relies on the EEG and magnetic resonance imaging (MRI) data in presurgical evaluation. If the scalp EEG data is insufficient or discordant, invasive EEG recording with placement of intracranial electrodes could identify the seizure focus prior to surgery. This paper highlights the general information regarding the use of EEG in epilepsy, EEG patterns resembling epileptiform discharges, and the interictal, ictal and postictal findings in mesial temporal lobe epilepsy using scalp and intracranial recordings prior to surgery. The utility of the automated seizure detection and computerized mathematical models for increasing yield of non-invasive localization is discussed. This paper also describes the sensitivity, specificity, and predictive value of EEG for seizure recurrence after withdrawal of medications following seizure freedom with medical and surgical therapy.

## 1. Introduction

The previous ILAE classification of epilepsy syndromes classified temporal lobe epilepsy under medial temporal lobe (mTLE) and lateral temporal lobe epilepsy (lTLE) [1]. In the revised classification, mTLE is under “distinctive constellations/electroclinical syndromes” with the most common pathological substrate being hippocampal sclerosis (HS) [2, 3].

mTLE-HS is the most common form of focal epilepsy. It has a distinct clinical presentation called “limbic seizure” resulting from epileptic activity within the limbic structures; however, they are not distinguishable from lTLE with other pathologies than HS. mTLE-HS also has specific electrographic features, neuroimaging, and pathological findings. The term hippocampal sclerosis denotes a specific pattern of cell loss mostly involving CA1 and hilar neurons and least the CA2 region [4]. Although the pathophysiology of this

condition based on human surgical tissue and in animal studies is well known, the sequence of events resulting in HS is not well understood [5]. Hippocampal sclerosis can now be detected by high-resolution MRI in majority of patients [6, 7].

The incidence and prevalence of mTLE are not well known, and the available information regarding natural history is biased by those patients with refractory seizures who are referred to the epilepsy surgery centers. In one series, pathologic analysis of the hippocampal tissue revealed that up to 70% of patients with intractable temporal lobe epilepsy may have HS [4]. Two longitudinal outpatient studies addressed the prevalence of this condition. The French study included tertiary referrals, and the other was conducted at a primary care clinic in Glasgow [8, 9]. In the former, half of patients had TLE. In both studies, about 25% of patients had hippocampal atrophy on MRI, and seizures were most refractory in this group. The Paris study reported

seizure freedom in only 11% and 3% of those with dual pathology (HS and another MRI lesion) in the previous year. This report suggested that mTLE-HS may be the most common form and most medically refractory epilepsy [8].

The autosomal dominant familial form of mTLE has been described to have a more benign course [10, 11]. The clinical and EEG manifestations of the familial form cannot be distinguished from the sporadic form. The patients with refractory seizures in this group similarly benefit from surgery [12].

The family history of epilepsy, history of prolonged febrile seizure or other insults such as trauma and infection in early life are typical of the syndrome of mTLE with HS [5]. The limbic seizure is often characterized by an aura followed by a dyscognitive state with variable degrees of impaired level of consciousness. The auras and seizure behaviour are fairly characteristic in most [13], however, in a subgroup of patients the clinical manifestations are atypical and make the diagnosis quite challenging. Examination is often normal except for memory deficits.

When the typical history is missing, the limbic seizure could have another pathological substrate or the epileptic abnormality projects to the mesial structures from the temporal neocortex or the close neighbouring structures such as orbitofrontal cortex, the insula or frontal/parietal operculum. These seizures could be clinically indistinguishable from mTLE-HS. The term temporal “plus” (T+) was introduced by Ryvlin and Kahane [14] to describe the form of seizures with a complex epileptogenic network. The ictal clinical presentation and scalp EEG assist in differentiating TLE from seizure originating in the neighbouring structures [15].

mTLE with HS is the most common refractory epilepsy in adults and has a poor prognosis with medical treatment. However, many of these patients have excellent response to surgery and removal of the epileptogenic zone. One prospective study found that surgery was clearly superior to medical therapy in this population of patients [16]. A large number of other studies have reported 60–80% of seizure freedom after the mesial temporal lobe resection [17–19]. In children, focal cortical dysplasia is more common pathological substrate than HS. Mittal et al. and Lerner et al. have reported the results of surgery for TLE in children [20, 21].

In presurgical evaluation of patients with TLE, the identification of seizure focus is the most important prerequisite for surgery. EEG in temporal lobe epilepsy has been recently reviewed [22, 23]. A detailed clinical assessment, interictal and ictal EEG findings with electroclinical correlation during continuous video/EEG monitoring, neuropsychological data, MRI, and sometimes single-photon emission computed tomography (SPECT)/positron emission tomography (PET) or magnetoencephalography (MEG) have been utilized for the identification of the epileptic focus. In more recent years significant advances in digital EEG, seizure detection technology, MRI, EEG/MRI superimposition, MR spectroscopy, and functional MRI (fMRI) have been very helpful in noninvasive localization of the seizure focus [24, 25]. Neuropsychological assessment and WADA for determining the language side and lateralized memory dysfunction aid in

surgical decision [26]. Electrocorticography in the operating room can localize the active seizure focus and guide the surgical resection [27].

When the information obtained from the scalp EEG, MRI and neuropsychological assessment are insufficient or nonconcordant, or when further data is required, invasive intracranial EEG recording will be planned. Placement of subdural strip/grid or depth electrodes provides valuable information for localization of the seizure focus. The extent and location of electrode placement is designed to test the hypotheses regarding the possible ictal onset zones. The hypotheses are generated from clinical semiology, scalp EEG, neuropsychological and imaging data.

The focus of this paper is on the electroencephalographic aspects of mTLE with some attention to the other aspects of this syndrome related to EEG. The semiology of TLE, mTLE, nTLE, surgical treatment of TLE, and pediatric TLE are subjects of other papers in this special issue, and the readers are referred to those papers for further details.

## 2. Method of This Review

The MEDLINE literature search was performed for the EEG information and pertaining to all the aspects of the mesial temporal lobe epilepsy. The focus of this search was mainly on the EEG features of mTLE and detail of clinical features, neuroimaging, pathology and surgical results are not included. All the original articles and pertinent references in the several main reference textbooks on this topic were reviewed. Although there were no age limits, most of the information regarding the EEG data were obtained from the adult literature.

## 3. Historical Aspects of EEG in Temporal Lobe Epilepsy

A specific form of EEG characterized by rhythmic sharp waves and 6 per second waves was first described by Gibbs et al. in 1935 as the typical manifestation of psychomotor seizures [28]. Lewis is one of the pioneers who recorded EEG in patients with behavioural disorders and epilepsy. He was able to identify epileptogenic foci based on ictal and interictal discharges in 55 patients with epilepsy. Using bipolar EEG, he could also predict the location of the lesion within 2–3 cm in 85% of patients being evaluated for brain surgery for other lesions [29]. The use of EEG significantly improved the surgical results and led others to utilize EEG prior to surgery in 1930s and 1940s.

Lewis could distinguish the “seizure onset zone” from the “epileptogenic lesion” identified by the only available pneumoencephalogram and EEG soon became an important tool in classification, pathophysiology, localization, and surgical treatment of epilepsy [29].

The role of EEG in temporal lobe epilepsy (TLE) and epilepsy surgery was first described by Kennedy and Hill in 1958 [30]. Bailey and Gibbs in 1951 [31] were the pioneers who resected the anterior temporal lobe mainly based on the EEG evidence. Since the time of Jasper EEG has remained the main tool to guide surgery. In 1975, Engel reviewed

the electrophysiological correlates of pathology and surgical results in temporal lobe epilepsy [32]. The role of EEG in epilepsy and the advancement of digital EEG and automatic spike and seizure detection have been reviewed elsewhere [33–35].

#### 4. Technical Considerations

Electrode placement using the international ten-twenty system was first introduced in 1958 [36]. This system is now widely accepted and used as the standard method of measurement and application of electrodes for recording scalp EEG. Standard electrodes can detect only up to 58% of spikes [37]. Recently the original 10–20 electrode system and alphanumeric nomenclature were modified. Additional and more closely spaced electrodes allow better identification and localization of the epileptiform discharges in the subtemporal and other areas in patients with partial seizures and TLE [38].

Utilizing special electrodes such as nasopharyngeal, sphenoidal [39], anterior temporal (AT or T1, T2), and mandibular notch (MN) electrodes have increased the yield of detecting epileptiform discharges in the mediobasal region [40]. Recently Wilkus et al. [41] evaluated and compared the ictal changes over different electrodes and reported equivalent results. Ives et al. [42] found the montages containing the sphenoidal electrodes detected the ictal onset usually by more than 5 seconds compared to the other montages and were able to detect ictal changes not apparent in the anterior posterior temporal montage.

Recently, using intracranial recording as gold standard, the sensitivity of the surface and sphenoidal electrodes was found to be comparable [43]. T1, T2, and MN electrode are able to record almost all the sphenoidal detected spikes. Nasopharyngeal electrodes are uncomfortable and have not been proven to be superior to the other electrode types and therefore are no longer widely used.

Activating procedures can increase the yield of detecting interictal epileptiform discharges. Hyperventilation is particularly useful for primary generalized epilepsies; however, it can also activate focal epileptiform discharges in up to 10% in partial epilepsies [44]. Photic stimulation is useful for activation of generalized epileptiform discharges and has not been used for partial seizures. Several studies have documented that sleep deprivation can increase the chance of detecting epileptiform discharges in both partial and generalized epilepsies [45, 46]. This is mainly due to the effect of sleep deprivation and not the sleep per se.

#### 5. The EEG Patterns Resembling Epileptiform Activity

**5.1. Benign EEG Variants.** The distinction between interictal epileptiform discharges (IED) and benign EEG variants (EEG patterns with unknown aetiology) is at times challenging and poses difficulty for the EEG interpretation. These patterns have been extensively reviewed in the literature [47, 48]. The waveforms that mimic epileptiform patterns of TLE are listed in Table 1.

TABLE 1: Benign EEG variants that could mimic epileptiform discharges.

Small sharp spikes of sleep (SSS or BETS)
Wicket spikes
Psychomotor variant (RMTD)
Mu rhythm
Subclinical rhythmic electrographic (theta) discharges in adults (SREDA)

*BETS* are short-duration (less than 50 milliseconds) and low-amplitude (less than 50 microvolts) spikes. They occur during early sleep and are located in the temporal and frontal regions unilaterally or bilaterally but in most instances they are asymmetrical. They do not have a prominent aftercoming slow wave although they may have a small dip or single aftercoming slow wave component. Unlike the temporal epileptiform sharp waves, *BETS* do not distort the background and do not occur in trains. They often have a broader field than temporal epileptiform discharges and do not have clinical significance related to TLE [49].

*Wicket spikes* are single or trains of sharply contoured monophasic arciform waves similar to train of wicket-like activity that occur mainly during drowsiness and light sleep. When they occur as a single high-amplitude waveform, they could be mistaken for an abnormal temporal lobe epileptiform discharge. *Wicket spikes* do not have after coming slow wave component and do not distort the background [50].

*Rhythmic mid-temporal discharges (RMTD)* or psychomotor variant occur in early sleep. This is a 5–7 Hz semirhythmic waveform with a notched appearance lasting few to several seconds, and it is often unilateral and predominantly in the temporal regions. It has an abrupt onset and ending without evolution which can differentiate RMTD from buildup of ictal activity. There is no associated clinical symptom, and this pattern is not related to TLE [51].

*Mu rhythm* is a central rhythm with arch-like configuration with an alpha range 8–10 Hz frequency, which occurs more in adult and less in elderly. It blocks with movements of the contralateral limbs. If sharply contoured and high amplitude over a bone defect, it may be mistaken for epileptiform discharges [52].

*Subclinical Rhythmic Electrographic Discharges in Adults (SREDA)*. This is an uncommon pattern mostly in people over the age of 50 years. It may occur during drowsiness or at rest. It contains theta delta frequencies evolving into a 5–7 Hz range maximum over the parietotemporal regions. It is usually bilateral, but it could be asymmetrical. *SREDA* may occur in a sharply contoured and single-waveform configuration, and it could be repetitive and evolving resembling subclinical seizures [53, 54].

**5.2. Artifacts and Breech Rhythm.** Different movements can cause artifacts on scalp EEG that could mimic epileptiform activity. These include chewing and swallowing movements, movements of the eyes, head or limbs, rubbing, tremor and

scratching, that could cause rhythmic changes or spike-like discharges. Mechanical artifacts are often due to instability of electrode on the scalp and electrode wire or cable movement.

Scalp changes by trauma, defects by craniotomy and breach rhythm, electronic devices that generate alternating current fields such as ventilators or intravenous pumps and static changes by dripping intravenous fluids could cause artifacts resembling epileptiform spikes or sharp waves [55]. Therefore, spike like discharges only during sleep and those without a recognizable field and aftercoming slow waves should be considered nonepileptiform.

## 6. Continuous Video/EEG Recordings (CV-EEG)

The probability of capturing a seizure during a routine 20–30 minutes EEG in a patient with average of one seizure per week is reported to be about 1% [56]. CV-EEG recording is the ultimate technology in the analysis of clinical and subclinical seizures for the diagnosis of the seizure type and epileptic syndrome as well as differentiating epileptic from nonepileptic spells [57]. CV-EEG has also been helpful in the correct diagnosis of epilepsy in those patients with the misdiagnosis of non-epileptic seizures [58, 59]. Other than increasing the likelihood of detecting interictal epileptiform activity, CV-EEG allows visual analysis of the seizures and simultaneous clinical and electrographic correlation helpful in presurgical evaluation. Although CV-EEG is mostly utilized in an inpatient setting, it is also used for shorter day recordings particularly in children with frequent seizures [60, 61]. The information from CV-EEG along with imaging and neurophysiologic data guides the clinicians in surgical resection of the epileptogenic zone in temporal lobe surgery.

## 7. Interictal Scalp EEG in Epilepsy

The first question the clinician asks is whether the patient with paroxysmal events has epilepsy. Although this is primarily a clinical diagnosis, EEG plays an important role. The pattern of interictal EEG assists in determining the seizure type; however, different EEG patterns have different association with epilepsy, and therefore the sensitivity and specificity of EEG patterns remain unclear. EEG abnormalities could be in the form of interictal epileptiform discharges (IEDs), focal-slowing or periodic-lateralized epileptiform discharges (PLEDs) or diffuse changes such as frontal intermittent rhythmic delta activity (FIRDA). Only IEDs and PLEDs have sufficiently high association with epilepsy [55]. In focal epilepsies, the interictal spike is a guide for seizure focus localization along with clinical and imaging data. Table 2 highlights the features helping to identify IED. Although not inevitable, these features are highly correlated with epilepsy.

Interictal EEG documents the background cortical function during the nonseizure state. For example, generalized epileptiform discharges in the context of normal background activity are more characteristic of genetic epilepsies. The presence of frequent IED or significant background slowing could be associated with the patient's cognitive abnormality. Table 3 indicates some of the clinical uses of IEDs.

TABLE 2: The characteristics of interictal epileptiform discharges [55].

Paroxysmal with spiky configuration standing out from the background
Duration 70–200 msec for a sharp wave and 20–70 msec for a spike
Abrupt change in polarity
Surface negative polarity
Have a physiological field

TABLE 3: The clinical information obtained by interictal epileptiform discharges [55].

Diagnosis of epilepsy in paroxysmal events
Identification of the refractory epilepsies
The risk of seizure recurrence after a single unprovoked seizure
Diagnosis of epileptic syndromes and predicting the prognosis
Identifying the surgically remediable epilepsies
Probability of seizure recurrence after medication withdrawal
Predication of seizure recurrence after medication withdrawal following surgery

*7.1. Sensitivity and Specificity of Interictal Epileptiform Discharges.* EEG could direct toward a particular type of epilepsy and help in distinguishing among several possible syndromes in complex and confusing clinical situations. However, critical analysis of sensitivity, specificity, and positive predictive value of different EEG features is not possible [55].

*7.1.1. Sensitivity.* Three large studies of mainly adult patients reported a range of sensitivity of EEG in detecting IEDs. The initial EEG is positive for epileptiform discharges in 29–55%, being more sensitive in generalized epilepsies [62]. Repeated EEGs and longer duration of recordings increase the yield to 80–90% [63]. EEG is persistently negative in about 8% of patients with epilepsy and higher proportions of patients with partial seizures have negative interictal EEG [64]. EEG has a lower yield, estimated between 12% and 50%, in patients who had only one seizure or those who were well controlled and would undergo medication withdrawal [65, 66]. Hence, the interictal EEG has variable sensitivity, and its yield depends upon a number of factors listed in Table 4 [67–69]. Automatic detection methods have been of great assistance in spike detection during long-term monitoring of epileptic patients [70].

Antiepileptic drugs such as benzodiazepines, valproic acid, and barbiturates can suppress IEDs [71–73]. Other than magnetoencephalography (MEG), several different computerized techniques have improved the sensitivity of IED detection by EEG signals [74, 75].

The yield of interictal abnormality in TLE depends on different factors such as duration of recording and the state of the patient. One video/EEG study with a mean of 6.9 days of continuous monitoring showed that 19% of patients with recorded seizures had no interictal abnormality [64]. In our

TABLE 4: Conditions that increase the yield of EEG detecting interictal epileptiform discharges.

In children and seizure starting in earlier life
Within 48 hours after a seizure
Certain epilepsy syndromes such as benign rolandic epilepsy, Lennox Gastaut, and Landau Kleffner
Greater seizure frequency
Sleep and sleep deprivation
Serial EEGs

patient population with mTLE who underwent surgery after video/EEG monitoring and had good surgical outcome, CV-EEG failed to reveal IED in 15 out of 171 patients (8.7%) (unpublished data).

*7.1.2. Specificity.* IEDs are very uncommon in people without epilepsy. Studies have reported IED in 0.5% in adults and 1.9% to 3.5% of normal children without epilepsy. The interictal epileptiform discharges typical of partial epilepsy are very rare in people without partial epilepsy [76–78].

*7.2. Positive Predictive Value of Interictal Epileptiform Discharges.* This is calculated by the ratio of the number of subjects with epilepsy who have IED to all subjects with or without epilepsy who have IEDs. This ratio is dependent on the sensitivity and specificity of IEDs and more importantly the population under study. Therefore it could vary depending on the outpatient versus hospitalized patients [64].

*7.3. Predictive Value of Interictal Epileptiform Discharges for Seizure Recurrence.* Factors associated with persisting seizure freedom versus seizure recurrence after withdrawal of antiseizure drugs following surgery have been studied. Shinnar et al. in a prospective study followed 407 children who presented with a first unprovoked seizure followed for a mean of 6.3 years from the time of the first seizure. Children with first seizure and unidentified cause and a normal EEG had a 5-year recurrence risk of only 21% [79].

Another study analyzed the sensitivity, specificity, and positive and negative predictive values of EEG for seizure recurrence on 831 children in four eligible studies searched between 1980 and 1998. They reported a low sensitivity of 61% and specificity of 71% and concluded that EEG should not be obtained routinely after first unprovoked seizure in childhood [80].

Prospective and randomized studies as well as one meta-analysis in adult population have revealed that an abnormal EEG was associated with an increased risk of recurrence, but in some studies there was considerable variability in the results, and the epileptiform activity was not differentiated in most studies [81–83].

Tinuper et al. assessed the role of the EEG in predicting seizure recurrence in partial epilepsies. They found that the interictal EEG at the time of antiepileptic drug withdrawal did not predict recurrence, however, a worsening of the EEG after withdrawal was predictive of seizure recurrence [84].

*7.4. The Value of EEG in Predicting Seizure Recurrence after Temporal Lobe Resection.* Studies have reported contradictory results in the literature. However, collectively it seems that an abnormal EEG can predict the possibility of seizure recurrence after withdrawal of medications following surgery for temporal lobe epilepsy.

The outcome of discontinuation of anti-seizure medications was retrospectively studied in 210 consecutive patients who were rendered seizure-free after epilepsy surgery performed between 1989 and 1993. Medications were reduced in 96 and discontinued in 84 patients. The seizure recurrence rate after complete anti-seizure withdrawal was 14% and 36% at 2 and 5 years. In contrast, only 3% and 7% of the 30 patients who did not alter anti-seizure medications after surgery had recurrent seizures in the same time intervals. Intraoperative electrocorticography and postoperative EEG were not predictive of seizure outcome after anti-seizure drug withdrawal [85].

In another study serial EEGs at 3 months, and at 1, 2, and 3 years after anterior temporal lobectomy were analysed in 262 consecutive patients with mTLE-HS. EEG was considered abnormal when interictal epileptiform discharges (IED) were present. Anti-seizure medication withdrawal was attempted in all seizure-free patients. Favourable outcome was defined as freedom from seizures/auras during the entire follow-up period (outcome 1) and during terminal 1-year followup (outcome 2). Those with IED had 3–26 fold increase in the risk of seizure recurrence. The authors concluded that EEG after anterior temporal resection predicts seizure outcome and seizure recurrence following medication withdrawal. Serial EEGs predict outcome better than single EEG [86]. Several other studies have addressed the prediction of seizure recurrence after temporal lobe surgery [87, 88].

## 8. Interictal Findings in mTLE: Scalp EEG Recording

The interictal changes in mTLE could be in the form of nonepileptiform abnormalities, epileptiform discharges, or both.

### 8.1. Non-Epileptiform

*8.1.1. Focal Dysrhythmia/Slowing.* Scalp EEG may reveal a persistent or intermittent 4–7 Hz (Theta) or 1–3 Hz (delta activity) unilaterally or bilaterally in the temporal regions. This is a nonspecific finding in various conditions such as tumours, stroke, and HS, or it may not have a pathological substrate. If persistent, it is more consistent with structural abnormality. However, if neuroimaging does not reveal any pathological substrate, the intermittent slow waves in the temporal region are often due to interictal or postictal activity [89].

Lateralized focal or regional polymorphic delta activity is frequently found in TLE and is highly associated with temporal spiking. Koutroumanidis et al. correlated the interictal temporal delta activity in TLE with the pathology and surgical outcome. They reported lateralized slow activity

in 66% of 141 patients who had temporal lobe resection for intractable partial seizures. The delta activity correlated well with the side of the temporal spikes. It provided additional information in 15%, in whom EEG did not show lateralized interictal spikes. The authors concluded that in patients with TLE, whose MRI was either normal or suggestive of HS, interictal temporal slow activity had a lateralizing value similar to that of temporal spiking and was significantly associated with favourable surgical outcome [90].

In another study, 82% of patients with seizures exclusively from one temporal lobe had unilateral delta activity ipsilateral to the side of the ictal onset; this activity never falsely lateralized the seizure onset [91].

**8.1.2. Temporal Intermittent Rhythmic Delta Activity (TIRDA).** This term consists of trains of rhythmic delta activity lasting 4–20 seconds and is observed in up to 25% of patients with TLE who are being evaluated for surgery. TIRDA is more specific to TLE and often associated with epileptiform discharges [92, 93]. In one study, TIRDA was found in up to 90% of patients with MRI evidence of hippocampal atrophy and mTLE [94]. The authors concluded that delta activity lateralized to the side of the atrophy had accuracy equal to the spikes and reflected the epileptogenic process rather than the structural pathology. This specificity of TIRDA was also confirmed by Di Gennaro et al. [95]. Figure 1 demonstrates an example of TIRDA.

## 8.2. Epileptiform

**8.2.1. Spikes and Sharp Waves: Interictal Epileptiform Discharges (IEDs).** The typical epileptiform abnormality is the characteristic spike or sharp wave with negative polarity and is often followed by a slow wave (Figure 2). The anterior temporal spikes have maximum negativity over the temporal basal electrodes (F7, F8, T1, T2, and sphenoidal electrodes) [96, 97]. In a temporal lobe surgical series, the anterior temporal spikes were present in up to 94% of 64 patients with mTLE [98]. Figure 2 demonstrates an example.

Computer field mapping technique has found that the maximum electronegativity of these spikes is anterior and inferior to the standard 10–20 electrode positions [99]. This field improves the sensitivity of the additional nonstandard electrodes. Furthermore, the analysis of the voltage topography revealed that the maximum region of electronegativity of these spikes was over the ipsilateral inferior temporal scalp associated with a more diffuse area of positivity over the contralateral central parietal scalp [100].

The precise anatomical generators of scalp and sphenoidal detected spikes have not yet been identified with certainty. Wilkus et al. in a study using simultaneous surface and intracranial recording found that electronegative sphenoidal spikes were recorded when electropositive hippocampal (HC) spikes were present. Although sphenoidal spikes are often associated with seizures originating from the hippocampus, they could also be present with seizures originating in the neocortical temporal or orbitofrontal area. Therefore, although sensitive, sphenoidal spikes are not very specific [41]. Spikes with maximum negativity over the

mid/posterior temporal electrodes (T3/T4 or T5/T6) are more likely to originate from the temporal neocortex [22].

Sleep can increase the frequency of interictal spikes. Since IEDs are more prevalent in nonrapid eye movement (NREM) sleep than in wakefulness, Malow et al. reported that when combined with other investigations, IEDs recorded on overnight studies added prognostic data to the epilepsy surgery evaluation which was not provided by daytime EEGs [101, 102].

Previous studies have reported significant correlation of the lateralized temporal spikes to the side of the ictal onset [103]. These spikes are highly predictive of the ictal onset when they are associated with ipsilateral hippocampal atrophy. However, a unilateral scalp recorded IED may falsely lateralize the seizure origin; therefore, ictal recording is still necessary in presurgical evaluation [104, 105].

About one-third of patients with mTLE have bitemporal independent spikes or sharp waves mostly during non-REM sleep [96, 97]. Williamson et al. reviewed interictal scalp EEG abnormalities in mTLE and reported 42% of 67 patients to have bitemporal independent spikes or sharp wave [98]. Typical IED and/or intermittent slow waves in the anterior temporal region were present in 94% of patients. The strictly unilateral changes (observed in 52%) correlated with the side of the seizure origin in 94% of patients. This was confirmed by subsequent depth EEG recording and surgical cure. The lateralized IEDs are often recorded during wakefulness and REM sleep. The more lateralized the spikes, the more predictive they are for the side of the seizure onset [102, 106].

Patients with bitemporal independent discharges could still be candidates for surgery and have a good surgical outcome when they have unilateral pathology, particularly when the side of the pathology and the ictal events are concordant. So et al. [107] reported the surgical outcome after a minimum of two years following temporal lobe surgery in 48 patients with bilateral independent temporal spikes. 14 were seizure free, 22 had greater than 50% seizure reduction, and three patients had less than three seizures a year. Chung et al. correlated the degree of lateralized IEDs with the surgical outcome after temporal lobectomy. When more than 90% of spikes were confined to one temporal lobe, 92% of patients had a good surgical outcome. When IED lateralization was less than 90%, only half of patients achieved a good outcome [96].

## 9. Ictal Scalp EEG in mTLE

**9.1. Seizure Onset.** Gastaut [108] made an observation that “the attacks of psychomotor epilepsy are almost equally complex from an electroencephalographic and clinical point of view, and they cannot be reduced to a single mode of expression.” Several factors such as the mesial versus lateral seizure onset, the underlying pathology, and the seizure propagation pattern could account for the variable EEG expression [23].

Some studies have indicated that the lateralized IED to the side of the temporal lobe lesion on MRI could be sufficient for surgical resection [104, 109]. However, in majority



FIGURE 1: Temporal Intermittent Rhythmic Delta Activity (TIRDA) recorded in a patient with left temporal lobe epilepsy. This patient also had epileptiform discharges in the left anterior temporal region. (HFF = 15 Hz, LFF = 0.5 Hz, and sensitivity =  $7 \mu\text{V}/\text{mm}$ ).



FIGURE 2: A 29-year-old woman with history of complex partial seizures. Scalp EEG demonstrates sharp waves phase reversing over F7-T3 and Sphenoidal SP1 electrodes. (HFF = 15, LFF = 0.5, and sensitivity =  $10 \mu\text{V}/\text{mm}$ ).

of patients with negative MRI, nonlateralizing IED or bilateral epileptiform discharges, ictal EEG recording provides the most important data regarding the seizure onset in presurgical evaluation of patients with refractory temporal lobe epilepsy.

EEG is often unremarkable during aura or at the beginning of the abnormal clinical behaviour [98]. The ictal EEG manifestation of limbic seizures could have a nonspecific beginning of low-voltage fast (electrodecrement) activity,

with focal or regional background attenuation. The low-voltage fast activity is seen in up to 25% of patients and does not provide lateralizing/localizing value [109, 110].

Blume et al. studied the EEG morphology of focal seizures. He found that other than initial attenuation, there were sinusoidal waveforms in 47% and repetitive epileptiform discharges in up to 39% of patients. Both EEG patterns were observed in 15% of patients. In the last stage of the seizure, the frequency decreased, while the amplitude had

often increased [111]. Not all patients in this study had temporal lobe onset seizures.

In seizures recorded by subdural electrodes, Blume and Kaibara [112] reported “start-stop-start” pattern at the seizure onset which was also reported in 13% of patients recorded by scalp electrodes in another study [113]. If the initial part of the seizure onset is missed, the restart of the EEG changes could be incorrectly considered as the seizure onset.

Williamson et al. found buildup of lateralized rhythmic 5–10 Hz sharp activity in 81% of seizures in mTLE. This appeared within 30 seconds of the first objective or subjective clinical symptoms and signs of a seizure and was observed in the anterior-inferior temporal scalp electrodes. This pattern was concordant with the side of the seizure onset in 47 out of 67 patients, and it was discordant in five patients. This characteristic rhythm occurs in 82–94% of patients with mTLE and has 95% specificity for lateralizing the seizure onset (Figure 3) [98, 114–116].

The frequency of the ictal onset EEG in neocortical temporal lobe seizures is often in the 2–5 Hz range [117]. The temporal-sphenoidal pattern is less common. There is also less stability of frequency and voltage. Absence of the ictal scalp discharge is more common in nTLE than in mTLE [114, 118, 119]. The overlap in EEG findings between mTLE and nTLE in limbic seizures does not allow confident distinction between the two by ictal EEG alone [55].

## 10. Reliability of Interictal and Ictal Scalp EEG Findings for Surgical Decision

*10.1. Accuracy of IEDs.* Recent literature agrees that IEDs are valuable predictors of the site of the seizure onset. Previous studies relied mainly on scalp EEG abnormalities or clinical picture to recognize temporal lobe seizures [120, 121]. Several recent studies have reported a strong association between the location and frequency of IEDs and the side of the seizure onset [91, 96, 103]. One study reported 93% of 56 patients with seizures originating from one temporal lobe had IED exclusively or predominantly in that temporal lobe [112].

Casino et al. studied 159 patients with intractable TLE who underwent anterior temporal lobectomy between 1988 and 1993. The epileptogenic temporal lobe was determined by ictal recording on long-term monitoring. Routine EEG revealed temporal lobe epileptiform discharges in 123 patients which correlated with the temporal lobe of seizure origin ( $P < 0.0001$ ) and the results of MRI volumetric studies ( $P < 0.0001$ ). However, it was discordant with interictal findings in another 20 patients. They concluded that in patients with TLE, IEDs localized to one temporal lobe on serial routine EEGs or during long-term recording may be adequate to identify the epileptogenic zone [109].

Patients with unifocal or highly predominant interictal temporal spike or sharp wave are very likely to have focal ictal onset from the same temporal lobe. However, some studies have reported 20–40% false lateralization in those

with predominant lateralized interictal finding on scalp EEG. Hence, the unilateral surface temporal IED did not exclude the possibility of bilateral independent ictal onset as documented by subsequent intracranial recordings [122].

The overall accuracy of scalp lateralization has been reported to be 60–83%. Barba et al. analyzed the differentiating features between temporal lobe (TL) and temporal plus (T+) epilepsy and concluded that interictal spikes could not definitely differentiate the TL from T+ group [123]. However in T+ group, scalp EEG recordings demonstrated more precentral interictal abnormalities and were topographically different from the frontotemporal sharp waves described in mTLE. In T+ group, there were more frequent bilateral interictal abnormalities previously reported to be associated with worse surgical outcome [124]. Temporal lobe interictal spikes or ictal EEG onset did not definitely rule out the possibility of T+ epilepsies similar to the study reported by Aghakhani et al. [125]. Interictal and ictal scalp data guide towards intracranial recording in order to delineate the epileptogenic zone for resection.

The presence of temporally located interictal abnormality in patients with extratemporal lobe epilepsy has been discussed in several studies [126–129].

*10.2. Ictal Accuracy in Scalp EEG.* Risinger et al. retrospectively analysed 706 noninvasive ictal recordings from 110 patients to study the reliability of scalp/sphenoidal ictal recording for localization. These patients subsequently underwent depth electrode study. The authors found that 52% of patients displayed 5 Hz or faster frequency maximum over on sphenoidal or temporal electrode early at the seizure onset. This pattern was predictive of the side of the ipsilateral temporal lobe seizure onset identified by depth recording in 82% of these patients. When exclusively focal on scalp, the predictive value of this pattern was 94%. This number reduced to 67% when mixed focal and nonfocal patterns were present. The interobserver reliability among the three interpreters was excellent. False lateralization of the 5 Hz frequency was seen in 18% of patients. The authors concluded that this pattern was misleading in minority of patients; however, it cannot be used in isolation for seizure localization [114].

Interobserver reliability in localizing ictal scalp EEGs comparing to the ictal data from depth recording was also studied by Spencer et al. [130]. They reviewed 144 seizures in 54 patients recorded by combination of scalp and intracranial electrodes and interpreted by three blinded electroencephalographers. The Kappa statistics, a measurement of index of agreement, found the reliability of lateralization between pairs of EEG interpreters was “fair to good.” However, this measure was “poor to fair” between interpreters when the lobe of seizure onset was considered.

Walczak et al. [116] used the seizure outcome as “gold standard” for the accuracy of the ictal EEG in identifying the epileptogenic zone. In retrospective analysis of 137 scalp ictal EEGs from 35 patients with temporal lobe resection, three blinded electroencephalographers correctly identified the side of the seizure onset in 76–83% of the 119 temporal lobe seizures with Kappa statistics of “fair to good.” In analysis

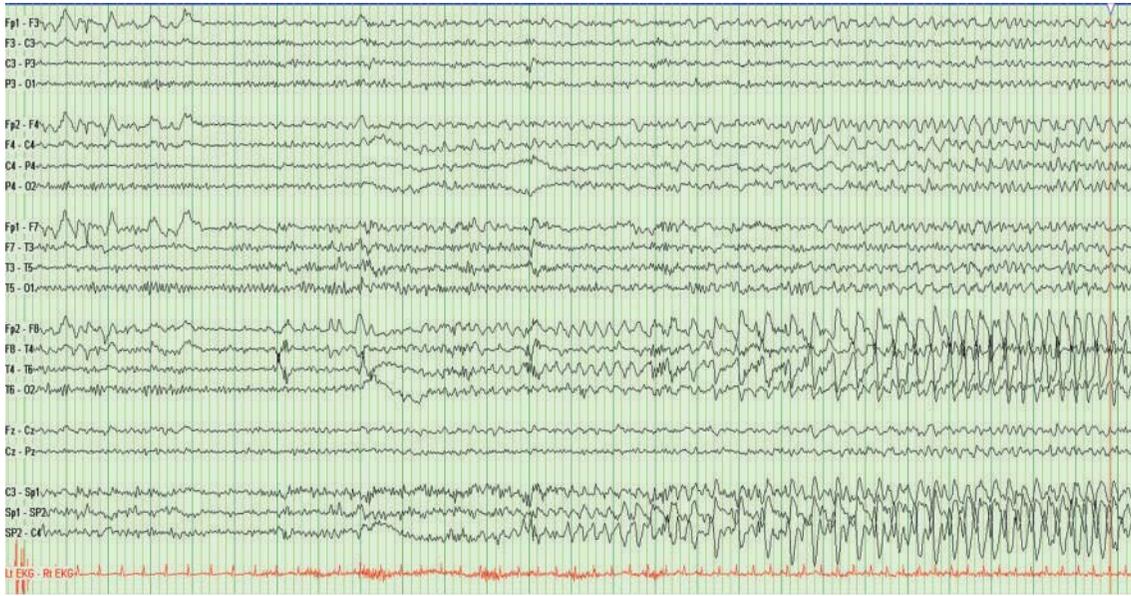


FIGURE 3: A 32-year-old man with right mesial temporal lobe epilepsy. EEG demonstrates generalized and predominantly right-sided electrodecrement followed by buildup of rhythmic activity in the right temporal region. He had a successful surgical result and has been seizure free (HFF = 70, LFF = 1, and sensitivity =  $10 \mu\text{V}/\text{mm}$ ).

restricted to only seizures that had lateralizing features, the accuracy of lateralization was 93–98%. Among individual EEG patterns, alpha theta frequency at the seizure onset was most accurate.

Differentiating mTLE from nTLE by clinical and scalp EEG characteristic could be quite challenging. However, in the latter the EEG changes are more widely distributed, with more involvement of the frontocentral electrodes and more variable frequency and amplitude at the onset [98].

## 11. Seizure Detection by Mathematical Models

Digital EEG technology has been pivotal in improving the detection of spikes and seizures mainly during continuous video/EEG monitoring. Gotman has been one of the pioneers in advancement of seizure detection technology and its progressive improvement and state-dependent algorithms [131]. Spatiotemporal digital filtering has allowed elimination of noncerebral artifacts analysis of the EEG signal at seizure onset improving the detection and lateralization [132, 133]. One has to be careful not to eliminate rhythmic cerebral slow waves when using EEG filters.

There has been much information regarding the localization and the frequency of the seizure onset and propagation using the computerized methodical models such as wavelet transforms [134]. Using a novel wavelet-based algorithm (wavelet packet transform) for real-time detection of epileptic seizures on scalp EEG, we were able to improve the seizure detection sensitivity to 90.5%, a false detection rate of 0.51 h-1 and a median detection delay of 7 seconds. This algorithm could also lateralize the seizure focus in patients with seizures originating from the temporal lobes [135].

## 12. Seizure Propagation

Lieb et al. studied the pattern of spread in 24 patients with mesial temporal lobe seizures who underwent depth electrode study. The authors reported that the seizure propagation and the EEG expression can be influenced by the state of the patient (awake or sleep), the use of anti-seizure drugs and unilateral versus multifocal epilepsy [136]. Medial versus lateral location of the seizure onset and the type of pathology (e.g., HS or neoplasm) also determine the pattern of seizure propagation on scalp EEG in TLE.

The localization of the epileptogenic zone and the spread pattern by simultaneous scalp and intracranial recordings was reported by Sakai et al. [137]. In this study, they recorded the ictal and the spread pattern in 28 medial and 14 lateral temporal onset seizures in 30 patients with mTLE and 8 patients with nTLE. They concluded that ictal discharges originating in medial temporal lobes propagated to the lateral part on the same side and the lateral part of the opposite side via contralateral medial area. Although this gives a reasonable accuracy in predicting the side of the seizure focus, at times the latency of spread to the ipsilateral temporal region is the same or even longer than contralateral spread. This results in observing earlier discharges on the contralateral side. Therefore, the side showing the leading ictal activity may not necessarily be the side of the seizure origin.

## 13. Postictal EEG Changes in mTLE

The ictal onset on scalp recorded EEG can be obscured by variety of artifacts. Therefore, sometimes postictal changes

could provide important information for lateralization of the seizure onset. Postictal EEG changes in TLE could be in the form of unilateral or bilateral slowing. Lateralized postictal slow waves could be present in up to 70% of patients with mTLE. When present, it has a lateralizing value of about 90%. Williamson et al. found lateralized postictal slowing in 45 of 67 patients (67%), and it was always concordant with the side of the seizure origin [98].

Kaibara and Blume [89] in a study of patients with TLE reported postictal changes in 69%. These changes consisted of regional delta activity and regional attenuation or activation of spikes. They were ipsilateral to the side of the seizure onset in all cases. Jan et al. analysed the relationship of the postictal delta activity to the side of the seizure onset in patients with TLE. The two EEG interpreters were blinded to the clinical and EEG data. Lateralized postictal delta was observed in 64% of all ictal EEGs and 76% in at least one record from 22 patients. There was a strong interobserver agreement. When present, the postictal delta activity was concordant with the side of surgery in 96% of the EEGs and strongly predicted the seizure onset [138].

## 14. Intracranial Recordings in mTLE

*14.1. Indications.* In most cases of medial temporal lobe epilepsy standard scalp EEG with the use of sphenoidal electrodes and the MRI evidence of HS will be sufficient to identify the seizure focus prior to surgery. However, considering the limitation of the scalp EEG, that is, contamination with muscle and movement artefact, equivocal scalp EEG changes, interobserver disagreement, and the possibility of false lateralization, the recordings could be obscured or misleading. The EEG recording with placement of the intracranial electrodes was introduced in 1960s and 1970s. King and Spencer described invasive EEG recording in mTLE [139].

Risinger et al. reported that only 19% of auras and 10% of subclinical seizures could have surface EEG expression. Using both surface and depth electrodes, they found that a large number of seizures revealed no scalp EEG expression at the onset when it already appeared on depth electrodes, and scalp EEG showed bilateral and nonlateralizing changes [114].

The advantages and disadvantages of this technique were recently reviewed in the study by Dubeau and MacLachlan [140]. Table 5 summarises the indications for intracranial recordings.

Intracranial recording is artefact free and more specific and has very good temporal resolution [141, 142]. It increases the yield of detecting IEDs when scalp EEG fails. It also allows identification of the seizure focus with more accuracy and reduces the risk of false lateralization. This is particularly important in those patients with ambiguous seizure onset, and with rapid seizure transfer from one to the other temporal lobe. In order to obtain accurate electrophysiological information, a working hypothesis must be developed before proceeding to invasive intracranial recording. Figure 4 demonstrates an example of seizure recorded by subdural electrodes.

TABLE 5: Indications for intracranial EEG recordings [140].

Temporal lobe syndrome with bilateral independent interictal or ictal abnormalities
Discordant data seizures originating from the side contralateral to the MRI abnormality or interictal discharges
Seizures with undetermined side of onset
Mesial versus neocortical seizure onset
Mesial versus onset in the neighbouring structures “temporal plus epilepsies”
Occipitotemporal epilepsy
To avoid false lateralization

In cases of mTLE with severe HS, the EEG changes of the seizure onset may not propagate to the ipsilateral scalp and instead, some seconds later the ictal discharge appears on the contralateral side resulting in false lateralization. False EEG lateralization in patients with temporal lobe seizures was reported as high as 10% [143]. Intracranial recording is crucial in such patients.

Temporal plus (T+) epilepsies has recently been addressed and reviewed by Munari et al. [144], Kahane et al. [15], and Ryvlin and Kahane [14]. In one study of clinical manifestations of insular lobe seizures, temporal lobe surgery alone was unsuccessful in controlling seizures that originated from the insula [145]. Barba et al. [123] retrospectively analysed clinical and EEG findings in 80 consecutive patients who were thought to suffer from nonlesional temporal lobe seizures. Stereotactic intracerebral EEG (SEEG) recordings could identify two groups of “purely temporal” (TL group) and temporal plus (T+ group). They concluded that the general clinical features or MRI data including the presence of HS could not differentiate the two groups. However, both ictal clinical symptoms and scalp EEG findings significantly differentiated TL from T+ patients.

When interictal and ictal EEG were correlated with MRI lesions in focal epilepsy, Remi et al. found the localization of IEDs was most congruent with MRI lesions in the temporal lobe compared to the lesions in other lobes. Temporal lobe IEDs are also frequently present in extratemporal lobe epilepsies; therefore, temporal IEDs could be misleading [146].

*14.2. The Types of Intracranial Electrodes.* They include depth, subdural, epidural, and foramen ovale electrodes. Depth electrodes are inserted through a bur hole and can be removed at the bedside with caution. They penetrate the brain and lie within the cortex. They are utilized for recording from buried cortex such as amygdala and hippocampus and sometimes orbitofrontal cortex. Foramen ovale electrodes are similar to the depth electrodes and are inserted under fluoroscopy in radiology or in the operating room.

Subdural electrodes lie on the pial surface of the brain. The strips have a single or double row of contacts. They can be placed through a bur hole and lie directly to the proximity of the brain. They record from gyral surface over multiple areas and from the epidural or subdural spaces. Subdural

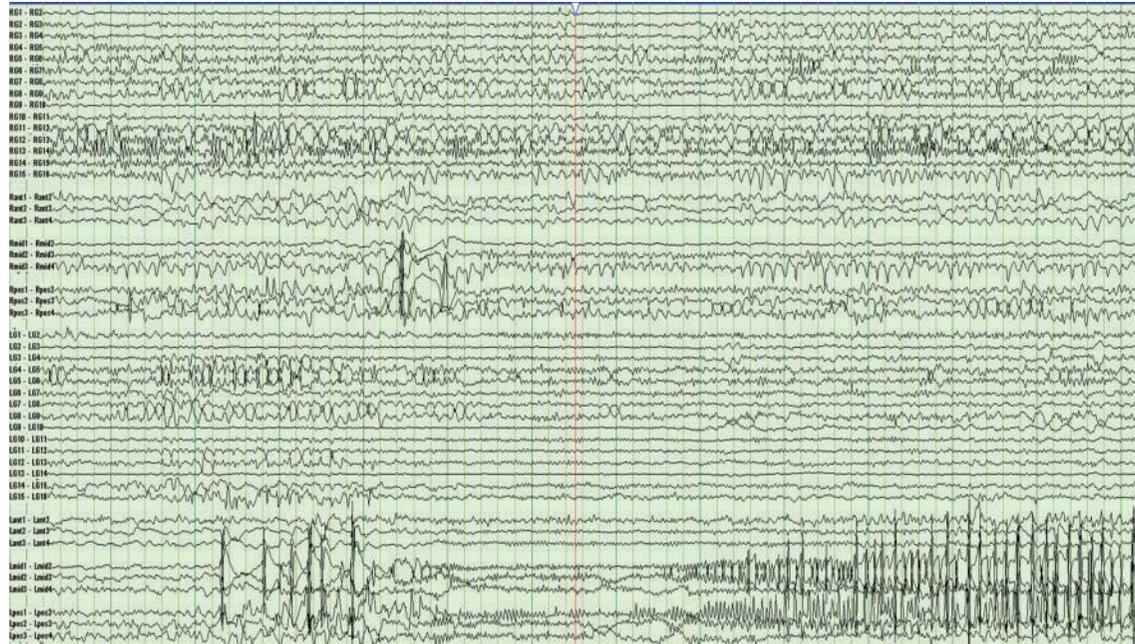


FIGURE 4: A seizure recorded using subdural electrodes. The top 24 channels are from the grid and subtemporal electrodes on the right. The lower 24 channels are from the left side. The lowest six channels are from the left subtemporal contacts. EEG demonstrates high-amplitude ictal discharges over the left anterior contacts of the middle subtemporal electrode (hippocampus) followed by high-frequency discharges over all eight contacts of the two subtemporal and the two contacts of the most anterior subtemporal electrode (amygdala) (HFF = 70, LFF = 1, and sensitivity =  $150 \mu\text{V}/\text{mm}$ ).

grids are larger in size and monitor a larger area of cortex. They are also used for brain mapping. Subdural strips are better tolerated than subdural grids and can be removed at the bed side; however, grids have to be removed in the operating room.

The chronic intracranial electrodes have 1–4% risk of morbidity and mortality. This includes haemorrhage and infection; brain swelling and herniation [55].

**14.3. Intracranial EEG Features in mTLE.** Pacia and Ebersole [147] in a comprehensive study of combined and simultaneous scalp-intracranial study using depth, subdural strips and grids, analysed the intracranial EEG features responsible for producing the three different scalp EEG manifestations (types 1, 2, and 3). They observed that seizures starting at the hippocampal contacts of the depth electrode, showed ictal rhythms recorded from the mesial contacts of the subdural strip electrodes. Simultaneous scalp recording showed no representation or diffuse disruption of the background.

The 6–7 Hz rhythm only appeared in the inferior and basal scalp electrodes when the seizure spread to the basal and inferolateral subdural contacts. The authors concluded that 5–9 Hz frequency recorded on the scalp (type 1a) electrodes was the result of the synchronous recruitment of the adjacent inferolateral temporal neocortex, and it was highly associated with seizure onset in the hippocampus, but it was not a direct manifestation of the hippocampal ictal activity. Seizures beginning in the temporal neocortical region did

not have this manifestation until the hippocampus was involved.

Type 2 pattern had slower (<5 Hz) frequency and mostly generated in the neocortical structures. There was an initial focal or regional low-voltage 20–40 Hz rhythm and widespread background flattening on interictal electrodes. On the scalp, only attenuation of the normal rhythm was observed, and it was followed by a slow and irregular rhythm. By intracranial EEG this type showed an extrahippocampal and probably temporal neocortical ictal origin. Interestingly, three of the patients with mesial temporal onset seizures showed similar scalp EEG manifestations.

The type 3 scalp EEG pattern, characterized by diffuse slowing or attenuation of the background, without typical rhythmic patterns resulted from seizure activity confined to the hippocampus in four of the seven and with the neocortical seizure onset in the other three patients. This scalp seizure onset pattern was seen when there was rapid seizure propagation to the contralateral temporal lobe or when cortical activity failed to achieve widespread synchrony.

Location of the seizure onset is also related to the degree of pathology in the medial temporal region. In a depth electrode study, the ictal discharges were restricted to the hippocampus in severe HS [148]. In other medial temporal pathologies such as tumours, there are often more than one ictal onset zone usually detected in the tissue adjacent to the tumor rather than within the tumor or in the mesial temporal structures; therefore, the accurate localization of

the ictal onset is critical for complete surgical resection of the epileptogenic zone and better surgical outcome [149].

## 15. Magnetoencephalography (MEG)

MEG has been used for localization of the epileptic spikes. EEG records the extracellular electrical current which is subject to distortion by different intervening tissues. MEG detects magnetic fields generated by neurons in the walls of cortical sulci. These neurons produce current dipoles tangential to the skull. However, currents produced by neurons at the tip of the gyri that are radial to the skull do not influence MEG. The intervening tissues can distort the electrical currents produced in the sulci and gyri when recorded by EEG. However, MEG can easily record magnetic fields without distortion by different tissues such as bone, muscle, and skin. In addition, MEG measurements are absolute without active reference contamination compared to differential measurement by EEG. Several studies have reported the benefits of MEG in clinical epilepsy and TLE [150, 151].

MEG could help to reduce the need for invasive monitoring in focal epilepsy. It has been concordant with localization by intracranial electrodes [152]. MEG has also been most helpful in non-lesional extratemporal lobe epilepsy [153]. Ebersole et al. found MEG spikes in the sublobar temporal and frontal regions in 30 patients. Half of these patients did not have focal abnormality such as hippocampal atrophy in their MRI/CT studies [154].

MEG dipole modeling identified two patient groups in mesial temporal lobe epilepsy. In one group spikes were modeled by anterior temporal vertical dipoles indicating epileptic activity in the medial basal temporal area and in another group spikes modeled by anterior temporal horizontal dipoles indicating the epileptic activity in the temporal pole and lateral temporal area. The first group had more consistent localization in the ipsilateral temporal lobe; however, half of the other group had bitemporal spikes on CV-EEG monitoring [155].

MEG is another noninvasive technology that provides simple method of recording the brain activity with spatial and temporal resolution of spikes superior but complementary to traditional EEG. However considering the high cost of MEG, EEG is still an inexpensive and easily available technology to monitor the activity of the brain.

## 16. Conclusion

EEG has been pivotal in the diagnosis, classification, and management of epilepsy since the early part of the last century. It has a special role in the presurgical evaluation of patients with focal epilepsy refractory to medications. Serial EEG is sensitive and specific for the diagnosis of epilepsy. In patients who withdraw medications after a period of seizure freedom following surgery, the presence of IEDs on EEG could be predictive of seizure recurrence.

In mTLE, scalp EEG in most instances can lateralize and localize the seizure focus. Other than epileptiform discharges, abnormal lateralized EEG patterns such as TIRDA

could be quite specific for the ipsilateral seizure onset. Interictal spikes or sharp waves are often unilateral; however, in about the third of patients they are bitemporal independent.

Ictal EEG patterns appear in the form of background attenuation, start-stop phenomena, 5–10 Hz rhythmic sinusoidal waveforms or repetitive sharp waves or spikes. The 2–5 Hz lateralized activity is often due to lateral neocortical focus. Postictal slowing if lateralized, is often ipsilateral to the seizure focus.

Invasive recording with intracranial electrode placement is required when the information from the surface recording is insufficient or nonconcordant for detection of the epileptogenic zone. The indications were highlighted in this paper. Implanted subdural strips, grids, or depth electrodes can provide information from medial or lateral temporal electrodes and could also help identifying temporal plus epilepsies with clinical semiology similar to mTLE.

The combination of clinical and MRI information with the EEG findings are most useful in identifying the seizure focus for surgical treatment of mesial temporal lobe epilepsy.

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## Review Article

# Microsurgical Anatomy of the Temporal Lobe and Its Implications on Temporal Lobe Epilepsy Surgery

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Received 30 November 2011; Revised 6 February 2012; Accepted 7 February 2012

Academic Editor: Seyed M. Mirsattari

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*Objective.* We review the neuroanatomical aspects of the temporal lobe related to the temporal lobe epilepsy. The neuronal, the ventricular, and the vascular structures are demonstrated. *Methods.* The previous articles published from the laboratory of the senior author are reviewed. *Results.* The temporal lobe has four surfaces. The medial surface has a complicated microanatomy showing close relation to the intraventricular structures, such as the amygdala or the hippocampus. There are many white matter bundles in the temporal lobe showing relation to the extra- and intraventricular structures. The surgical approaches commonly performed to treat temporal lobe epilepsy are discussed under the light of these data. *Conclusion.* A thorough knowledge of the microanatomy is necessary in cortical, subcortical, and intraventricular structures of the temporal lobe to achieve better results.

## 1. Introduction

This paper describes the anatomic features of the temporal lobe which are important in the most commonly performed surgical approaches for temporal lobe epilepsy (TLE): the anterior temporal lobectomy (ATL), the transcortical selective amygdalohippocampectomy (TCAH), and the transylvian selective amygdalohippocampectomy (TSAH). The differences between these approaches and the expected outcomes are best understood by knowing their microanatomical differences.

Two main objectives in epilepsy surgery are removal of the epileptogenic tissue and avoidance of surgical morbidity. Three approaches will be reviewed from the perspective of (1) avoidance of visual pathways (optic tract, lateral geniculate body Meyer's loop, and optic radiations), (2) white matter pathways involved in the neurocognitive sequelae, (3) extent of the incision to the temporal stem, (4) extent of amygdalotomy, and (5) avoidance of vascular injury.

## 2. Neural Features

*2.1. Cortical Anatomy.* The temporal lobe has four surfaces: lateral, medial, superior, and inferior (Figure 1(a)).

*2.1.1. Lateral Surface.* The lateral cortical surface of the temporal lobe is located below the sylvian fissure. While its anterior and inferior limits are natural bone structures, the temporal lobe is separated posteriorly from the occipital lobe by the lateral parietotemporal line, an imaginary line connecting the preoccipital notch and the parietooccipital sulcus, and it is also separated from the parietal lobe by the occipitotemporal line, a line connecting the most posterior limit of sylvian fissure with the lateral parietotemporal line (Figure 1(a)) [1]. The lateral surface of temporal lobe consists of three gyri: superior, middle, and inferior, which are separated by two parallel sulci: superior and inferior. While the superior temporal sulcus lies between the superior and middle temporal gyri, the inferior temporal sulcus courses

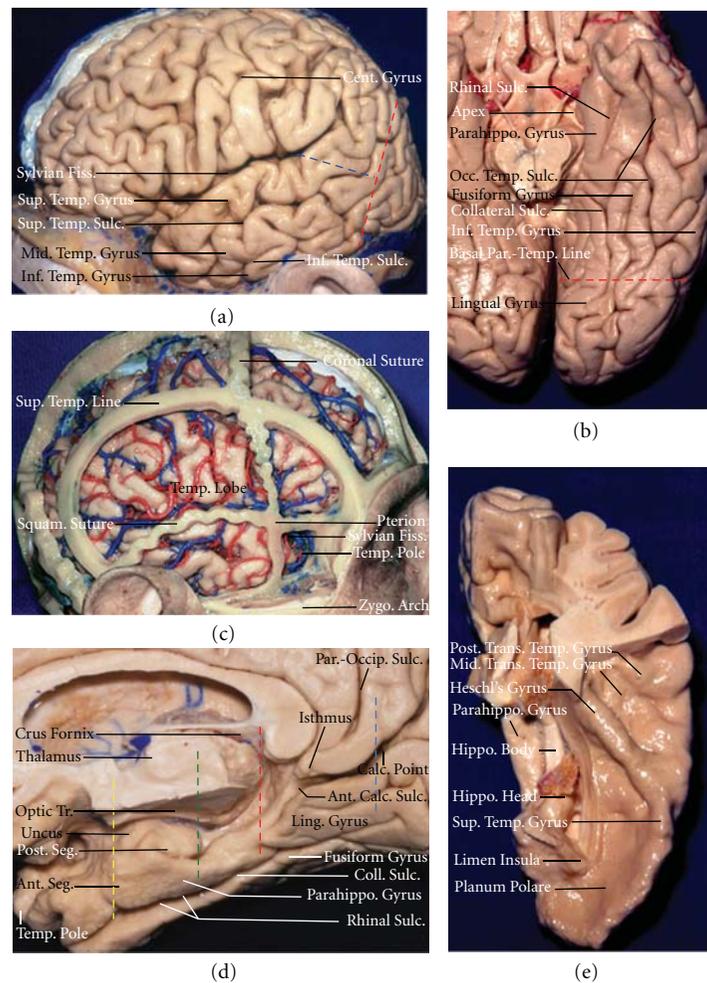


FIGURE 1: (a) *Lateral view of the left hemisphere.* The lateral surface of the temporal lobe consists of three parallel gyri: superior, middle, and inferior temporal gyri. These gyri are separated by the superior and inferior temporal sulci. The lateral parietotemporal line (red dashed line), an imaginary line connecting the preoccipital notch and parietooccipital sulcus, separates the temporal and occipital lobes, and the occipitotemporal line (blue dashed line), an imaginary line connecting the posterior margin of the sylvian fissure with lateral parietotemporal line, separates the temporal and parietal lobes. (b) *Inferior view of the left temporal lobe.* The basal surface of the temporal lobe consists of, from lateral to medial, the inferior margin of the inferior temporal gyrus, the fusiform gyrus, and the parahippocampal gyrus. The fusiform gyrus is separated laterally from the inferior temporal gyrus by the occipitotemporal sulcus, and medially from the parahippocampal gyrus by the collateral posteriorly and rhinal sulci anteriorly, which are not continuous in every case. The basal parietotemporal line connecting the preoccipital notch and inferior end of parietooccipital sulcus separates the temporal and occipital lobes at the basal surface. (c) *The relationship of the temporal lobe with bony structures in a right hemisphere.* The cranial sutures and the superior temporal line have been preserved, and the dura has been opened. The pterion is located at the lateral margin of the sphenoid ridge near the junction of the coronal, squamosal, and frontosphenoid sutures and the lateral end of the greater sphenoid wing and stem of the sylvian fissure. The squamosal suture follows the anterior part of the posterior limb of the sylvian fissure before turning downward, at the level of the postcentral and supramarginal gyri, to cross the junction of the middle and posterior third of the temporal lobe. The pole of the temporal pole fits into the cupped inner surface of the greater wing of the sphenoid bone. Most of the lateral surface of the temporal lobe is positioned deep to the squamous part of the temporal bone, except, the posterior part of the lateral surface extending deep to the parietal bone. The basal surface of the temporal lobe sits on the floor of the middle fossa and is positioned at the level of the upper edge of the zygomatic arch. (d) *The medial view of the temporal lobe in a right hemisphere.* This region is divided into three segments: anterior, middle, and posterior. The anterior segment begins at where the rhinal sulcus turns upward at the posterior edge of the temporal pole (yellow interrupted line) to a vertical line crossing the posterior edge of the uncus (green interrupted line), the middle segment extends from this point to the level of the quadrigeminal plate (red interrupted line), and the posterior segment extends from the quadrigeminal plate to the calcarine point (blue interrupted line) located at the junction of the parietooccipital and calcarine sulci. (e) *The superior view of the left temporal lobe.* This surface facing the the sylvian fissure is divided, from anterior to posterior, in three portion: the planum polare, the anterior transverse temporal gyrus, referred to as the Heschl's gyrus, and the planum temporale containing the middle and posterior transverse temporal gyri. Ant.: anterior; Cent.: central; Calc.: calcarine; Fiss.: fissure; Hippo.: hippocampus; Inf.: inferior; Mid.: middle; Occ.: occipital; Parahippo.: parahippocampal; Par.-Occip.: parieto-occipital; Par.-Temp.: parietotemporal; Post.: posterior; Squam.: squamous; Sulc.: sulcus; Sup.: superior; Temp.: temporal; Trans.: transvers Tr.: tract; Zygo.: zygomatic.

between the middle and the inferior temporal gyri. The superior temporal gyrus is continuous with the transverse temporal gyri on the temporoopercular surface. The angular gyrus, a parietal lobe structure, caps the most posterior end of the superior temporal sulcus. The temporal gyri, especially the inferior temporal gyrus, are often separated into small parts by sulcal bridges (Figure 1(a)). Ono et al. stated that the inferior temporal sulcus is separated into three or more parts in 92% of cases [2].

**2.1.2. Superior Surface.** The superior surface of temporal lobe faces the sylvian fissure and the sylvian cistern. This surface, from anterior to posterior, has three parts: the planum polare, the anterior transverse temporal gyrus or Heschl's gyrus, and the planum temporale (Figure 1(e)). The planum polare is a relatively flat surface without any gyri on the anterior part of the superior surface. It is limited posteriorly by the Heschl's gyrus, the most anterior of the transverse temporal gyri, which blends around the margin of the sylvian fissure into the superior temporal gyrus. Posterior to the Heschl's gyrus lies the planum temporale, which consists of middle and posterior transverse temporal gyri [3].

The sylvian fissure is a very important landmark on the lateral surface of the cerebrum. It crosses deep between opercular surfaces of the frontal, parietal, and temporal lobes reaching the carotid cistern anteriorly and the insular surface posteriorly. The superficial part of the sylvian fissure has a stem and three rami. The stem begins at the anterior clinoid process in the frontobasal area, extends lateral and adjacent to the sphenoid ridge, and divides at the surface into three rami: anterior horizontal, anterior ascending, and posterior. The deep part of the Sylvian fissure, referred to as the Sylvian cistern, has two compartments: the sphenoidal and the operculoinsular. The sphenoidal compartment is positioned between the carotid cistern medially, the posterior part of the frontoorbital area superiorly and the planum polare of the temporal lobe, and the amygdala inferiorly. The operculoinsular compartment is formed by two clefts: opercular and insular. The opercular cleft lies between the opercular surfaces of frontal and parietal lobes superiorly, and opercular surface of the temporal inferiorly. The insular cleft has an upper lip that lies between the frontal and the parietal lobes and the insular surface, and a lower lip that lies between the temporal lobe and the insular surface [4].

**2.1.3. Inferior Surface.** The sulci and gyri, which constitute the inferior surface of the temporal lobe, are continuous with the basal surface of the occipital lobe (Figure 1(b)). This surface is formed by three gyri and two longer and one shorter sulci [2, 5]. Of these longer sulci, the occipitotemporal sulcus courses laterally and separates the lower surface of the inferior temporal gyrus and the fusiform gyrus. The other longer sulcus, the collateral sulcus, separates the fusiform gyrus from the medially placed parahippocampal gyrus. The rhinal sulcus, the shorter sulcus, courses at the lateral edge of the uncus between the uncus and the fusiform gyrus and may or may not be continuous with the collateral sulcus. The indentation of the collateral sulcus towards the temporal

horn generates a prominence at the floor of the temporal horn, called the collateral eminence, and at the floor of the atrium, called the collateral trigone (Figures 3(f), 5(a), 5(e), and 5(f)).

**2.1.4. Medial Surface.** The medial surface of the temporal lobe, or medial temporal region (MTR), is the most complicated of cortical surfaces. For a better understanding, Fernández-Miranda et al. divided this surface into three segments: anterior, middle, and posterior [6]. The anterior segment begins where the rhinal sulcus turns superiorly at the anterior edge of the uncus and ends at the posterior limit of the uncus; the medial segment begins at the posterior edge of the uncus and ends at the level of the quadrigeminal plate; the posterior segment begins at this point and ends at the calcarine point where the parietooccipital and calcarine sulci join (Figure 1(d)).

The anterior MTR is formed mostly by the uncus and the entorhinal cortex. The uncus has an anterior and a posterior segments, which come together at a medially directed prominence, the apex of the uncus. The anterior segment of the uncus belongs to the parahippocampal gyrus and contains two gyri: the semilunar gyrus and the ambient gyrus. The semilunar gyrus is positioned on the upper part of the anterior segment, above the cortical nucleus of amygdala. The semilunar gyrus is separated from the anterior perforated substance by the entorhinal sulcus and optic tract superolaterally and from the ambient gyrus by the semiannular sulcus medially and anteriorly. The ambient gyrus, formed mainly by the entorhinal cortex, occupies the anterior and inferior parts of this segment (Figures 2(a)–2(c)). The posterior segment of uncus has two parts, superior and inferior, which are separated by the uncus sulcus. The inferior part, formed by the parahippocampal gyrus, is occupied by the entorhinal area. The entorhinal area also occupies the inferior surface of the anterior segment of the uncus and is limited on the lateral side by the rhinal sulcus anteriorly and the collateral sulcus posteriorly. The posterior limit of the entorhinal area is accepted as the posterior limit of the uncus. The entorhinal area has an important role in afferent and efferent connections of the hippocampus [1]. The superior part of the uncus is formed by the hippocampal head and has the fimbria of fornix at its posterior limit. This part is the site of three small gyri, the uncinata gyrus, the band of Giacomini, and the intralimbic gyrus. The band of Giacomini is the continuation of the dentate gyrus. The intralimbic gyrus contains the CA3 and the CA4 sectors of the hippocampal formation. The anterior segment of the uncus faces the carotid cistern, the internal carotid artery (ICA), and the proximal M1 segment of middle cerebral artery (MCA); the apex of the uncus faces the oculomotor nerve; the posterior segment of the uncus faces the crural cistern, the posterior cerebral artery (PCA) below and the anterior choroidal artery (AChA) above, and the crus cerebri.

The middle MTR, when viewed medially, is formed from inferior to superior by the parahippocampal gyrus, the dentate gyrus, and the fimbria of fornix (Figure 2(a)). The fimbriodentate sulcus separates the fimbria of fornix

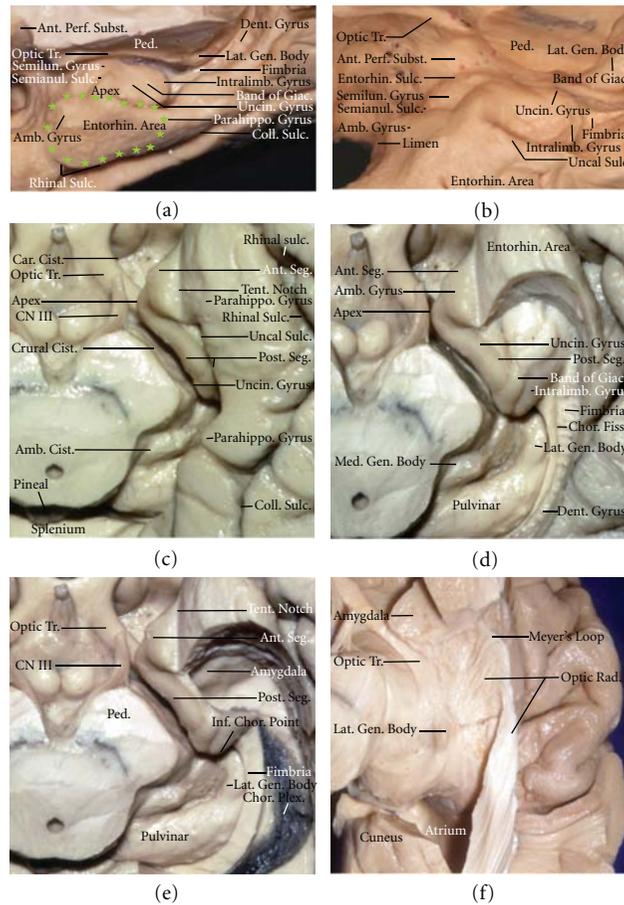


FIGURE 2: (a) *Enlarged view of the anterior and middle segments of the medial temporal region (MTR).* The anterior segment is formed by the uncus and the entorhinal area. The uncus is divided into anterior and posterior segments meeting at the medially directed apex. The entorhinal area shown with green stars occupies the inferior surfaces of the anterior and posterior segments of the uncus but does not have a clearly demarcated borders. The parahippocampal gyrus forming the cortical component of the middle segment of the MTR has 3 surfaces: inferior, medial, and superior. The superior surface faces the lower surface of the pulvinar across the upper part of the ambient cistern and has superiorly the dentate gyrus and the fimbria of the fornix. (b) *Enlarged view of the anterior segment of the MTR.* The anterior segment of the uncus contains the semilunar gyrus and the ambient gyrus. The semilunar gyrus covers the cortical nucleus of the amygdala. The ambient gyrus located anterior and inferior to the semilunar gyrus is separated by the semiannular sulcus from it. The posterior segment of the uncus is divided into an upper and lower part by the uncal sulcus. The upper part is formed by the medially folded extraventricular (cisternal) head of the hippocampus, and the lower part is formed by the anterior part of the parahippocampal gyrus. The intralimbic gyrus forms the posterior end of the uncus and is the site of attachment of the fimbria. (c–f) *Stepwise dissection of the basal surface of the temporal lobe.* (c) The anterior segment of the uncus faces the carotid cistern, and posterior segment faces the crural cistern and the cerebral peduncle. The uncal apex is positioned lateral to the oculomotor nerve. The cortical component of the middle MTR formed by the parahippocampal gyrus faces the midbrain across the ambient cistern. (d) The part of the posterior uncal segment located below the uncal notch has been removed to expose the lower surface of the upper part of the posterior uncal segment formed by the extraventricular head of the hippocampus. The fimbria is situated above the dentate gyrus. The choroidal fissure, located between the thalamus and fimbria, extends along the lateral edge of the lateral geniculate body and pulvinar. (e) The hippocampus and dentate gyrus have been removed while preserving the fimbria and the choroid plexus attached along the choroidal fissure. The amygdala forms the anterior wall of the temporal horn and fills most of the anterior segment of the uncus. The inferior choroidal point, located at the lower end of the attachment of the choroid plexus in the temporal horn, is positioned behind the head of the hippocampus, anterior to the lateral geniculate body, and lateral to the posterior edge of the cerebral peduncle. (f) The fimbria and choroid plexus have been removed to expose the roof of the temporal horn. The tapetum fibers forming the roof of the temporal horn have been removed to expose the optic radiations arising from the lateral geniculate body and passing across the roof and around the lateral wall of the temporal horn. Amb.: ambient; Ant.: anterior; Car.: carotis; Chor.: choroidal; Cist.: cistern; CNIII.: oculomotor nerve; Coll.: collateral; Dent.: dentate; Entorhin.: entorhinal; Fiss.: fissure; Gen.: geniculate; Giac.: Giacomini; Inf.: inferior; Intralim.: intralimbic; Lat.: lateral; Parahippo.: parahippocampal; Ped.: peduncle; Perf.: perforated; Plex.: plexus; Post.: posterior; Rad.: radiation; Seg.: segment; Semianul.: semianular; Semilun.: semilunar; Subst.: substantia; Sulc.: sulcus; Tent.: tentorial; Tr.: tract; Uncin.: uncinete.

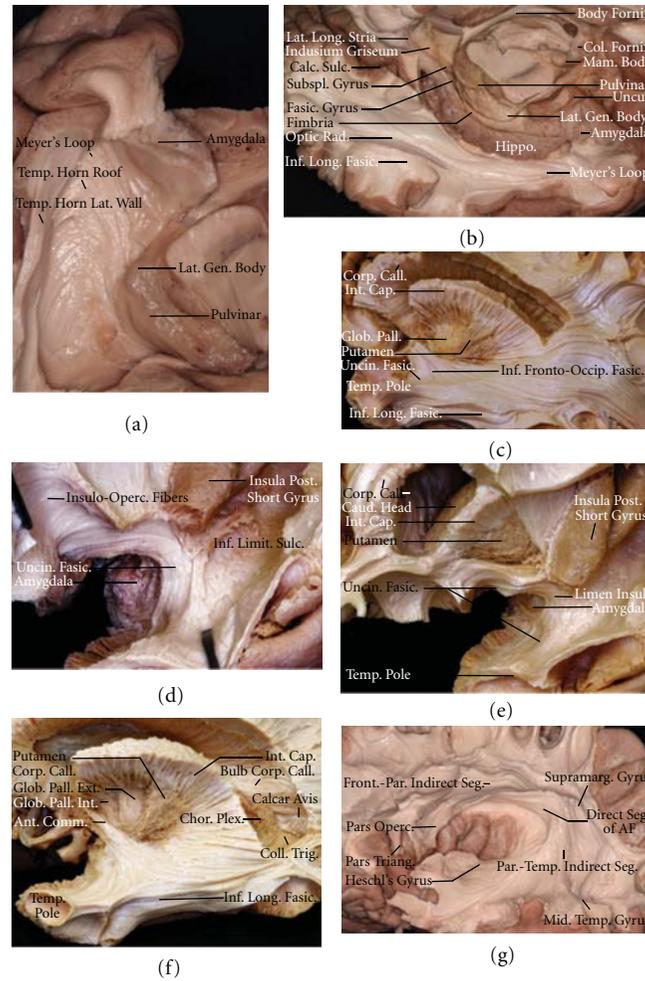


FIGURE 3: (a) *The inferior view of the roof of the temporal horn.* The roof and the lateral wall of the temporal horn are formed by the tapetum fibers of the corpus callosum, which is covered by optic radiations with the only exception of the anterior portion of the lateral wall. Optic radiations arise from lateral geniculate body as three unseperable bundles. The anterior bundle making a prominent anterior curve is referred to as the Meyer's loop. (b) *Inferomedial view of the left hemisphere.* The cortical gray matter of the isthmus and the lingual, parahippocampal, and fusiform gyri have been removed. The cingulum travels inside the isthmus and parahippocampal gyrus. The fasciolar gyrus and its continuation, the subsplenial gyrus, form part of the hippocampal tail below the splenium. (c) *Superolateral view of the temporal subcortical structures, the central core, and the lateral ventricular space.* The insula and the underlying extreme and external capsules have been removed to expose the central core. The internal capsule course between the caudat nucleus medially and lentiform nucleus laterally. The corpus callosum forms the anterior wall and the roof of the lateral ventricle. The uncinate fasciculus (UF) and the inferior occipitofrontal fasciculus (IFOF) form the temporal stem. The UF forming the anterior part of the temporal stem interconnects the orbitofrontal cortex and the anterior part of the temporal lobe. (d) *Closer view of the UF.* The UF travels in the extreme and external capsules and deep to the limen insula to connect the the orbitofrontal cortex to the temporal pole and the amygdala. (e) *The view of the left hemisphere.* The anterior and middle short gyri of the insula and the callosal fibers forming the anterior portion of the roof of the lateral ventricle have been removed to expose the central core. The lateral wall of the frontal horn is formed by the head of the caudate nucleus situated medial to the internal capsule. The lentiform nucleus formed by the putamen and the globus pallidus is located lateral to the internal capsule. (f) The fibers contributing to the lateral wall of the lateral ventricle and the atrium have been removed. The medial wall of the atrium is built by two prominences. The superior prominence, referred to as the bulb of corpus callosum, is formed by the fibers in the forceps major, and the inferior prominence, referred to as the calcar avis, is the bulge of the calcarine sulcus to the ventricular space. Globus pallidus has an external and internal parts separated by the internal medullary lamina. The anterior commissure is located ventral to the globus pallidus. The inferior longitudinal fasciculus (ILF) connecting the anterior temporal lobe to the posterior part of the temporal lobe and occipital lobe is situated lateral to the optic radiations at the lateral wall of the temporal horn. (g) *The view of the superior longitudinal fasciculus (SLF) in a left hemisphere.* The SLF consists of three segments: a frontoparietal segment, a parietotemporal segment, and a frontotemporal segment, referred to as the Arcuate fasciculus providing a direct connection between the speech areas located at the inferior frontal gyrus and the posterior part of the superior temporal gyrus. AF: Arcuate Fasciculus; Ant.: anterior; Calc.: calcarine; Call.: callosum; Cap.: capsule; Chor.: choroidal; Col.: column; Coll.: collateral; Comm.: commissure; Corp. Corpus; Ext.: external; Fascic.: fasciculus; Front.-Occip.: fronto-occipital; Front.-Par.: frontoparietal; Gen.: geniculate; Glob.: globus; Hippo.: hippocampus; Inf.: inferior; Insulo-operc.: insulo-opercular; Int.: internal; Lat.: lateral; Long.: longitudinal; Mam.: mamillary; Mid.: middle; Operc.: operculum; Pall.: pallidus; Post.: posterior; Rad.: radiation; Seg.: segment; Subspl.: subsplenial; Sulc.: sulcus; Supramarg.: supramarginal; Temp.: temporal; Triang.: triangular; Uncin.: uncinate.

and the dentate gyrus, and the hippocampal sulcus separates the dentate gyrus and the parahippocampal gyrus. In this region, the subiculum is positioned on the superior surface of the parahippocampal gyrus. The presubiculum, a six-layered modified cortex between the subiculum and the cortex of the parahippocampal gyrus, occupies the medial surface of the parahippocampal gyrus.

The posterior MTR is formed by the posterior end of the parahippocampal gyrus, which is divided by the anterior end of the calcarine sulcus into the isthmus of the cingulate gyrus superiorly and the lingual gyrus inferiorly. Functionally, the parahippocampal gyrus shows a closer functional relationship with the isthmus of the cingulate gyrus, because the cingulum bundle passes from the isthmus into the parahippocampal gyrus. Superiorly, the fimbria of the fornix courses posteriorly to become the crus of the fornix, which wraps around the posterior aspect of the pulvinar. The hippocampal tail passes posterior to blend into the fasciolar gyrus, just below the splenium of the corpus callosum (Figure 3(b)). The quadrigeminal cistern is located medial to the posterior MTR.

**2.2. Subcortical Anatomy.** The main debate in selecting the best surgical approach for temporal epilepsy, other than the long-term seizure control, focuses on two topics: damage to the optic radiations and memory deficit after the surgery. However, there are clinical series that favor different types of surgery understanding the microanatomy of white matter bundles is important to achieving better results [7–11].

The optic radiations, the geniculocalcarine pathway, have a complex anatomy [12–14]. The visual input is carried to the lateral geniculate body (LGB) of the thalamus via the optic nerve, the optic chiasm, and the optic tract. The LGB is located on the inferolateral side of the thalamus and just posterior to the cisternal side of the inferior choroidal point. The fibers divide into three bundles after leaving the LGB. The posterior bundle passes posteriorly to reach the superior lip of the calcarine sulcus without making any anterior curve. The middle bundle makes a partial anterior curve on its course to the calcarine cortex, and the anterior bundle of optic radiations makes a prominent anterior curve, referred to as the Meyer's loop, at the roof of the temporal horn on its way to the inferior lip of the calcarine sulcus. Damage to the Meyer's loop causes an upper contralateral quadrantanopia. The optic radiations are separated from the temporal horn by a thin layer of tapetal fibers originating from the corpus callosum. The optic radiations completely cover the roof of the temporal horn and exceed the anterior wall of the temporal horn by a few millimeters. They also cover the lateral wall of the temporal horn except its anterior part [12–14]. At the level of the atrium, optic radiations cover only the lateral wall; the medial wall of the atrium is always free from the optic radiations [15].

The uncinate fasciculus (UF) and inferior longitudinal fasciculus (ILF) also have important role in epilepsy surgery because of their importance in memory function. The UF connects the anterior temporal lobe with the orbitofrontal cortex by forming a curve deep to the limen insula and courses within the ventral extreme and external capsules. The

UF occupies the anterior part of the temporal stem (Figures 3(c)–3(e)) [16]. Its functions are not fully understood [17], but the orbitofrontal cortex and the anterior temporal lobe are reported to have an important role in recognizing faces, actions, and objects and also emotion [18–20].

The ILF courses adjacent to the inferior part of the lateral wall of the temporal horn and is located lateral and inferior to the optic radiations (Figures 3(c) and 3(f)) [21]. The ILF connects the anterior temporal lobe to the fusiform gyrus and dorsolateral parts of the occipital lobe. It is suggested that the ILF has a role in learning and remembering visual stimuli. Cohen et al. stated that the process of learning to read occurs by remembering visual stimuli of words. They suggested that the posterior part of the occipitotemporal sulcus referred to as the “visual word form area” is involved in this process [22]. Therefore, the ILF can be important in learning to read. It was debated, until recently, whether the ILF consists of only long horizontal fibers; however, Catani et al. have shown in their DTI study that the ILF consists of both long horizontal fibers (direct part) and interconnecting U fibers (indirect part) [23].

The arcuate fasciculus (AF) is considered to be a subsegment of the superior longitudinal fasciculus [24, 25]. The structure of this white matter bundle was further detailed in a DTI study by Catani et al. [26]. In their study, they proposed that the AF consists of two indirect parts and one direct part. The first indirect part connects the inferior frontal gyrus to the supramarginal gyrus, and the second indirect part connects the supramarginal gyrus to the posterior part of superior temporal gyrus. The direct part of the AF is proposed to connect the inferior frontal gyrus to the posterior areas by coursing dorsal to the insula by forming an arch (Figure 3(g)). The AF has a major role in language processing, which is thought to involve both a ventral pathway and a dorsal pathway [27]. It is suggested that the AF forms the dorsal pathway and plays a role in the phonological part of language [28]. This subcortical structure functions in the mapping of sound into articulation [29]. Therefore, damage to the AF causes a deficit in the production of speech or appropriate words.

The inferior occipitofrontal fasciculus (IOFF) plays another crucial role in language processing. The IOFF connects the inferior frontal cortex and the dorsolateral prefrontal cortex to the posterior part of the inferior surface of the temporal lobe and to the parts of the occipital lobe superior to the calcarine sulcus. From a functional point, the ventral pathway connecting areas known to have a role in picture naming and object recognition has a semantic role in the naming of sounds or recognition of speech [30, 31]. In a previous report from the laboratory of the senior author, it was shown that the IOFF occupies the ventral part of the extreme and external capsules and the ventral claustrum (Figure 3(c)) [16].

The IOFF is situated at the posterior two-thirds of the temporal stem. White matter tracts connecting the temporal lobe with other parts of the brain, such as the insula, basal ganglia, and frontal and parietal lobes, course through temporal stem. In the transylvian route to the MTR, the IOFF may be damaged with the incision to the inferior

limiting sulcus. Ebeling and von Cramon [32] stated that the temporal stem is the area between the roof of the temporal horn and the inferior limiting sulcus. On the other hand, Choi et al. described the temporal stem as the area between the inferior limiting sulcus, limen insula, entorhinal sulcus, and tail of caudate nucleus [33]. According to this organization, the following fiber tracts are included in the temporal stem: the extreme capsule, the UF, IOFF, the anterior commissure, the ansa peduncularis, and the inferior thalamic peduncle, which includes optic radiations. Separation of these white matter tracts, located around posterior limit of the inferior limiting sulcus, is very difficult. This intermixed structure of fiber tracts, including the IOFF, optic radiations, the anterior commissure, and the ILF, is referred to as the sagittal stratum.

**2.3. Ventricular Anatomy.** The anatomy of the temporal horn and atrium will be discussed with their relationship to the three parts of the MTR [6, 34].

The anterior part of the temporal horn is located lateral to the anterior MTR. The posterior limit of this part is the inferior choroidal point, which is the entry point of the AChA into the temporal horn in most cases (Figures 4(a), 4(f), 5(f), and 5(g)) [6]. The inferior choroidal point is located at the lower end of the attachment of the choroid plexus and is positioned just behind the head of the hippocampus. The uncus recess is situated anterior to the hippocampal head and separates it from the amygdala. The uncus recess is the intraventricular counterpart of the uncus apex.

The amygdala sits in the lateral part of the anterior segment of the uncus. It forms the anterior wall and the anterior part of the roof of the temporal horn. The bulge of the amygdala to the ventricle is the intraventricular representation of the semilunar gyrus, which occupies the anterior segment of the uncus. Note that the amygdala in this region is the temporal amygdala and contains the basolateral, the corticomедial, and the central nuclei groups [35]. The extended amygdala is in close relation with the ventral striatum and the anterior commissure and should be avoided during surgery for temporal lobe epilepsy [35]. The amygdala joins with the globus pallidus superomedially without any clear border.

The collateral eminence located lateral to the head of the hippocampus occupies the floor of the temporal horn and is the indentation of the collateral sulcus into the temporal horn (Figures 4(a), 4(d), and 4(f)). The collateral sulcus courses between the parahippocampal gyrus and the fusiform gyrus.

The posterior part of the temporal horn is related to the middle MTR and begins at the inferior choroidal point to open to the atrium. The floor of this part is formed by the collateral eminence similar to the anterior part. The collateral eminence is a reliable landmark to determine the medial limit of the neocortical removal. The medial wall of this part is formed by the body of the hippocampus.

The medial surface of the temporal lobe and the perimesencephalic cisterns can be reached by opening the choroidal

fissure. The choroidal fissure begins at the inferior choroidal point, which is located at the posterior limit of the uncus. The choroidal fissure is a natural cleft between the thalamus superiorly and the fimbria of the fornix inferiorly. The choroid plexus is attached on each side to the thalamus and the fimbria of the fornix, via the taenia choroidea and taenia fimbria, respectively. The choroid plexus is adjacent to the body of the hippocampus in this part of the temporal horn. The head of the hippocampus is located in the anterior MTR; therefore, it is not related to the choroidal fissure and the choroid plexus. The ambient cistern can be reached by opening the choroidal fissure in the medial MTR. The roof and the lateral wall of the temporal horn are formed by a layer of tapetal fibers and then are covered by optic radiations. Optic radiations do not cover the most anterior part of the lateral wall of the temporal horn.

The atrium is the ventricular space situated lateral to the posterior MTR. The floor of the atrium is formed by the collateral trigone that is the indentation formed by the posterior end of the collateral sulcus. The intraventricular part of the tail of the hippocampus is located at the most anterior part of the floor. The anterior wall of the atrium has two parts: a lateral part formed by the pulvinar and a medial part formed by the crus of fornix. The medial wall of the atrium is formed by two prominences: the inferior prominence, referred to as the calcar avis, is the indentation of the calcarine sulcus into the ventricular space, and the superior prominence, referred to as the bulb of corpus callosum, is formed by the callosal fibers of the forceps major. The lateral wall of the atrium is formed by the optic radiations.

### 3. Vascular Features

**3.1. Arterial Supply.** The temporal lobe is close to important vascular structures both arterial and venous. The PCA, the MCA, the AChA, and also the ICA are met in surgical interventions directed to the different parts of the temporal lobe. A clear understanding of microvascular anatomy of the temporal lobe is needed to perform epilepsy surgery with minimal morbidity.

**3.1.1. Posterior Cerebral Artery.** The PCA has the main role of supplying the MTR and the inferior surface of the temporal lobe. The PCA is divided into 4 segments: P1, P2, P3, and P4 (Figures 4(e) and 4(f)) [36]. The P1 arises at the bifurcation of the basilar artery and is situated medial to the anterior segment of the uncus during its course in the interpeduncular cistern. The P1 ends after posterior communicating artery (PCoA) joining the PCA and the P2 begins. The P2 terminates at the posterior margin of the midbrain and is divided into an anterior segment (P2a) and a posterior segment (P2p). The P2a courses in the crural cistern located between the posterior segment of the uncus and the cerebral peduncle. The P2p courses in the ambient cistern located between the parahippocampal gyrus and the midbrain. The P3 begins at the posterior part of the ambient cistern, posterolateral to the midbrain, and courses back into the quadrigeminal cistern to end at the anterior end of the

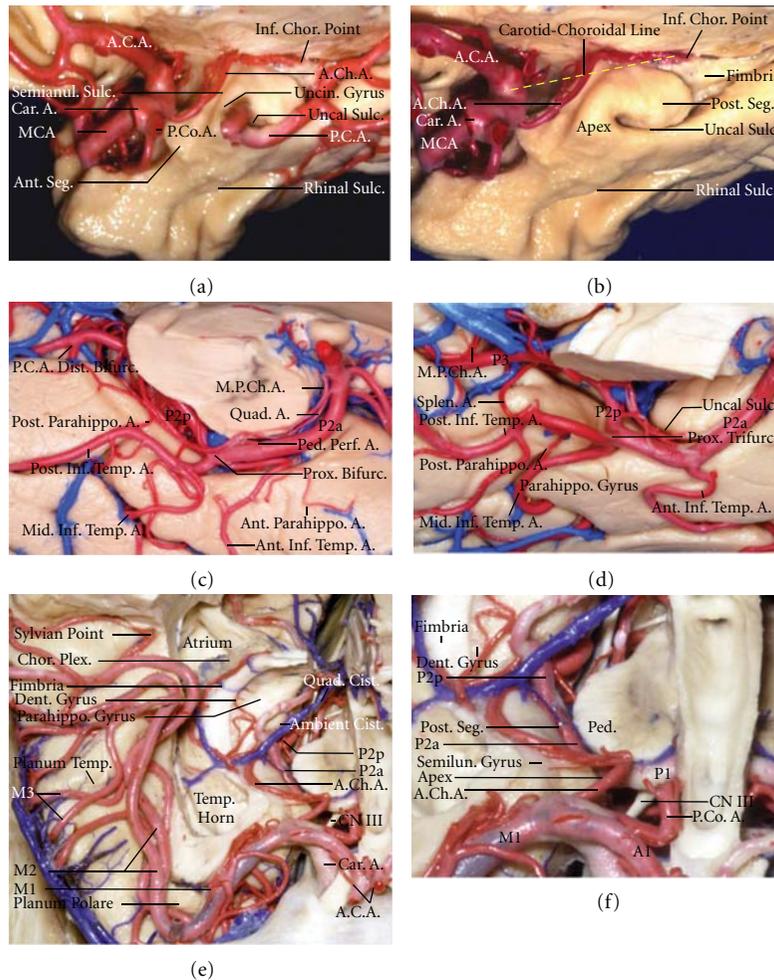


FIGURE 4: (a) Medial view of the anterior segment of the medial temporal region (MTR) and adjacent vascular structures. The anterior choroidal artery (AChA) passes above the semiannular sulcus and uncinete gyrus to reach the lower end of the choroidal fissure, where it enters the temporal horn through the inferior choroidal point. The posterior cerebral artery (PCA) courses medial to the uncal sulcus that divides the posterior segment of the uncus into upper and lower parts. (b) The PCA has been removed. An imaginary line (yellow dashed line), referred to as the carotid-choroidal line, drawn from the bifurcation of the internal carotid artery or the M1 segment of the middle cerebral artery (MCA) to the inferior choroidal point is a reliable landmark to determine the superior extent of the amygdalar resection. (c) The PCA is the main arterial supplier of the MTR and typically has a proximal bifurcation situated adjacent to the middle segment of the MTR and a distal bifurcation formed by the posterior inferior temporal artery and the parietooccipital arterial trunk (P2p). The PCA gives off the anterior inferior temporal artery, from which the anterior parahippocampal artery arises, just before the proximal bifurcation. In this case, the middle inferior temporal artery and the posterior parahippocampal artery arise from the posterior inferior temporal artery. The medial posterior choroidal artery and the quadrigeminal artery arise from the proximal part of P2a. (d) The branching pattern of the PCA in another case. A trifurcation into the middle and posterior inferior temporal arteries and the parietooccipital trunk (P2p) was seen instead of the distal bifurcation. The posterior parahippocampal artery arises from the middle inferior temporal artery and the medial posterior choroidal artery from the parietooccipital trunk (P3). (e) The frontal lobe and the central core of the right cerebral hemisphere have been removed to expose the temporal horn, atrium, and the basal cisterns. The M1 segment of the MCA courses on the upper surface of the temporal pole, the M2 segment crosses the insular surface, and the M3 travels on the opercular surfaces. The PCA passes posteriorly in the crural and ambient cisterns (P2a and P2p segments, resp.) to reach the quadrigeminal cistern (P3 segment). (f) *Enlarged view of (e)*. The AChA enters the choroidal fissure at the inferior choroidal point located at the posterosuperior edge of the uncus. A.: artery; A1.: A1 segment of ACA; A.C.A.: anterior cerebral artery; A.Ch.A.: anterior choroidal artery; Ant.: anterior; Bifurc.: bifurcation; Car.: carotid; Ch.: choroidal; Chor.: choroidal; CNIII.: oculomotor nerve; Cist.: cisternal; Dent.: dentate; Dist.: distal; Inf.: inferior; M.C.A.: middle cerebral artery; M1.: M1 segment of MCA; M2.: M2 segment of MCA; M3.: M3 segment of MCA; Mid.: middle; Parahippo.: parahippocampal; P.C.A.: posterior cerebral artery; M.P.Ch.A.: medial posterior choroidal artery; P1.: P1 segment of PCA; P2a.: anterior part of the P2 segment of PCA; P2p.: posterior part of the P2 segment of PCA; P.Co.A.: posterior communicating artery; Ped.: peduncle; Post.: posterior; Quad.: quadrigeminal; Seg.: segment; Semianul.: semiannular; Semilun.: semilunar; Splen.: splenial; Sulc.: sulcus; Temp.: temporal; Trifurc.: trifurcation; Uncin.: uncinete.

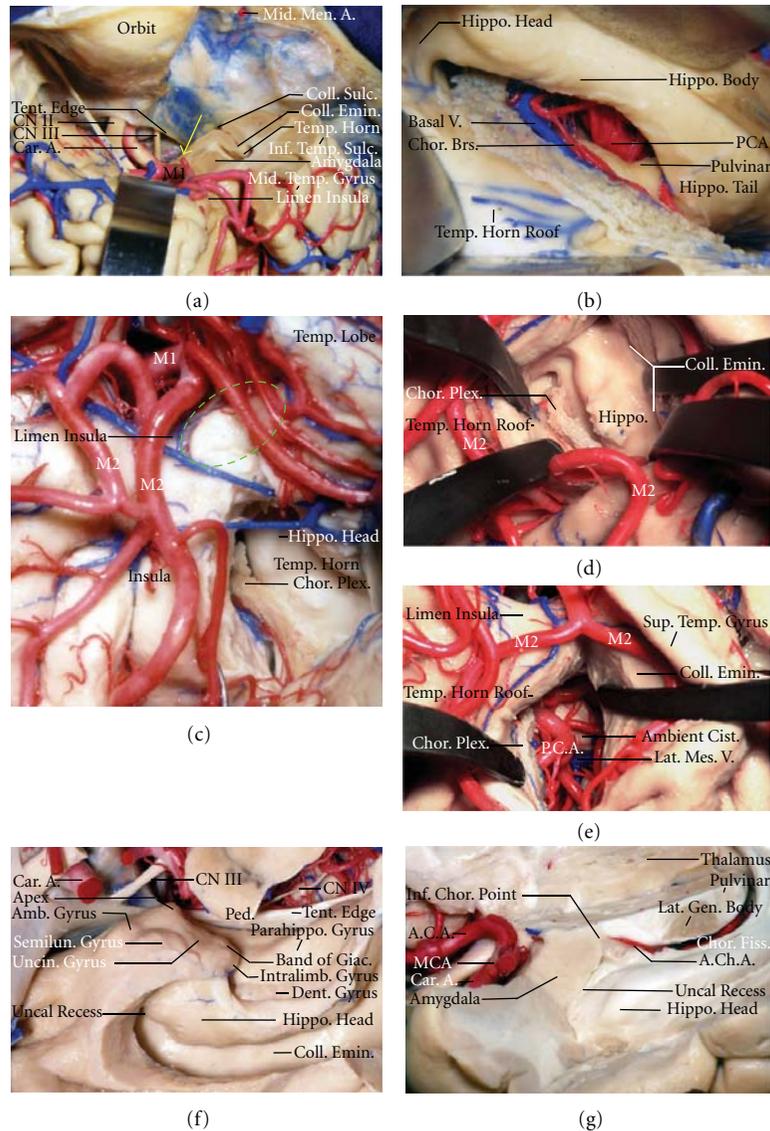


FIGURE 5: (a) A coronal cut is performed to the specimen positioned as in a pterional craniotomy at the level of limen insula to have a similar view of the anterior temporal lobectomy after the removal of lateral temporal neocortex. The yellow arrow shows the origin of an early cortical branch of MCA. (b) The choroidal plexus is attached to the choroidal fissure with taeniae for fornical and thalamic sides. The choroidal fissure should be opened always at fornical side to prevent both to thalamus and choroidal arteries and veins passing close to thalamic side of the choroid plexus. In this view, arachnoid membrane of the ambient cistern is removed to show the PCA and the basal vein. (c–e) *Stepwise dissection of the sylvian fissure, the temporal horn, and the choroidal fissure.* (c) The presentation of the amygdala at the temporo-opercular surface is shown in green oval line. An incision in the inferior limiting sulcus has been completed to expose the head of the hippocampus, the choroidal fissure, and the anterior choroidal artery. (d) *Closer view of the (c).* The roof of the temporal horn has been elevated to have a better view of the temporal horn, the hippocampus, the choroid plexus, and the collateral eminence. (e) Amygdalohippocampectomy has been completed, exposing the vascular elements in the ambient cistern. Inferior surfaces of the anterior and posterior segments of the uncus are related to internal carotid artery and the posterior cerebral artery, respectively. The anterior choroidal artery is related to the superior surfaces of both uncus segments in most cases. (f) *Superior view of the left MTR showing the relation of the ventricular and the cisternal components of the MTR to the tentorial edge and cerebral peduncle.* The posterior part of the uncus faces the cerebral peduncle across the crural cistern, the apex of the uncus is positioned lateral to the oculomotor nerve. The tentorial edge crosses below the medial part of the uncus. (g) *Lateral view of the ventricular surface of the medial temporal lobe.* The lateral geniculate body is located just above the choroidal fissure and the middle segment of the medial temporal lobe. The choroidal fissure, along which the choroid plexus (removed) attaches, is located between the fimbria and the thalamus. A.: artery; A.C.A.: anterior cerebral artery; A.Ch.A.: anterior choroidal artery; Amb.: ambient; Ant.: anterior; Brs.: branches; Car.: carotid; Chor.: choroidal; Cist.: cisternal; CNII.: optic nerve; CNIII.: oculomotor nerve; CNIV.: trochlear nerve; Coll.: collateral; Emin.: eminence; Fiss.: fissure; Giac.: Giacomini; Hippo.: hippocampal; Inf.: inferior; Intralimb.: intralimbic; Lat.: lateral; M1.: M1 segment of middle cerebral artery; M2.: M2 segment of middle cerebral artery; Men.: meningeal; Mes.: mesencephalic; Mid.: middle; Parahippo.: parahippocampal; P.C.A.: posterior cerebral artery; Plex.: plexus; Post.: posterior; Semilun.: semilunar; Sulc.: sulcus; Sup.: superior; Temp.: temporal; Tent.: tentorial; Uncin.: uncinata; V.: vein.

calcarine sulcus. The P4 contains the cortical branches of the PCA.

The P2a is in close relation to the anterior MTR which gives many branches. These branches, the anterior inferior temporal artery, the anterior hippocampal-parahippocampal artery, and the main trunk of P2a, have the main contribution to the arterial supply of the anterior MTR [6].

The P2p is in close relation to the middle MTR. The PCA shows a bifurcation or trifurcation in most hemispheres (in 89% of hemispheres) at the middle part of this region at a distance of 6.7 mm (range 0–21 mm) to the posterior limit of the uncus. The most common bifurcation pattern is a division into a parietooccipital arterial trunk and a posterior inferior temporal artery. The next common bifurcation pattern is a division into a parietooccipital arterial trunk and an inferior common temporal artery, which then divides into anterior, middle, and posterior inferior temporal arteries (Figures 4(c), 4(d), 6(c)–6(e)). The posterior parahippocampal arteries originating from the posterior inferior temporal artery give the arterial supply to the middle MTR [6].

The P3 and the P4 segments are related to the posterior MTR and do not give any branches to the inferior surface of the temporal lobe. The PCA courses below the isthmus of the cingulate gyrus towards the calcarine sulcus to make its distal bifurcation into the parietooccipital artery and the calcarine artery (Figure 4(c)). The posterior inferior temporal artery, the posterior hippocampal arteries, the splenial artery, the calcarine artery, and the parietooccipital artery are the branches of the PCA emerging at this segment which contribute to the arterial supply of the posterior MTR [6].

**3.1.2. Internal Carotid Artery.** The C4 segment of the ICA begins where the artery enters the dura and courses superior, posterior, and lateral to its bifurcation into the anterior and middle cerebral arteries. The C4 is divided into 3 subsegments: the ophthalmic, the communicating, and the choroidal [34]. The first segment after the ICA enters into the intradural space is the ophthalmic segment, which has the origin of the ophthalmic artery at its distal limit. The second segment is the communicating segment, which starts at the origin of the ophthalmic artery and ends at the origin of the PCoA. The third segment is the choroidal segment, which continues from the origin of AChA to the bifurcation of the ICA.

These segments may come into view during a pterional craniotomy or its variations. The surgeon finds the AChA before the PCoA because the AChA is closer to the bifurcation of the ICA, the AChA originates closer to the lateral wall of the ICA than the PCoA, and the AChA follows a more lateral course than the PCoA after their origin.

Fernández-Miranda et al. [6] stated that arterial branches of the ICA, which supply the MTR, were present in 45% of hemispheres. If present, these arteries always arose from the choroidal segment of the ICA. They suggested that their presence is in close relation to the absence of the branches of the AChA and the MCA.

**3.1.3. Anterior Choroidal Artery.** The AChA arises from the posterior wall of the ICA. Its origin is nearer to the origin of the PCoA than to the bifurcation of the ICA in most cases. Additionally, it can arise directly from the PCoA [6]. The AChA may show two different types of duplication. It can arise from the posterior wall of the ICA and then immediately divide into two arteries, or the AChA arises as two different trunks from the C4. The AChA is divided into two segments: cisternal and plexal [37]. The cisternal segment follows an initial posteromedial direction in the carotid cistern but then follows a posterior, lateral, and superior direction under the optic tract by staying lateral to it. It follows the superior surface of the posterior segment of the uncus and enters into the ventricle through the choroidal fissure. This entry point into the ventricle is the inferior choroidal point in most cases. Another entry point is also possible a few millimeters posterior to the inferior choroidal point. The length of this segment was measured as 23 mm and 24 mm in two different neuroanatomical studies [6, 34].

The cisternal segment of the AChA supplies only the anterior MTR. This arterial supply can be divided into three areas: anterosuperior, medial, and inferior. The anterosuperior area is the anterior segment of the uncus and is supplied by the anterior uncal arteries. The medial area depicts the posterior segment of the uncus and is supplied by the posterior uncal arteries. The inferior area is the entorhinal area, and Fernández-Miranda et al. described that the AChA gives only a minimal contribution to the arterial supply of this area (Figure 6(b)) [6]. The arterial supply of the entorhinal area, which occupies the anterior portion of the parahippocampal gyrus, depends mainly on the PCA and the MCA. The PCA gave the anterior hippocampal-parahippocampal arteries and its branches, called the anterior parahippocampal arteries, to the entorhinal area in all cases (Figure 6(e)).

The plexal segment of the AChA begins at the entry point of the artery into the ventricle. This segment mainly gives the arterial supply of the choroid plexus in the temporal horn, but it may also supply the choroid plexus at more posterior levels. This segment gives off one to four perforating branches.

**3.1.4. Middle Cerebral Artery.** The MCA is divided into four segments (Figures 4(e) and 5(c)) [34]: M1 or the sphenoidal segment, M2 or the insular segment, M3 or the opercular segment, and M4 or the cortical segment. All four segments supply different parts of the temporal lobe. The M1 starts at the origin of the MCA and ends at the genu. The M2 segment consists of the arteries lying on the insular surface. The M3 is the segment within the sylvian cistern starting at the circular sulcus of the insula to end at the surface of the sylvian fissure. The M4 consists of cortical branches at the lateral convexity.

The bifurcation of the MCA occurs just proximal to the end of the M1; thus, the M1 is divided into prebifurcation and postbifurcation parts. Two other important vascular structures arise from the M1 other than the superior and inferior trunks after the bifurcation. The cortical branches arising from the M1 proximal to the bifurcation are referred to as early branches. Early branches may reach to the frontal

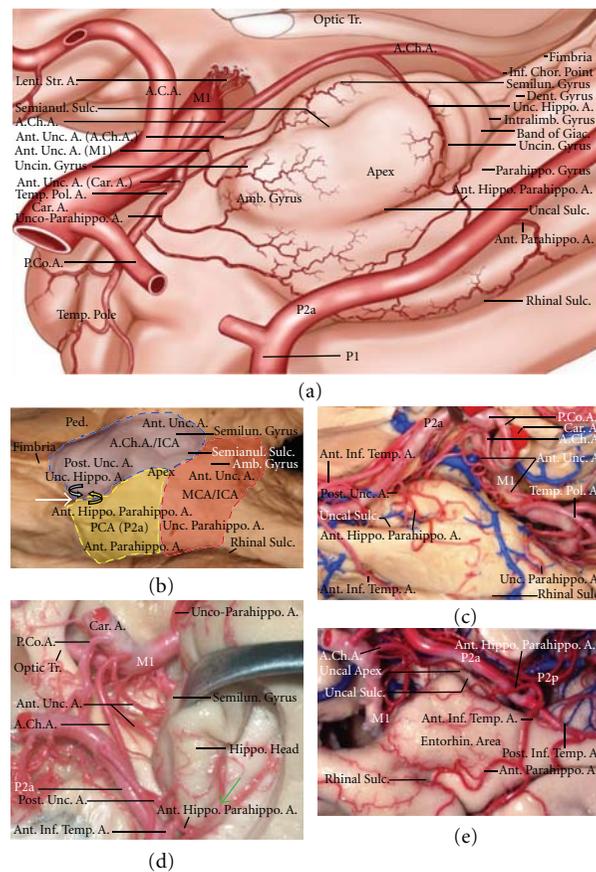


FIGURE 6: (a) *The medial view of the anterior segment of the medial temporal region (MTR).* (This illustration correlates with Figures 6(b) and 6(c)). The anterior choroidal artery (AChA) gives off an anterior uncinate artery that irrigates the semilunar gyrus and an uncohippocampal artery that irrigates the uncinate gyrus and band of Giacomini and penetrates the uncal sulcus to vascularize the extraventricular hippocampal head. The internal carotid artery (ICA) gives off an anterior uncinate artery that supplies the semilunar gyrus. This branch usually is present when the anterior uncinate artery of the AChA is absent. An anterior uncinate artery also arises from the M1 segment of the middle cerebral artery (MCA) and supplies the ambient gyrus. An unco-parahippocampal artery arises from the temporopolar artery and irrigates both the ambient gyrus and the anterior parahippocampal area. Branches from the P2a segment of the PCA irrigate the anterior parahippocampal region (anterior parahippocampal artery) or both the anterior parahippocampal gyrus and hippocampal head (anterior hippocampal-parahippocampal artery). (b) *The medial surface of the anterior segment of the left MTR.* The white arrow points the posterior end of the uncal notch. The anterior part of this segment is irrigated by middle cerebral branches (orange shaded area), the posterosuperior part is supplied by anterior choroidal branches (blue shaded area), and the posteroinferior part is vascularized by posterior cerebral branches (yellow shaded area). The ICA typically supplies the area supplied by the AChA and the MCA if their branches are absent. The branches of the MCA are the anterior uncinate artery superiorly and the unco-parahippocampal artery inferiorly. The branches of the AChA are the anterior uncinate artery anteriorly, the posterior uncinate artery posteriorly, and the unco-hippocampal artery posteroinferiorly. The branches of the PCA are the anterior hippocampal-parahippocampal artery medially and the anterior parahippocampal artery laterally. Areas of vascular anastomosis are typically found at the confluence of vascular territories (curved arrows). (c) The same view of (a) in a silicon injected anatomic specimen. (d) *Inferior view of the anterior segment of the left MTR.* The inferior lip of the posterior uncal segment has been removed to expose the extraventricular hippocampal head. The semilunar gyrus has been retracted to expose the branches of the AChA. Two anterior uncinate arteries arise from the first one-third of the AChA and irrigate the semilunar gyrus. A posterior uncinate artery from the AChA penetrates the uncal sulcus and irrigates the extraventricular hippocampal head. An anterior hippocampal-parahippocampal artery arising from the anteroinferior temporal branch of the PCA gives rise to an anterior hippocampal branch that supplies the extraventricular hippocampal head and anastomoses with the unco-hippocampal branch of the AChA (green arrow). (e) *Lower surface of the anterior segment of the right MTR.* The entorhinal area is irrigated medially by the parahippocampal branch of the anterior hippocampal-parahippocampal artery that arises from the P2a, and laterally by a large anterior parahippocampal artery that originates from the anterior inferior temporal artery. A.: artery; A.C.A.: anterior cerebral artery; A.Ch.A.: anterior choroidal artery; Amb.: ambient; Ant.: anterior; Car.: carotid; Chor.: choroidal; Dent.: dentate; Entorhin.: entorhinal; Giac.: Giacomini; Hippo.: hippocampus; ICA: internal carotid artery; Inf.: inferior; Intralimb.: intralimbic; Lent.: lenticulo; M.C.A.: middle cerebral artery; M1.: M1 segment of middle cerebral artery; Parahippo.: parahippocampal; P.C.A.: posterior cerebral artery; P2A.: anterior part of the P2 segment of posterior cerebral artery; P2P.: posterior part of the P2 segment of posterior cerebral artery; P.Co.A.: posterior communicating artery; Ped.: peduncle; Pol.: polar; Semianul.: semiannular; Semilun.: semilunar; Str.: striate; Sulc.: sulcus; Temp.: temporal; Tr.: tract; Unc.: uncal; Uncin.: uncinate; V.: vein.

or the temporal lobes with the temporopolar area being the most common temporal area supplied by an early branch [38]. The M1 supports the arterial supply of the MTR with 1 to 3 branches in 94% of the specimens. Fernández-Miranda et al. further detailed this data. They described that these branches originate from the main M1 trunk in 42% of the cases, from a temporopolar artery in 41% of the cases, and from an early branch other than temporopolar artery in 14% of the cases [6].

Three types of the distribution of the MCA branches can be identified. The anterior group, which supplies the anterior segment of the uncus, was named as the anterior uncal arteries. The anteroinferior group, which has the distribution to the anterior entorhinal area, was named as the unco-parahippocampal arteries. These two groups contain 92% of all branches directed to the MTR from the MCA. The third group of arteries, which gives supply to the anterior part of the entorhinal area, was named as the anterior parahippocampal arteries. While anterior uncal arteries arise mostly from the main M1 trunk, the unco-parahippocampal arteries and anterior parahippocampal arteries arise mainly from the temporopolar artery [6].

The arteries at the superior surface of the temporal lobe belong to the opercular segment (M3), which come into view during the splitting of the sylvian fissure; the cortical branches at the lateral surface belong to the M4 which are grouped into distribution areas as, from anterior to posterior, the temporopolar, anterior, middle, and posterior temporal areas [34].

**3.2. Venous Drainage.** The venous drainage of the cerebrum is divided into a superficial group and a deep group [34]. This also applies to the temporal lobe. The microvascular anatomy of the venous drainage of the cerebrum was described in other reports [39, 40], and the venous drainage of the sylvian fissure was further detailed by Tanriover et al. [4].

Two most important venous structures at the lateral surface of the temporal lobe are the superficial sylvian vein (SSV) and the vein of Labbe. The SSV usually arises as a single trunk at the most posterior end of the sylvian fissure but may also start as two trunks that join together before their drainage. Tanriover et al. described that the SSV emptied into the sphenoparietal sinus in 35 of 43 hemispheres [4]. In the remaining hemispheres, the SSV drained directly into the cavernous sinus or into a sphenopetrosal sinus. In their study, the mean distance between the limen insula and the junction of the SSV with the sphenoparietal sinus is measured 24.8 mm. The vein of Labbe is the largest vein on the lateral surface of the temporal lobe that connects the SSV and the transverse sinus and is located in the drainage area of the middle temporal vein in more than half of the hemispheres [39]. The SSV and the vein of Labbe may be hypoplastic or absent. The most consistent dominant superficial anastomotic veins are the SSV and the vein of Labbe followed by vein of Labbe and the vein of Trolard [41].

Oka et al. divided the superficial venous anatomy of the temporal lobe into a lateral group and an inferior group [4, 39]. The lateral group of veins is further divided

into two additional groups: an ascending group consists of temporosylvian veins that drain towards the sylvian fissure and a descending group consists of anterior, middle, and posterior temporal veins that drain into the tentorial sinuses. Tanriover et al. stated that there are a mean of four temporosylvian veins draining into SSV [4]. These veins drain the temporopolar area and the superior temporal gyrus anterior to the posterior limit of the sylvian fissure. Also, temporosylvian veins have a minor role at the venous drainage of the inferior limiting sulcus and the posterior long gyrus of the insula. The anterior temporal vein collects the venous drainage from the anterior one-third of the lateral surface except the superior temporal gyrus and drains mostly into a tentorial sinus. The middle temporal vein drains the midportion of the lateral surface and empties into the transverse sinus, a tentorial sinus, or the vein of Labbe. The posterior temporal vein drains the posterior third of the lateral convexity of the temporal lobe and courses in a nearly vertical route to drain into a tentorial sinus or less commonly into the vein of Labbe.

The lateral part of the inferior surface of the temporal lobe is drained via the anterior, middle, and posterior temporobasal veins. They empty into tentorial sinuses.

The deep middle cerebral vein and the venous drainage of the MTR empty into the deep venous system. The deep venous system begins with the basal vein which has three segments [42] (Figures 7(a)–7(c)). The deep middle cerebral vein is formed by the junction of the insular veins at the level of limen insula [4]. The first (striate) segment is composed of the deep middle cerebral vein and inferior striate veins that unify to form the basal vein. The joining of the anterior cerebral, olfactory, and frontoorbital veins completes the striate segment, which courses posterior at the upper part of the anterior segment of the uncus to meet with the peduncular vein at the apex of the uncus. The second (peduncular) segment begins at this point to course posterior in the crural cistern. The peduncular segment is divided into an anterior part and a posterior part. The anterior part of the peduncular segment is referred to as the anterior basal anastomotic vein, because it joins the striate segment and the posterior part of the peduncular segment. The posterior peduncular segment starts where the inferior ventricular vein joins the basal vein and finishes where the lateral mesencephalic vein joins the basal vein. The third (mesencephalic) segment is also known as the posterior anastomotic vein, since it unifies the peduncular segment with the vein of Galen.

The anterior MTR has relationship with the striate segment and the anterior peduncular segment. This region shows mainly two types of drainage. If typical variant is present, the venous drainage empties into the posterior peduncular segment via the anterior basal anastomotic vein. Fernández-Miranda et al. found this variant in 23 of 37 cases [6]. The other variant is present if there is no anastomosis between the striate segment and the posterior peduncular segment. In this group, the venous drainage of the anterior MTR emptied into the cavernous sinus or into the sphenoparietal sinus via a large preuncal vein.

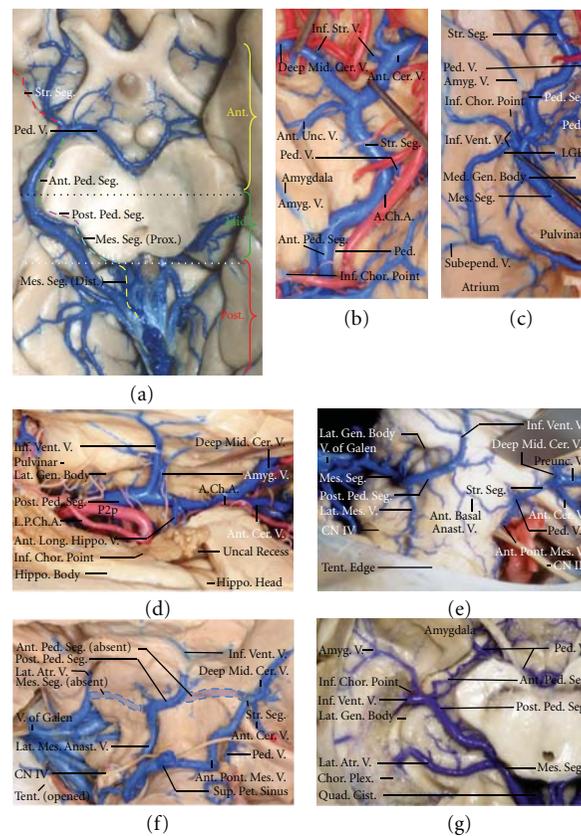


FIGURE 7: (a) *Inferior view*. The basal vein and its tributaries have been exposed. The segmental classification of the basal vein (right hemisphere) and the segmental classification of the MTR (left hemisphere) are shown. The striate (red interrupted line) and anterior peduncular (green interrupted line) segments of the basal vein are located along the anterior MTR (yellow bracket). The posterior peduncular (purple interrupted line) and proximal mesencephalic (aqua interrupted line) segments of the basal vein are situated in the middle MTR (green bracket). The distal mesencephalic segment (yellow interrupted line) of the basal vein belongs to the posterior MTR (red bracket). The anterior peduncular segment is also referred to as the anterior anastomotic vein, because it allows the striate segment to communicate with the posterior peduncular segment. The mesencephalic segment of the basal vein also is referred to as the posterior basal anastomotic vein because it connects the peduncular segment to the vein of Galen. (b) *Basal view of the striate and anterior peduncular segments of the basal vein*. The part of the amygdala below the level of the optic tract has been removed. The carotid and crural cisterns have been opened to expose the striate and anterior peduncular segments of the basal vein. The anterior and deep medial cerebral veins meet to form the striate segment of the basal vein. The anterior peduncular segment begins where the peduncular vein joins the basal vein, and the posterior peduncular segment starts at the junction with the inferior ventricular vein. (c) *Inferior view of the roof of the temporal horn in another right hemisphere*. The junctional point between the inferior ventricular vein and the peduncular segment corresponds to the cisternal level of the inferior choroidal point and the junction of the crural and ambient cisterns. Several large subependymal veins draining the roof and lateral wall of the temporal horn join to form the inferior ventricular vein. (d) The right temporal horn has been opened, and the ambient and crural cistern have been exposed by opening the choroidal fissure. The amygdalar vein drains separately from the inferior ventricular vein into the basal vein. The anterior longitudinal hippocampal vein empties into the basal vein anterior to the inferior ventricular vein. (e) *Lateral view of the right tentorial incisura*. The temporal lobe has been removed to expose the basal vein. The anterior peduncular segment of the basal vein is hypoplastic. Failure of anastomosis between the striate and peduncular segments of the basal vein results in formation of a prominent preuncal vein that drains forward into the sphenoparietal sinus. (f) *Same view as (e) in a different specimen*. Both the anterior peduncular (anterior anastomotic vein) and the mesencephalic segment (posterior anastomotic veins; blue shaded areas) are absent, and the striate, peduncular, and mesencephalic segments of the basal vein are disconnected from each other. The striate segment drains inferiorly via the anterior pontomesencephalic vein, the peduncular segment drains inferiorly through a prominent lateral mesencephalic vein, and the tributaries of the mesencephalic segment drain directly into the vein of Galen. (g) *Inferior view of the right basal vein*. The anterior peduncular segment (anterior anastomotic vein) of the basal vein is hypoplastic. The inferior ventricular vein empties into and forms the posterior peduncular and mesencephalic segments of the basal vein, and the anterior segment of the basal vein drains anteriorly. A prominent lateral atrial vein drains into the mesencephalic segment. A.Ch.A.: anterior choroidal artery; Amyg.: amygdalar; Anast.: anastomotic; Ant.: anterior; Atr.: atrial; Cer.: cerebral; Chor.: choroidal; cist.: cistern; CNIII.: oculomotor nerve; CNIV.: trochlear nerve; Dist.: distal; Gen.: geniculate; Hippo.: hippocampus; Inf.: inferior; Lat.: lateral; Long.: longitudinal; Med.: medial; Mes.: mesencephalic; Mid.: middle; LGB.: lateral geniculate body; L.P.Ch.A.: lateral posterior choroidal artery; Ped.: peduncle; Plex.: plexus; Pon.: ponto; Post.: posterior; Preunc.: preuncal; Prox.: proximal; Seg.: segment; Str.: striate; Subepend.: subependymal; Quad.: quadrigeminal; Tent.: tentorial; Unc.: uncus; V.: vein; Vent.: ventricular.

The middle MTR is in close relation with the posterior peduncular segment and the proximal part of the mesencephalic segment. The inferior ventricular vein drains the roof and the lateral wall of the temporal horn as well as the anterior part of optic radiations. In the absence or hypoplasia of the peduncular segment, the inferior ventricular vein forms the second segment of the basal vein. Other tributaries to the second segment of the basal vein are anterior hippocampal vein, which drains the extraventricular head of hippocampus, and anterior longitudinal hippocampal vein, which drains the body of the hippocampus (Figures 7(a), 7(d)–7(g)).

The posterior MTR is in close relation with the distal part of the mesencephalic segment of the basal vein, which courses in the quadrigeminal cistern and drains into the vein of Galen or the internal cerebral vein. The tributaries from this region into the basal vein are the posterior longitudinal hippocampal vein, medial temporal vein, lateral and medial atrial veins. The posterior longitudinal hippocampal vein takes the drainage of the tail of hippocampus. The medial temporal vein drains the inferior surface of the posterior part of the parahippocampal gyrus.

#### 4. Discussion

Although thousands of patients with temporal lobe epilepsy were operated, there is still controversy regarding the best surgical approach [8, 10, 43, 44]. The main goal is long-term seizure free outcome while avoiding functional deficits. The main risks for functional decline are visual deficit or neurocognitive damage, which may be related to the choice of operative route to the medial temporal lobe. Different surgical methods will be discussed with these concerns in mind.

Surgical methods for temporal lobe epilepsy can be divided in three groups from a neuroanatomical view: lateral approaches, inferior approaches, transsylvian approaches [14]. The lateral approaches are the anterior temporal lobectomy (ATL) and the transcortical selective amygdalo-hippocampectomy (TCAH); the inferior approaches are the subtemporal approach and the transparahippocampal approach; and the transsylvian approaches are the transsylvian selective amygdalohippocampectomy (SelAH) and the transcisternal approach. In this chapter, the ATL, TCAH, and the SelAH will be discussed. The subtemporal approach [45], the transparahippocampal approach [46], and the transcisternal approach [47] will not be discussed since they are performed only in selected centers.

**4.1. Neocortical Removal and Approach to the Temporal Horn.** After sufficient exposure of the lateral surface of the temporal lobe, the sulcal and vascular anatomy should be inspected carefully. The arterial structures in view are the M4 segment of the MCA and divided into the temporopolar area and anterior, middle, and posterior temporal areas. The temporopolar area can be supplied occasionally by an early branch of the MCA [38]. The location of the vein of Labbe should also be noted. This vein is located at the drainage area of the middle temporal vein in most cases [39], and

care should be taken to preserve it, since it is commonly the dominant superficial anastomotic vein [41].

After the neocortical removal, the temporal horn comes into view which has the collateral eminence at its floor. The collateral eminence is the indentation of the collateral sulcus towards the temporal horn and lies lateral to the hippocampus [34]. The neural tissue lateral to the collateral eminence can be removed safely without any risk of damaging midbrain structures. Another reliable landmark to achieve a safe neocortical resection is the tentorial edge (Figure 5(a)). As long as the resection is aimed lateral to the free edge of the tentorium, the damage to the inferior limiting sulcus, the sylvian fissure, and midbrain structures will be avoided.

Clinical data suggests that the ATL causes high risk of damaging optic radiations. Yeni et al. stated that this risk is higher during the ATL comparing to the TSAH [9]. The neuroanatomical data support these findings. The Meyer's loop was found to cover the roof of temporal horn and to exceed the anterior wall of the temporal horn a few millimeters, thus opening the ventricle at the superior wall may damage optic radiations [12]. Additionally, Meyer's loop was found an average of 31.4 mm posterior from the temporal pole [13]. Therefore, any resection posterior to this extent carries the risk of causing damage to optic radiations.

The neocortical removal can also lead to negative neurocognitive sequelae. The ILF connects anterior parts of the temporal lobe to the fusiform gyrus and the occipital lobe. The neocortical resection may include the ILF itself or the cortical areas it originates. And since the areas the ILF connects are thought to have role in learning and remembering of visual stimuli [22], the neocortical resection can cause memory problems.

A cortical incision to the middle temporal gyrus or deep to the superior temporal sulcus is made at the TCAH to reach to the ventricle through its lateral wall. Olivier described that the cortical incision is made to the middle temporal gyrus rather than the superior temporal sulcus [48]. Although transsulcal approach has less distance to reach to the temporal horn, the need for the retraction of the sulcal lips and possible presence of vascular structures deep to sulcus makes this incision demanding. The difficulty of this technique is to find the temporal horn, because a blind dissection in the white matter can lead to significant deficits. Wen et al. described a very useful technique to find the temporal horn [5]. The TCAH carries the risk of damaging both optic radiations and the ILF. But the risk of damaging optic radiations is less than the risk with the ATL, since optic radiations do not cover the anterior portion of the lateral wall of the temporal horn [12].

The TSAH, described by Wieser and Yasargil, is performed with a different route to the temporal horn. The incision is made near to the inferior limiting sulcus after the sylvian fissure is opened [10]. This incision is placed at the temporal stem between the temporopolar artery and anterior temporal artery and carried back 15–20 mm from the limen insula. This approach has its own risks to cause functional deficits by damaging optic radiations, the UF, and the IOFF.

The distance of the LGB to the limen insula is on average 25.1 mm, and there is no clear demarcation between the LGB and the thalamus. During the incision to the inferior limiting sulcus, the thalamus or the LGB can be harmed. Choi et al. stated that it is impossible to avoid the optic radiations if the incision is carried 15–20 mm posterior to the limen insula. Optic radiations can be avoided at a level 10 mm posterior to the limen insula, if the dissection is made between 7 and 25 degrees medially from the sagittal plane, while damaging the mesencephalon and diencephalic structures is highly possible with such dissection. They described that an incision straight inferiorly to the limen insula and to the following 5 mm of the inferior limiting sulcus avoids Meyer's loop [13]. Although the anatomy is more complicated with the TSAH, the risk of damaging optic radiations is lower than the risk ATL carries [9].

It is impossible to preserve the UF with an incision extending posterior from the limen insula. The destruction of this white matter bundle can be the cause of the memory deficits occurring after TSAH, because it is stated that the UF functions at recognizing faces and objects by connecting the orbitofrontal and temporopolar areas [18–20].

The IOFF is another important white matter structure coursing in the temporal stem. Its average distance to limen insula was found 10.9 mm [49]. The incision to the inferior limiting sulcus can cause damage to the IOFF and produce semantic paraphasias [28].

**4.2. Hippocampectomy.** The hippocampectomy begins with the opening of the choroidal fissure beginning at the inferior choroidal point anteriorly. The AChA enters into the temporal horn through the inferior choroidal point or just a few millimeters posterior to it. The inferior choroidal point is also the intraventricular representation of the posterior limit of the uncus and determines the border between anterior and middle MTR. The head of the hippocampus is situated anterior to inferior choroidal point, thus located in the anterior MTR. The body of the hippocampus located posterior to this point is in the middle MTR. Since the choroid plexus is attached to the choroidal fissure, the choroid plexus is related only to the body of the hippocampus. The choroid plexus originates from the tela choroidea, which is attached to fimbria of the fornix and to the thalamus at the edges of the fissure. The tela attached to the fimbria and thalamus is called the taenia fimbriae and taenia thalami.

The choroidal fissure should be opened on the fornical side to avoid damage to the diencephalic structures and to the vascular structures, such as the AChA, lateral posterior choroidal arteries, and the inferior ventricular vein, by leaving them at the thalamic side (Figures 4(a), 5(b), and 7(g)). Once the anterior part of the choroidal fissure is opened, the PCA comes into view under the arachnoidal membrane of the ambient cistern. One should note that the PCA is related to the inferior part of the posterior segment of the uncus. The parahippocampal gyrus coursing medially throughout the ambient cistern can be seen once the opening of the choroidal fissure is extended posterior. At this point, a prominence on the thalamic side, the pulvinar, can be marked.

The next step is the anterior and medial disconnection of the head of hippocampus via the uncus recess that leads the surgeon to the apex of the uncus. The oculomotor nerve located medial to the apex of the uncus and the P2a located inferomedial to the posterior segment of the uncus may come into the view under the arachnoid membrane. This view shows that the inferior part of the posterior segment of the uncus is also removed.

The medial disconnection via the choroidal fissure follows the anterior disconnection. After the choroidal fissure is opened, an arachnoid membrane adjacent to the hippocampus is met before reaching the arachnoid membrane of the crural and the ambient cisterns. The hippocampal branches from the AChA and the PCA enter through this membrane. The medial disconnection will be carried out by separating the structures of the MTR from these arteries by following a direction towards the inferior surface of the parahippocampal gyrus until reaching the collateral sulcus.

The last step is the posterior disconnection. The posterior limit of the tail of hippocampus is where he tail meets the calcar avis, which is the inferior prominence at the medial wall of the atrium.

**4.3. Amygdalectomy.** The temporal amygdala is located entirely in the anterior segment of the uncus. The removal of the anterior segment of the uncus exposes the ICA and the proximal M1. The oculomotor nerve and the PCA have already been exposed during the medial disconnection of the head of the hippocampus.

Resection of the superior part of the uncus carries risk of damaging the globus pallidus unintentionally, since there is no clear border between the globus pallidus and the amygdala. The proximal part of the cisternal segment of the AChA is related to the superior surface of the anterior segment of the uncus in 68% of the hemispheres and the distal part of the cisternal segment of the AChA is related to the superior surface of the posterior segment of the uncus in 86% of the hemispheres [1]. Since this relationship is not present in every case, the AChA itself is not a reliable landmark to determine the superior limit of resection of the uncus and the amygdala.

Wen et al. described an imaginary line starting at the ICA bifurcation or the proximal M1 and ending at the inferior choroidal point (carotid-choroidal point) important in avoiding extension of the amygdala resection in the globus pallidus, but add that the optic tract may also be useful to determine the superior extent of the amygdala removal in TSAH (Figure 4(b)) [1].

## 5. Conclusion

While the main goal in epilepsy surgery is long-term seizure control, avoidance of motor, visual, and cognitive deficits helps to optimize an improved quality of life for these patients. Despite advances in image guided neurosurgical navigation, a three-dimensional knowledge of the microsurgical anatomy is the best resource for precise TLE surgery. A thorough knowledge of the microanatomy of this region leads epilepsy surgeon to a better understanding of

the functional anatomy, and a better appreciation of predicted results from different surgical approaches.

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## Review Article

# Role of Functional MRI in Presurgical Evaluation of Memory Function in Temporal Lobe Epilepsy

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Received 16 May 2011; Revised 7 March 2012; Accepted 11 March 2012

Academic Editor: Warren T. Blume

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Many diagnostic tools have been employed to predict the likelihood of a postoperative memory decline after a standard temporal lobectomy, including the intracarotid amobarbital testing (IAT) or Wada, regarded as the gold standard test for over the past half a century. Functional MRI (fMRI) is also a promising tool in that regard. Its routine use to predict the postoperative memory decline has been limited because of the varied study paradigms, discrepancies in analysis, and interpretation of the results. Based on the existing literatures, fMRI cannot replace IAT for the routine presurgical evaluation of the patients with temporal lobe epilepsy (TLE) yet. Large multicentre studies with a panel of memory test are required to determine the full potential of fMRI and use it reliably to replace IAT in the routine clinical practice. In this paper, we review various aspects of memory fMRI, including the experimental designs, data analysis, and findings.

## 1. Introduction

Epilepsy is a common chronic neurological disorder that is characterized by recurrent spontaneous seizures. Its prevalence varies between 0.5% and 1% in the general population. Epileptic seizures may be generalized or partial in onset. Temporal lobe epilepsy (TLE) is the most common partial epileptic syndrome in adult patients. Etiology of TLE is diverse, but mesial temporal sclerosis (MTS), focal cortical dysplasia, and low-grade neoplasm such as ganglioglioma or dysembryoplastic neuroepithelial tumor (DNET) account for most cases of TLE. These lesions involve amygdala, hippocampus, and parahippocampus to a variable extent (Figure 1).

The amygdala is implicated in emotional memory of fearful events, mood, and the conscious emotional response to an event. Amygdala receives its afferent inputs from the visual, auditory, and somatosensory association cortices and sends efferents to the hypothalamus and brainstem autonomic centers, including the vagal nuclei and the sympathetic neurons. The amygdala is also interconnected with the frontal cortex, the mesiodorsal thalamus, and the mesial striatum

(Figure 2). Electrical stimulation of the amygdala causes intense hallucinations that are often accompanied by fear. The hippocampus is involved in formation and retrieval of declarative memory. The hippocampus includes dentate gyrus, cornu ammonis (CA) 1–3, and subiculum (Figures 1–3). The dentate gyrus constitutes a dense dark layer of cells at the tip of the hippocampus. The subiculum is located at the base of the hippocampus in the coronal plane and is continuous with entorhinal cortex. The latter is part of the parahippocampal gyrus. Information enters the hippocampus through the perforant pathway. The entorhinal axons synapse on cells in the dentate gyrus. The axons of dentate neurons, that is, mossy fibers, end in CA3. Axons of the CA3 neurons, that is, Schaeffer collaterals, synapse on neurons in CA1, which sends its efferents to the subiculum (Figure 3). The subiculum is responsible for the output of the hippocampus. It sends its efferent axons directly to the hypothalamus and mammillary bodies via the fornix, or it passes the information back to the entorhinal cortex to relay it back to the sensory cortices. The hippocampus, CA1 in particular, is commonly involved in MTS.

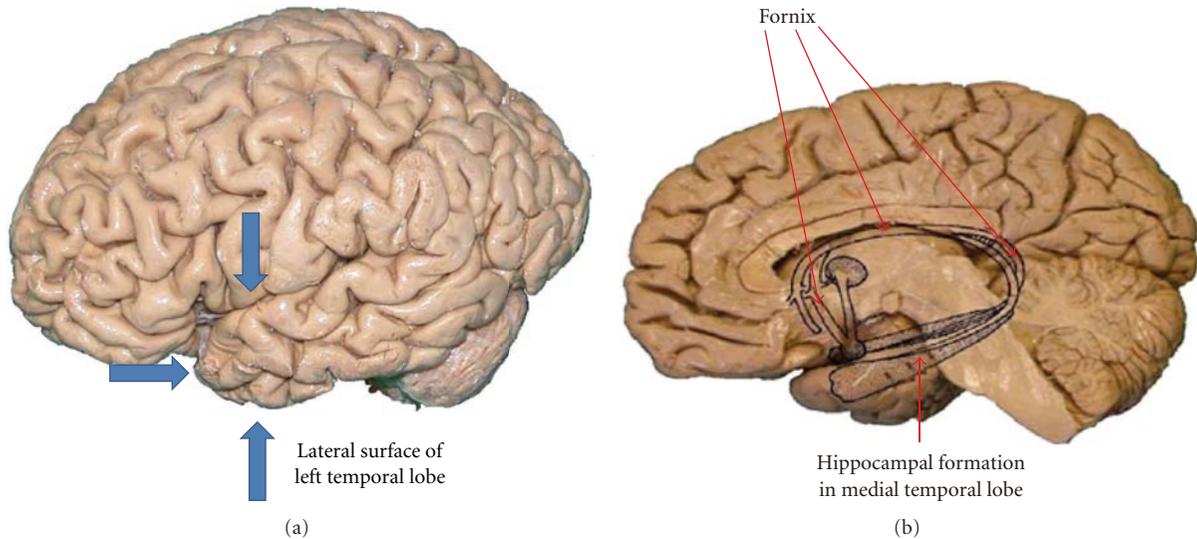


FIGURE 1: Lateral (a) and mesial (b) surfaces of temporal lobe. (Courtesy of Dr. John Kiernan, Department of Anatomy and Cell Biology, The University of Western Ontario.)

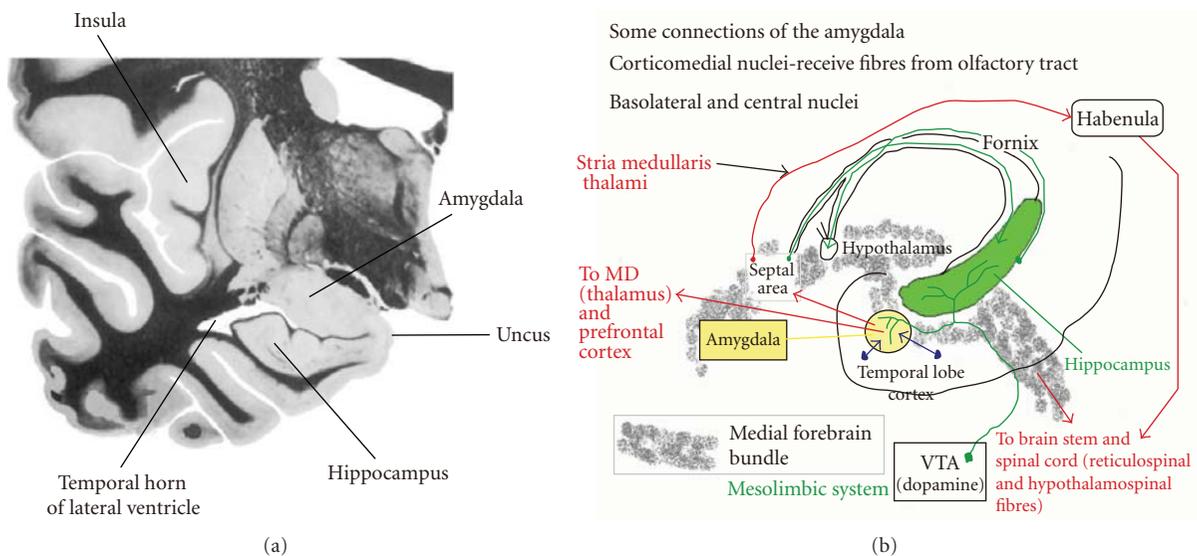


FIGURE 2: Gross coronal section of mesial temporal structures (a) and connections between amygdala and other brain regions (b). (Courtesy of Dr. John Kiernan, Department of Anatomy and Cell Biology, The University of Western Ontario.)

Different types of memory involve different neural circuitry (Figure 4). The working memory is short-term memory, which requires prefrontal cortices. The declarative memory is long-term memory, which involves personal experiences and conscious memory and requires the hippocampus for encoding. The procedural memory includes automatic actions, habits, or skills that are learned by repetition and requires the striatum and the cerebellum.

Given the overlap in declarative memory circuitry and pathology of TLE, memory impairment is common in the TLE patients. Verbal memory decline can be observed in 30–60% of the patients who undergo left anterior temporal lobectomy (ATL) [1–4]. Memory dysfunctions in TLE

patients before or after temporal lobectomy (TLY) can be used to understand human memory [5–8].

Epilepsy surgery is aimed at improving seizure outcome in patients that are resistant to medical therapy. The greater the resection area, the greater is the likelihood of achieving the surgical goals. However, the extent of resection is limited by the potential cognitive deficits. Intracarotid amobarbital (IAT), also known as Wada test, is used to minimize post-operative memory and language deficits in the TLE patients. Wada test is limited to the lateralization of function than its localization, and it carries certain inherent risks for being an invasive test. Several noninvasive techniques have the potential to replace Wada as a presurgical tool to evaluate

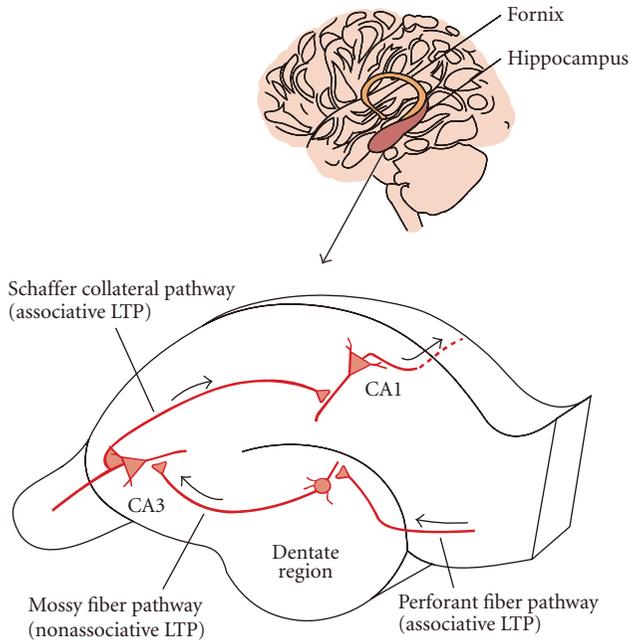


FIGURE 3: Perforant and intrahippocampal pathways.

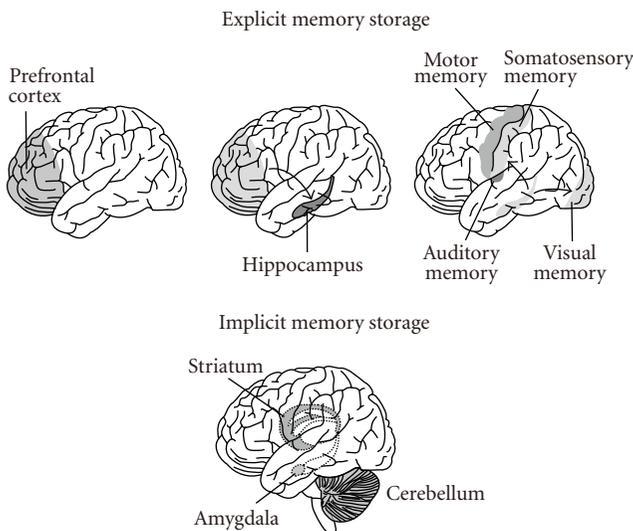


FIGURE 4: Neural substrates for different memory system.

language and memory functions in patients with TLE. These include positron emission tomography (PET), functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), and magnetoencephalography (MEG) [9, 10]. In this paper, we will focus on the role of fMRI in the assessment of memory function in the TLE patients. Language fMRI is highly reliable with a 90% concordance rate to the IAT [11–17]. Therefore, language fMRI has become a routine presurgical evaluation tool in most epilepsy surgery centers. One of the limitations of memory fMRI is a lack of an ideal memory paradigm that has high sensitivity and high specificity. Evidently, areas of activation during memory fMRI can be varied, depending on the nature of memory

and other cognitive demands introduced by the specific task paradigms. It also depends on other factors including the field of strength of the magnet, fMRI pulse sequence, and the level of cooperation and education of the participants. This paper will begin with a review of the memory systems and their anatomical correlates. This will be followed by a discussion on memory functions subserved by medial temporal structures and related functional imaging studies, the study fMRI paradigms, the role of memory fMRI in epilepsy, particularly its role in predicting a postoperative memory decline following TLY, and the prospect of replacing the IAT with memory fMRI.

## 2. Classification of Memory Systems and Its Implication in fMRI Studies

The memory is either explicit or implicit. Explicit memory refers to a memory in which instructions are given to remember the material during initial exposure. Implicit memory, on the other hand, refers to unintentional remembering of materials that were previously seen or learned. Conscious recollection of those learned materials is referred to as “declarative memory,” whereas recollection of the skill-based information where what has been learned is embedded in acquired procedures is referred to as nondeclarative (procedural) memory [18]. Procedural memory is the memory of how to do things. When needed, procedural memories are automatically retrieved and utilized for the execution of the step-by-step procedures involved in both cognitive and motor skills.

Memory can also be defined as episodic, semantic, working, or procedural memory. Episodic memory refers to a system that records, retains, and retrieves autobiographical knowledge about experiences that occurred at a specific place and time. Semantic memory stores general conceptual and factual knowledge that is not related to any specific temporal or spatial context. Working memory is a system for temporarily storing and managing the information required to carry out complex cognitive tasks such as learning, reasoning, and comprehension. Episodic memory, semantic memory, and working memory are explicit and declarative. Procedural memory is nondeclarative and can be explicit with conscious learning and implicit by effortless learning.

Most of the fMRI studies have used explicit memory-encoding paradigms, which depend more strongly on the cognitive ability and compliance of the subjects. Few studies have used implicit memory paradigm [19] during which the subjects were not asked to remember the items and no recognition test was administered after the scanning.

## 3. Memory Circuit and Neural Correlates

The role of mesial temporal structures in memory function was demonstrated by the case of H.M. who was rendered seizure free by bilateral temporal lobectomies but was unable to convert new memories into permanent memories while his working memories, long-term memories, and procedural memories were intact [20]. Episodic memory involves

encoding, registration, consolidation, retrieval, and reconstruction. Encoding is the process of transforming information into a format that is eventually used in long-term storage. Retrieval is the process of taking information out of the long-term storage. Mesial temporal structures, hippocampus in particular, are responsible for both encoding and retrieval processes. This explains why H.M. had marked impairment of converting short-term memory into a long-term memory. Working memory requires prefrontal cortex, whereas long-term memory is stored in the association cortices of the relevant sensory modalities (Figure 4). H.M.'s preserved implicit and procedural memory were due to his intact striatum and cerebellum [20]. Encoding and retrieval have been studied by the fMRI paradigms.

#### 4. Medial Temporal Lobe (MTL) Memory Functions and Related Functional Imaging Studies

Recognition of previously experienced stimuli has two distinct underlying memory processes, which are recollection and familiarity. MTL is involved in both recollection and familiarity. The mesial temporal lobe (MTL) structures can be subdivided into perirhinal cortex, the parahippocampal cortex (called postrhinal cortex in rodents), the entorhinal cortex, and the hippocampus (Figure 5).

The hippocampus is critical for recollection but not familiarity. The parahippocampal cortex also contributes to recollection, possibly via the representation and retrieval of contextual (especially spatial) information, whereas perirhinal cortex contributes to and is necessary for familiarity [22].

The perirhinal cortex and the lateral entorhinal area encode distinct items such as people, objects, or events (i.e., “What” information). Through reciprocal connections with neocortical association areas, this can facilitate subsequent judgments of familiarity. The parahippocampal cortex and the medial entorhinal area encode contextual representations (i.e., “Where” information), while the hippocampus associates items with their context resulting in recollection upon a memory cue.

Functional imaging studies regarding subregion neuronal substrates for memory processes have shown variable results; partly because the currently used task paradigms are unable to selectively activate the region of interests. For instance, a “recollection” task paradigm may also result in some familiarity-related activation. Moreover, structures within the MTL are in close proximity of each other and most of them are highly interconnected. Thus, neural processing that originates in one region can be expected to closely activate connected neighboring regions, resulting in more extensive MRI signal changes. As a result, many authors have concluded that activity in different MTL subregions tends to be correlated with recollection and/or familiarity [22].

Dissociation in the areas of activation is observed during recollection and familiarity. Activation of the hippocampus and the parahippocampal cortex is noted during both encoding and retrieval processes. In contrast, during familiarity

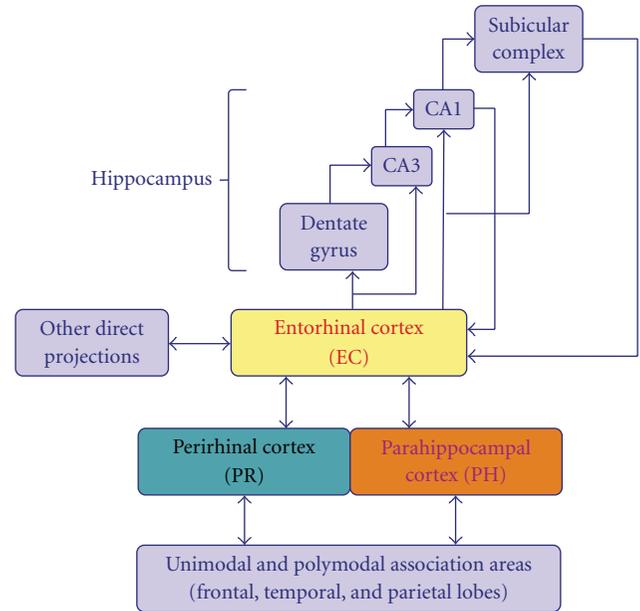


FIGURE 5: Diagram represents the MTL memory system connection for declarative memory; reciprocal connection among medial temporal subregions is demonstrated [21].

tasks, different pattern of activation is seen for encoding and retrieval processes with increased activation during encoding but reduced activation during retrieval because of increased familiarity.

There have been growing studies of functional neuroimaging including fMRI and diffusion tensor imaging (DTI) in TLE. Aside from functional mapping of the language and memory functions, many studies have demonstrated evidences of presumed epileptic networks and functional connectivity disturbance in patients with TLE. These observations provide additional support for performing functional neuroimaging studies in addition to the conventional anatomical studies, particularly in nonlesional cases. Bernhardt et al. proposed that the thalamus is an important hub in the epileptic network in TLE. They studied 36 patients with medically intractable TLE and compared them to 19 age- and sex-matched healthy controls [23]. For functional connectivity disturbance, a recent fMRI study by Morgan et al. demonstrated an increase in interhemispheric hippocampal connectivity as the epilepsy progresses longer than 10 years, even though it was initially disrupted. This is likely due to the fact that over time contralateral hippocampus exerts more influence over the ipsilateral hippocampus [24].

A recent DTI study by Keller et al. demonstrated widespread and bilaterally distributed water diffusion abnormalities, which are beyond the resolution of the conventional anatomical MRI, in patients with unilateral TLE of unknown cause. Another study revealed that DTI was able to demonstrate hippocampal abnormalities in normal-conventional MRI of the patients with TLE, which was different from those found in patients with hippocampal sclerosis (HS) [25].

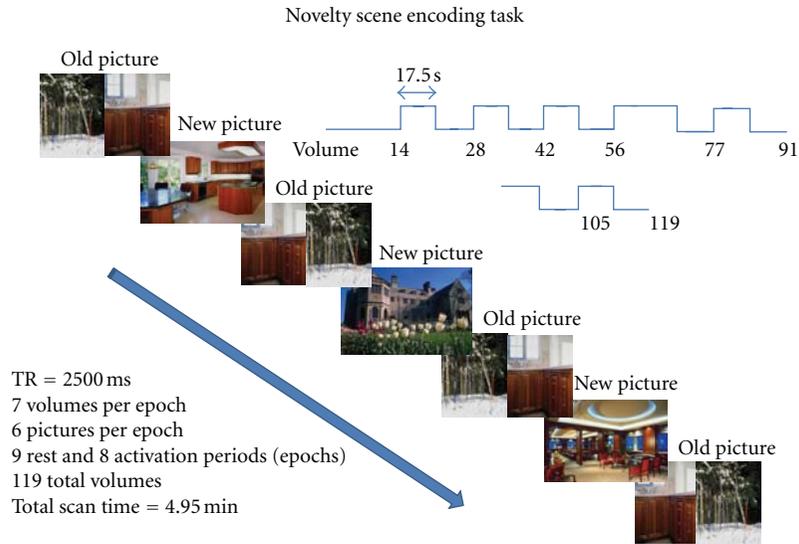


FIGURE 6: Novelty scene encoding task. At the time of encoding, participants are presented novel scenes that are either indoor or outdoor. During the baseline phase, repeated scenes are presented. Participants are instructed to classify the scenes as “indoor” or “outdoor.”

Combining functional neuroimaging with high-field conventional anatomical MRI should increase our understanding of the epileptic and functional networks and may facilitate localization of potential epileptogenic focus.

## 5. Memory Paradigms for fMRI

The main objective of the memory fMRI in TLE is presurgical evaluation. This may help to predict the risk of memory deficits after TLY and to plan strategies that spare functional tissue. Memory fMRI may also have a predictive value for lateralization of the seizure foci in TLE. PET studies by Lepage et al. demonstrated different areas of activation within MTL, encoding in the anterior MTL, and retrieval in the posterior MTL [26]. These findings were contradictory to the fMRI findings, posterior MTL was associated with encoding [27–29]. There are few fMRI studies on retrieval that show activation in the anterior MTL, particularly the subiculum [30]. The same study showed increased activation for novelty encoding in the posterior MTL, particularly the parahippocampus [30].

Most of the preoperative memory fMRI studies have employed an encoding task for the episodic memory. These studies have dealt with different aspects of episodic memory such as novelty, verbal or nonverbal tasks. Event-related or block-designed paradigms have been used in different studies.

## 6. Material-Specific Memory fMRI Paradigms (Verbal versus Nonverbal)

The lateralization of encoding process is invariably dependent on the material types. Golby et al. found that verbal encoding tasks (i.e., sentence completion) activated the

inferior prefrontal cortex and the MTL more on the left side, pattern encoding (i.e., colour images of abstract patterns) more on the right side, whereas scene encoding (i.e., indoor and outdoor scenes) and faces symmetrically on both sides [31]. Powell et al. also noted that activation was left-lateralized for word encoding, bilateral for picture encoding, and right-lateralized for face encoding [32].

fMRI paradigms that produce bilateral MTL activation of MTL structures in the healthy control subjects are ideal for the presurgical evaluation of memory function in the TLE patients. Novelty scene encoding paradigm is suitable for this purpose that has shown an asymmetry of activation between the affected and unaffected MTL structures in patients with TLE [33–36] (Figures 6, 7, 8, and 9). One fMRI study using scene encoding task revealed that extent of activation within the ipsilateral MTL structures detected by fMRI during complex visual scene encoding was predictive of memory outcome [34]. This needs to be confirmed by larger studies before it can be used clinically to predict memory outcome after TLY. Greater hippocampal activation contralateral to the epileptic focus may indicate low risk of developing global amnesia. However, it is less reliable in predicting the postoperative memory deficits because the activation in that hemisphere may partly reflect brain reorganization with shift of activation from the epileptic hemisphere. The shifted activation may not necessarily represent functionally meaningful memory. In other words, a large area of activation on the contralateral side may serve as a compensatory mechanism and the patients may still have postoperative memory decline. Richardson et al. noted that activation of the right hippocampus during a verbal memory task in the left TLE patients was “dysfunctional” and it did not predict memory function postoperatively [35]. This was recently confirmed in a study by Binder et al. [36] in which they compared the predictive value of language lateralization and scene encoding

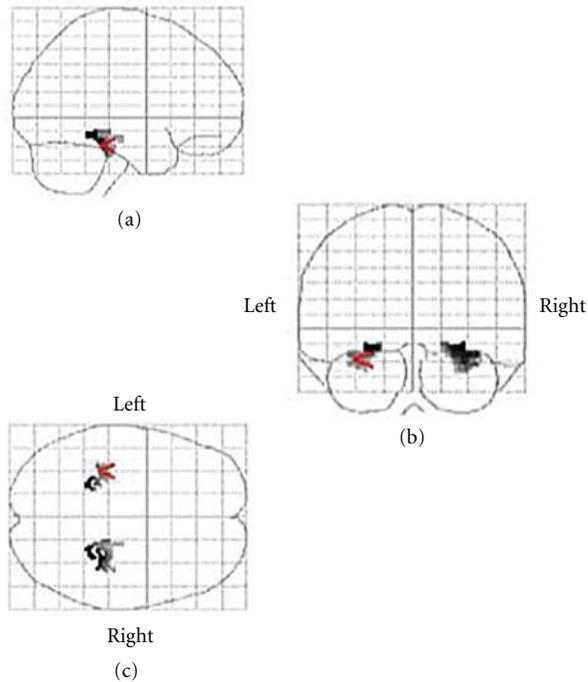


FIGURE 7: Relatively symmetrical mesial temporal structures are activated in the healthy normal control subjects during a novelty scene encoding task.

task paradigms. They found that hippocampal activation asymmetry during scene encoding was strongly correlated to the side of seizure focus and memory asymmetry scores in Wada test but it was unrelated to verbal memory outcome. Among their 30 left TLE patients, 13 had markedly discordant language and hippocampal laterality indexes (LIs). In at least five of the discordant cases, there were large memory declines despite preoperative hippocampal activation that strongly lateralized to the right. However, there was a tendency that the more area of activation on the same side as seizure focus, the more likely do the patients have postoperative memory decline. This was first observed by Rabin et al. who showed that absolute activation in the MTL structures ipsilateral to the epileptic focus had a significant negative correlation with a change in discrimination scores postoperatively. Lower activation in the epileptic temporal lobe was associated with a smaller decline or improvement in memory performance postoperatively, supporting the functional adequacy model [34].

To define functional area of verbal memory in hoping to predict the postoperative memory decline, we need a paradigm that is capable of specifically identifying this area (material-specific paradigm). Verbal memory encoding paradigm is a good option. Richardson et al. showed that right-handed patients with left hippocampal sclerosis preferentially activate the right hippocampal formation in a verbal memory encoding task. The distribution of activity between left and right hippocampi during this verbal encoding task reflects the severity of left hippocampal sclerosis [37]. They subsequently showed that relatively greater verbal memory

encoding activation in left hippocampus compared to the right hippocampus predicted the extent of verbal memory decline in right-handed patients with left hippocampal sclerosis undergoing left anterior temporal lobe resection [38].

A recent study by Bonelli et al. showed that among 72 patients with unilateral mTLE (41 left) and 20 healthy controls who underwent memory encoding for pictures, words, and faces. They reported greater left than right anterior hippocampal activation that in left TLE patients on word encoding correlated with greater verbal memory decline after left anterior TLY, while greater right than left anterior hippocampal activation on face encoding predicted greater visual memory decline after right anterior TLY. This supports the benefit of using purely verbal memory paradigm as words and purely nonverbal memory paradigm as face (or pattern) in predicting verbal and nonverbal memory decline in left and right mTLE, respectively [39].

Binder et al. carried out a preoperative language mapping to predict postoperative verbal memory decline. They demonstrated that language lateralization measured was the second most powerful predictor for verbal memory decline (added 10% additional predictive power), for which preoperative memory performance was accounted for the most powerful predictor. Patients with higher preoperative test scores showed larger declines. Whereas neither Wada memory asymmetry, nor did Wada language asymmetry have additional predictive values beyond other noninvasive measures [40].

## 7. Block Design and Event-Related Paradigms

Even though several studies have shown predictive value of performing fMRI with encoding memory paradigm to predict postoperative memory decline, one fact should be kept in mind is that these encoding-related activation was localized to the posterior hippocampus and parahippocampal regions, not anterior MTL structures, which is resected during a standard TLY. Most studies which have used block designs have generally revealed more posterior mesial temporal activations in individual subjects [33, 41]. Therefore, ideally, a paradigm that is able to activate the anterior temporal structures should be an optimal paradigm for this purpose.

The more anterior mesial temporal activations, particularly the hippocampal activations, have so far been reported at group levels, especially when event-related designs were used. Constable et al. demonstrated that the block design paradigm provides strong posterior activation, likely related more to visual scene processing, whereas the event-related design provides more anterior hippocampal activation with the encoding of novel scenes [42].

Powell et al. demonstrated that only event-related studies allow the identification of brain regions showing greater activation during the encoding of items that are subsequently remembered compared with items that are forgotten, which are then taken as candidate neural correlates of memory function. They argue that event-related paradigm is more

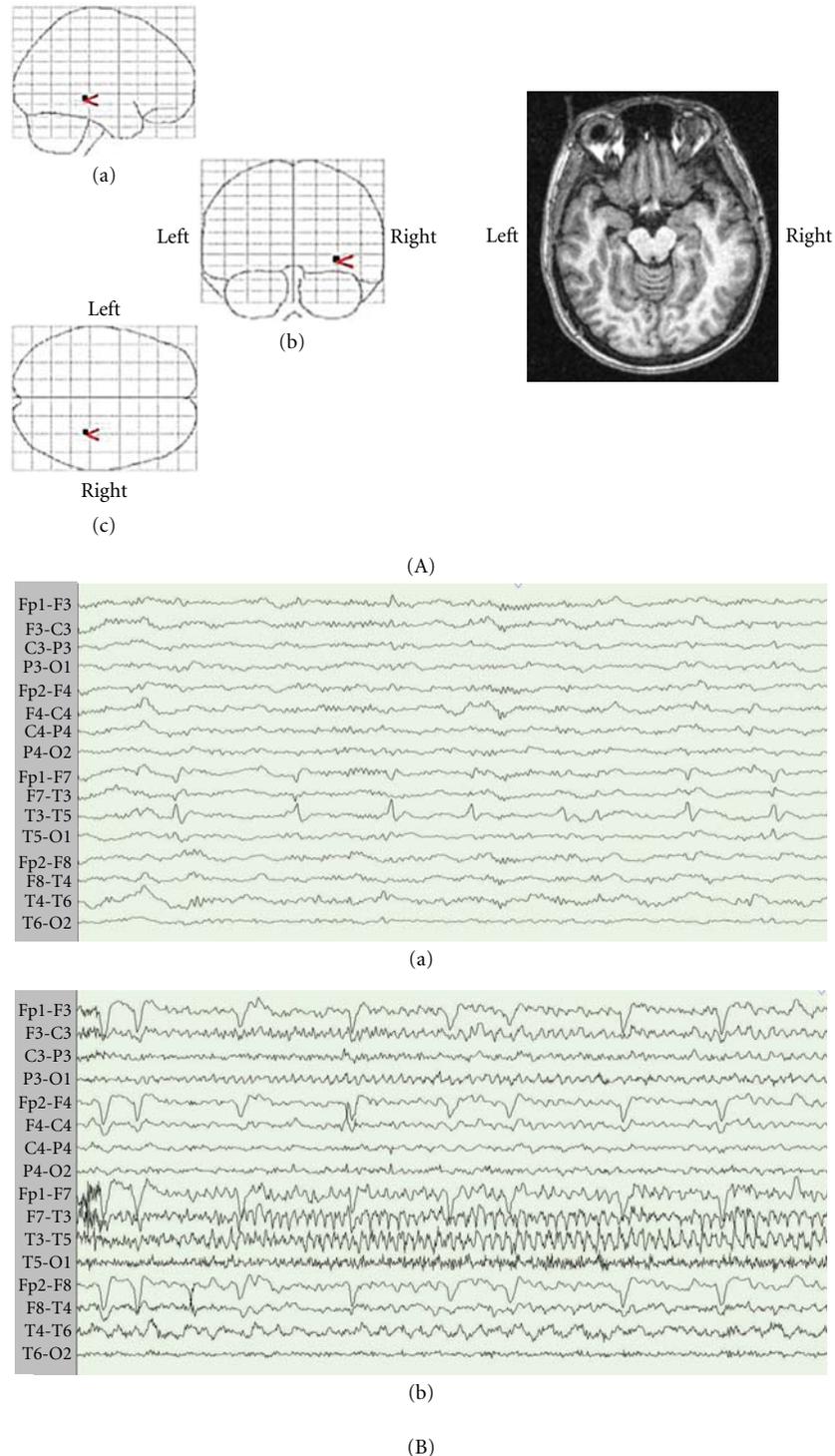


FIGURE 8: (A) Unilateral activation of the right mesial temporal structures in a patient with left mesial temporal sclerosis, during the novelty scene encoding task. (B) Left anterior to mid-temporal interictal epileptiform discharges (a) in the same patient as (A), and ictal EEG revealed left temporal originating seizure (b).

reliable than block designs, revealing anterior hippocampal activation. However, there is a relatively less activation with event-related paradigms than block design paradigms [32]. Autobiography memory retrieval task is one of the promising

event-related paradigms that has been shown to demonstrate discernible activation in the memory network [43]. This may be employed in the future study to predict the postoperative memory decline.

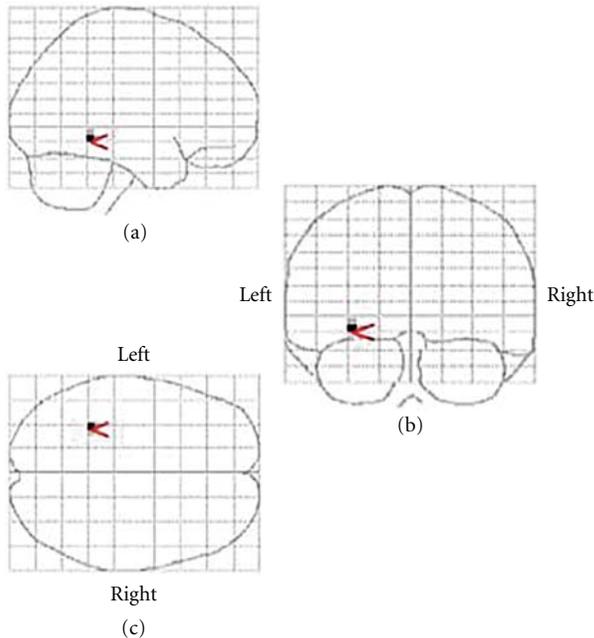


FIGURE 9: Unilateral left mesial temporal structures activation in the patient with right mesial temporal sclerosis, during novelty scene encoding task.

## 8. Novelty and Repeated Tasks (Familiarized) Paradigms

Some earlier studies failed to show activation within the MTL structures during a novelty encoding task [44, 45]. Henke et al. found hippocampal and parahippocampal activation only during associative learning and it was not seen during other tasks including novelty encoding.

Subsequently, in a study by Gabrieli et al., five of six subjects showed greater activation in the posterior MTL location for novelty encoding scenes. They concluded that parahippocampal activation could reflect memory processes that distinguish between familiar and unfamiliar stimuli [30]. Many subsequent studies have supported the possibility that the activation associated with novelty occurs more often in the posterior parahippocampus and adjacent fusiform gyrus than in the hippocampus proper [27, 46, 47].

However, a number of other imaging studies have shown stronger hippocampal activation for meaningful relative to meaningless stimuli and associative/semantic relative to non-semantic tasks. Hunkin et al. demonstrated that mesial temporal novelty-related activations occurred for novel verbal associations (subjects were required to generate a vivid, imaginable sentence linking the three words given together), but not for novel verbal items. Binder et al. studied hippocampal activation patterns during encoding protocols emphasizing either novelty or relational processing. In the novelty contrast, they compared activation between encoding of novel scenes and a repeated pairs of scenes. In the relational processing contrast, to exclusively elucidate the effect of relational process, they compared between encoding novel scenes and structural encoding of scrambled scenes. They found that

the relational processing protocol resulted in a larger volume of hippocampal activation when compared with the novelty contrast protocol.

Novelty scene encoding paradigm has been used in most fMRI studies. Some of these studies employed scrambled images as their control, while others have used repeated scenes. We have adopted the latter protocol using repeated scenes as controls at our centre (Figure 6). Lately, there was a study directly comparing the hippocampal activation patterns of two paradigms, the authors found that the relational processing contrast encoding of novel scenes compared with structural encoding of scrambled images control design resulted in a larger volume of hippocampal activation, as compared to the novelty contrast encoding of novel scenes compared with encoding of a repeated pair of scenes [48]. However, this has to be proved by further studies.

## 9. Predictive Value of fMRI for Memory Decline after Temporal Lobectomy

There has been some progress in using preoperative fMRI to predict postoperative verbal memory decline. However, this is of limited clinical utility in patients with nondominant TLE where postoperative neuropsychological testing shows no deficits or improvement in verbal memory because patients are on less medication. There is still controversy on the presence of fMRI paradigm(s) that can be equally used in patients with dominant and nondominant TLE. It remains unclear on how to interpret the asymmetry in fMRI activation patterns. More contralateral activation than ipsilateral activation may support the functional reserve model, while unilateral activation on the ipsilateral side may support the functional adequacy model. Hippocampal reserve refers to the capacity of the contralateral hippocampus to support memory after surgery, while the functional adequacy refers to a possible significant decline in memory after ATL in patients with a higher baseline memory performance than those with lower baseline memory performance.

Most of the memory fMRI studies have been supportive of functional adequacy model, implying that individuals with greater ipsilateral activation compared with the contralateral mesial temporal activation have a greater memory decline following temporal lobectomy [39, 40, 49–51]. Similarly, Rabin et al. showed a significant inverse correlation between ipsilateral activation and memory outcome after TLY [34]. Additionally, Powell et al. demonstrated that reorganization of the intact MTL was incapable of preserving memory function [52]. Memory and language fMRI studies in prediction of postoperative verbal memory decline following a temporal lobectomy are summarized and shown in Table 1.

## 10. Can fMRI Replace the Intracarotid Amobarbital Test (IAT) for Presurgical Evaluation of Memory Function?

The intracarotid amobarbital (IAT), also known as Wada test, is an invasive procedure with a potential for complications

TABLE 1: Memory and language fMRI studies in prediction of postoperative verbal memory decline following a temporal lobectomy.

Authors	Year	Number	Memory paradigms	Summary	Remarks
Rabin et al. [34]	2004	35 (20 Rt/15 Lt)	Complex visual scene encoding	Significant inverse correlation between activation ipsilateral to temporal lobectomy and memory outcome. No significant correlation in the contralateral activation	fMRI ARs correlated significantly with memory lateralization by IAT
Richardson et al. [37]	2004	10 (all Lt)	Verbal memory encoding	Relatively greater verbal memory encoding activity in left HC compared with right HC, as measured using fMRI, predicts the extent of verbal memory decline in the same subjects	Material specific (verbal)
Richardson et al. [35]	2006	30 (all Lt, 12 underwent ATL)	Verbal memory encoding	Functional adequacy of left HC best predicts postoperative memory outcome in left HS	Material specific (verbal), event related
Binder et al. [40]	2008	60 (all Lt)	Language	Lateralization of language is correlated with lateralization of verbal memory	Wada memory testing is insufficiently reliable
Powell et al. [49]	2008	15 (7 Rt/8 Lt)	Encoding of words (verbal), pictures, and faces	Relatively greater ipsilateral activation had greater memory decline	Supports the functional adequacy theory of HC function
Frings et al. [50]	2008	22 (10 Rt/12 Lt)	Encoding and recognition of object locations	Positive correlation between the degree of ipsilaterality lateralized HC activation and postsurgical verbal memory decline	Nonverbal paradigm predicts postsurgical verbal memory decline
Binder et al. [36]	2010	67 (37 Rt/30 Lt)	Language and scene memory encoding	Risk of verbal memory decline is more closely correlated with language lateralization than with overall asymmetry of episodic memory processes	Language paradigm to predict verbal memory decline
Bonelli et al. [39]	2010	72 (31 Rt/41 Lt)	Encoding of words (verbal), pictures, and faces	Preoperative memory fMRI was the strongest predictor of verbal and visual memory decline	Memory fMRI in prediction of both postsurgical verbal and visual memory decline
Dupont et al. [51]	2010	25 (14 Rt/11 Lt)	Scene encoding and recognition	fMRI activation during a delayed-recognition task is a better predictor of individual postoperative verbal memory outcome than is the Wada test	Only one study revealed marked discordant LI between memory fMRI and Wada test (only 48% of the patients showed concordant result)

Rt: right; Lt: left; AR: asymmetry ratio; IAT: intracarotid sodium amytal test; HC: hippocampus; ATL: anterior temporal lobectomy; HS: hippocampal sclerosis; LI: laterality index.

such as stroke or death [53]. Predictive value of IAT for postoperative memory decline is not conclusive. Since its first use by Wada to lateralize language function in 1950s [54, 55] and Milner to predict the postoperative decline in memory after TLY [56], the predictive accuracy and added values of IAT to other noninvasive data remain controversial. It has been shown that IAT was of no added benefits to predict postoperative memory decline to a comprehensive preoperative neuropsychological evaluation [2, 4, 57–59], age at onset of epilepsy [60, 61], plus high resolution anatomical MRI in left TLE [59, 62, 63], even though is considered the gold standard test. Several advanced noninvasive technologies including fMRI have the potential to replace IAT. Additionally, it is still debated on how to interpret the IAT results. Some authors support the functional reserve model [57, 64], whereas many others support the functional adequacy model [2, 65, 66].

Over the past decade, all of these have led to a question that it is time to replace Wada test with other techniques [67–70].

*10.1. Concordance between fMRI and IAT Results.* In a study by Detre et al., there was 100% concordance between fMRI and IAT in nine patients [33]. Deblaere et al. demonstrated that fMRI activation pattern in the MTL that lateralized to the contralateral hemisphere was stronger than the IAT result, that is, relatively higher laterality index (LI) from the fMRI result when compared with IAT. This might help better determine the side of seizure focus with certainty. However, the side of lateralization obtained from fMRI was in agreement with IAT results in only those patients with right-sided TLE [35]. Binder et al. noted that the anterior hippocampus LI and whole hippocampus LI were significantly correlated

with Wada memory asymmetry in either left- or right-sided TLE [36]. Over the past decade, most of the studies have shown that memory asymmetry with fMRI is concordant to the memory asymmetry scores in IAT. Dupont et al. demonstrated striking discordance between fMRI LI and Wada LI. Only 48% (12) of their 25 patients showed concordance between fMRI LI and Wada LI. They noted fMRI was better than IAT in accurately predicting postoperative memory changes [51].

## 11. Summary

Memory decline is a major concern after TLY. With optimal study paradigms and higher resolution MR scanners, fMRI has the potential to replace IAT to evaluate this risk non-invasively. Given the diverse nature of human memory and multiple roles served by the temporal lobes for this function, a panel of tests is necessary to probe each aspect of the memory, including verbal, nonverbal, encoding, and retrieval. Sentence completion task and naming paradigms are better suited to study verbal memory, while face recognition is better suited for nonverbal memory. Novelty scene paradigm and autobiographical memory result in a relatively symmetrical activation bilaterally and each tests a unique feature of temporal lobe function, that is, encoding and retrieval, respectively. Given the inherent limitations to perform fMRI in patients with epilepsy such as fatigue, possible seizures during the study, poor concentration, and so forth paradigms with higher specificity and sensitivity should be utilized. Novelty scene encoding and autobiographical memory have the potential to serve this role but further studies in larger population are required to validate this. Language paradigms have shown promising results in predicting verbal memory decline after TLY especially in dominant hemisphere for language function. Paradigms that result in greater activation of the anterior MTL are ideal because standard TLY removes the anterior portions of temporal lobes. Novelty scene encoding results in greater activation of the mid to posterior regions of the MTL. The role of language fMRI to predict postoperative decline in verbal memory is promising. The prognostic accuracy of fMRI to aid in prediction of postoperative memory changes is equal to better than that of the IAT.

## Acknowledgments

The authors wish to thank Dr. John Kiernan, Frank Bihari, Chukiat Limotai, and Dr. Natlada Limotai for preparing figures and providing them helpful suggestions.

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## Review Article

# Atypical Febrile Seizures, Mesial Temporal Lobe Epilepsy, and Dual Pathology

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Received 25 December 2011; Revised 2 February 2012; Accepted 7 February 2012

Academic Editor: Seyed M. Mirsattari

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Febrile seizures occurring in the neonatal period, especially when prolonged, are thought to be involved in the later development of mesial temporal lobe epilepsy (mTLE) in children. The presence of an often undetected, underlying cortical malformation has also been reported to be implicated in the epileptogenesis process following febrile seizures. This paper highlights some of the various animal models of febrile seizures and of cortical malformation and portrays a two-hit model that efficiently mimics these two insults and leads to spontaneous recurrent seizures in adult rats. Potential mechanisms are further proposed to explain how these two insults may each, or together, contribute to network hyperexcitability and epileptogenesis. Finally the clinical relevance of the two-hit model is briefly discussed in light of a therapeutic and preventive approach to mTLE.

## 1. Introduction

Mesial temporal lobe epilepsy (mTLE) is the most common form of partial epilepsy in humans and is generally refractory to treatment [1]. It is characterized by seizures that originate in limbic structures, namely, the hippocampus, the parahippocampal gyrus and the amygdala. In approximately 65% of people suffering from this form of epilepsy, the underlying pathology is Ammon's horn sclerosis characterized by neuronal loss, gliosis and atrophy of the hippocampus. While mTLE classically begins in teenagers and sometimes even adulthood, the initial insult is thought to be neurodevelopmental and to happen in early life, namely, after prolonged febrile seizures (FSs) [2]. Two prevailing hypotheses exist to explain the possible relationship between prolonged FS, hippocampal sclerosis, and mTLE. The first hypothesis states that hippocampal sclerosis predisposes to prolonged FS and mTLE. The second, supported by a wide body of recent evidence, suggests that prolonged FS may in fact arise from an already predisposed brain due to anatomical and/or

genetic alterations, but it is the prolonged FS that leads to hippocampal sclerosis and mTLE later in life [3].

To study the pathophysiology of mTLE, several animal models have been developed in the past two decades. Experimental animal modeling stands on the important assumption that understanding fundamental mechanisms of action will help us in the elaboration of more effective treatments and therapeutic strategies for human diseases. The translational impact of experimental evidence from the study of FS and mTLE has been limited by the complexity of these clinical conditions, more specifically their uncertain causal relationship. However, recent clinical data appear to support the fact that prolonged FS, more specifically febrile status epilepticus, directly leads to hippocampal injury and mTLE [4]. Here, we will review several animal models that have been developed to study the putative biological substrate and risk factors behind the development of mTLE in humans. We will focus on two important developmental risk factors, namely, prolonged febrile seizures and cortical malformations as we propose a two-hit model of mTLE. To conclude

we will discuss the impact of these findings on future clinical management.

## 2. Animal Studies

**2.1. Animal Models of Febrile Seizures.** Febrile seizures (FSs) are a common neurological disorder that usually involves 2 to 5% of children between the age of 6 months and 6 years old with a peak incidence in toddlers of 12 to 18 months [5–7]. FSs can be separated into two categories: simple and atypical. Simple FSs are generalized and brief seizures (lasting <15 min) that do not recur within 24 hours. Atypical FSs are prolonged (>15 min), recurrent within 24 hours, or lateralized seizures or express more than one of these characteristics. In contrast to simple FSs that generally have no long-term consequences, prolonged FSs, more specifically febrile status epilepticus (lasting >30 min), have been associated with mTLE [3, 5, 8–10]. Based on retrospective clinical studies, it has been shown that up to 30 to 60% of patients with mTLE have a past history of prolonged FSs [2, 7, 11–13]. In one important yet controversial series, children with atypical febrile seizures showed an eightfold increased risk of developing epilepsy compared to those with simple FSs and controls [14]. Thus, one needs to understand what causes some individuals to experience prolonged FSs in order to try to prevent them. To study this, several animal models have been elaborated to mimic fever and FSs.

**2.1.1. Hyperthermia as a Model of Febrile Seizures.** Several experimental paradigms have been used to mimic the increase in core body temperature occurring during episodes of fever. Multiple studies have artificially evoked hyperthermia-induced seizures (HSs) to determine how FSs are generated. The most stable and most accepted model is hyperthermia-induced by hot dry air [11, 15–17]. HSs have been provoked in rats by many other methods such as exposure to an infrared lamp [18], infrared rays [19], microwaves [20, 21], a heated pad [22], or warm water [23]. However, the use of these apparatus was restricted because of high morbidity, mortality, and clinical variability. In contrast, models of HSs induced by exposure to heated dry air develop highly stereotypical generalized seizures that are reproducible and easy to characterize, with minimal or no mortality [2, 3, 7, 9, 11, 12, 15, 17, 24]. Like in humans, this model leads to the development of age-specific seizures that, when brief, do not lead to the development of spontaneous seizures later in life. However, when seizures are prolonged, up to 33% of naive rats develop electroclinical seizures in adulthood [11, 24]. The original studies have reported changes in hippocampal excitability, gene expression, and network effects but without the typical changes observed in mTLE such as neuronal loss, mossy fiber sprouting, or neurogenesis [25–27]. However, in these models, the duration of the seizure is determined by the duration of the exposure to high temperature rather than by individual vulnerability.

**2.1.2. Lipopolysaccharide- (LPS-) Induced FSs.** Many experimental models have used hyperthermia to induce convulsions as a model to study FSs [15, 18, 28, 29]. This is because

most of the developing animals experience seizures when they reach a high core temperature and because hyperthermia and fever share common mechanisms to elicit seizures such as the release of cytokines including interleukin-1 $\beta$  (IL-1 $\beta$ ) [11, 27, 30]. This particular cytokine seems key to generate FSs in young rats based on the evidence that rats lacking the interleukin-1 receptor type I (IL-1R1) gene exhibit a much higher temperature threshold necessary to develop FSs [11, 27]. In the hippocampus, IL-1 receptors are expressed in high density [31] and their stimulation triggers a cascade of downstream effects through mitogen-activated protein (MAP) kinase and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) signalling. This could alter gene expression and transform normal neuronal circuitry into a proconvulsive epileptic network [5, 8, 32]. However, even if the IL-1 $\beta$  pathway seems to be a crucial and shared mechanism of both hyperthermia and fever, its activation may not fully or appropriately imitate FSs as fever reflects a regulated increase of body temperature resulting from a broader immune challenge. The common precipitating event in both simple and prolonged FSs is an infection with a bacterial or viral agent. This induces a febrile response, which involves the elaboration of several inflammatory cytokines that include not only interleukin-1 $\beta$  but also IL-6 and tumor necrosis factor (TNF)  $\alpha$ . These cytokines, released by activated leukocytes, lead to the production of prostaglandins such as cyclooxygenase-2/3 and prostaglandin E2 in the preoptic nuclei of the hypothalamus. This then results in an upregulation in thermostatic set point for body temperature and then fever [33, 34]. However, apart from the fibrogenic properties of inflammatory cytokines, there is increasing evidence that they play a direct role in the generation of FSs. Clinical studies have shown that peripheral leukocytes obtained from children with FSs show an exaggerated IL-1 $\beta$  release to a challenge with lipopolysaccharide (LPS) [35–37] or viral RNA [38]. Injection of bacterial lipopolysaccharide (LPS) *in vivo* in animals is another interesting experimental approach to study the role of proinflammatory cytokines in fever challenge at the systemic level. However, the rise in temperature is somewhat limited and is not sufficient to induce seizures in naive animals. Heida et al. were the first to demonstrate a causal relationship between IL-1 $\beta$  and FSs in an experimental model of FSs using LPS [28, 30]. In this study immature rats were first injected with LPS, which produced a mild fever without a seizure but by giving a subconvulsive dose of kainite, seizures are induced in 50% of pups pretreated with LPS [28]. IL-1 $\beta$  is thought to lead to the generation of FSs through its effects on inhibition, by reducing GABA<sub>A</sub> receptor currents [39], or through promoting glutamatergic mediated excitatory effects, by increasing calcium conductance through N-methyl-d-aspartate (NMDA) receptors [40].

**2.1.3. Viral Mediation of Febrile Seizures?** Some clinical studies have pointed that the human herpes virus 6 (HHV-6) could be a putative link between FSs and mTLE. Some studies suggest that HHV-6 infection happens prior to the occurrence of FSs. Other studies found HHV-6 DNA in brain tissue removed during surgery for mTLE [41, 42]. However,

only a minority of primary HHV-6 infections may be associated with FSs [5, 43, 44]. Another virus of the herpes family, the Herpes simplex virus type 1 (HSV-1), causes the limbic seizures by reducing dynorphin expression in the dentate gyrus of hippocampus in rats, leading to seizures [45, 46]. Inherited dynorphin promoter polymorphisms are associated with temporal lobe epilepsy and febrile seizures in human. In animals, the dynorphin system in the hippocampus regulates excitability. These findings show a vulnerability of hippocampal dynorphin during herpes infection, and this may highlight a neurochemical basis for limbic seizures following viral infections.

Overall the evidence summarized here indicates that prolonged FSs contribute to epileptogenesis rather than being simply a marker of an epileptic tendency. In addition, the duration of the FSs seems to be an important factor of the development of subsequent epilepsy in the nonpredisposed brain. These findings suggest that preventing prolonged FSs could be a key therapeutic goal. However, it has recently been shown that prolonged FSs are often unrecognized in the emergency room [10]. Therefore, early identification of children at risk for prolonged FSs and epileptogenesis could be a better strategy to prevent mTLE.

**2.2. Animal Models of Cortical Malformation.** In order to understand how underlying cortical malformations may be implicated in epileptogenesis and developmental delay, various animal models were developed. A good animal model for malformation of cortical development should display (1) hyperexcitable brain regions and (2) macroscopic as well as microscopic structural abnormalities that are similar to the human pathology [47]. Many of these models have been yielding interesting results.

**2.2.1. MAM Chemical Lesion Model.** Methylazoxymethanol acetate or MAM is a teratogenic alkylating neurotoxin which specifically blocks mitosis of neuroepithelial cells actively dividing during development, without affecting the postmitotic cells. When administered to pregnant rats (intraperitoneal injection at embryonic day 15 (E15)) [48], MAM causes multifocal cerebral malformations in the rat pups including microcephaly, cortical thinning, loss of lamination, and cortical and hippocampal heterotopia [49, 50]. The heterotopic neurons displayed hyperexcitable properties, and these animals showed a diminished seizure threshold to various proconvulsant agents such as kainic acid [48, 51] or hippocampal electrical kindling [52]. Interestingly, no long-term spontaneous recurrent seizures (SRSs) were generally reported in this model, although Harrington et al. [54] described some electrographic seizures in 2 out of 11 MAM-treated animals. Some of the molecular and cell mechanisms of MAM-induced hyperexcitability include altered cell firing due to smaller calcium-activated potassium ( $K^+$ ) currents affecting membrane potential after-hyperpolarization [53, 54], lack of fast A-type  $Kv4.2K^+$  currents on heterotopic neurons [55], modification of N-methyl-D-aspartate receptor subtype 2A/B (NR2A/B) expression in heterotopic neurons [56], and diminution in inhibitory synaptic activity

in heterotopic neurons [57] suggesting profound changes of heterotopic neurons. The MAM model has the advantage of having a specific effect on neuroepithelial cells, not affecting astrocytic cells and not affecting cells from other organs which have a different ontogenic precursor [58]. However, in order for the MAM administration to be reliable, the first day of gestation must always accurately be identified. In any case, this model yields a more diffuse cortical dysplasia than what is observed clinically [59] and does not show spontaneous recurrent seizures alone [47]. Nonetheless, MAM-treated pups are more susceptible to the epileptogenic effects of prolonged FSs with all animals developing epilepsy [60].

**2.2.2. In Utero Irradiation Model.** The *in utero* irradiation model is obtained by exposing pregnant rats at E17 to radiation doses as low as 100 centigray (cGy) to as high as 225 cGy of external gamma radiation from a linear accelerator source [61, 62]. The irradiated cortex shows diffuse cortical dysplasia, similar to the MAM model, along with microcephaly characterized by a 50% diminution in cortical thickness [63], agenesis, hypoplasia, and the presence of heterotopic neurons, sign of a severe migrational abnormality [64]. Indeed, at E17 layer II/III cortical neurons are still migrating and are therefore most severely affected by the radiation [65]. Treated animals have been shown to display interictal epileptiform activity visible in the cortex as well as in the hippocampus; however, spontaneous recurrent seizures occurred only in a subset of irradiated animals, depending on the radiation dose. The manifestations of these clinical seizures was quite typical of limbic seizures including staring, facial twitches, wet dog shakes, and limb clonus [61, 64, 66]. Looking at the network and cellular levels, slices obtained from radiation-treated animals are more excitable as seen by spontaneous and evoked field potentials in slices of neocortex [62]. Furthermore, electrophysiological recordings have shown that the excitatory activity in slices coming from irradiated animals is greater relative to untreated controls and that the inhibitory activity is diminished [26], which may be explained by a diminution in activity of somatostatin and parvalbumin containing inhibitory interneurons in the irradiated group [67]. Therefore, an imbalance between excitation and inhibition is involved in the neocortical hyperactivity leading to the presence of epileptiform events in this model. The *in utero* irradiation model has the advantage of being noninvasive to the offspring, which induces less stress; however, it yields a diffuse type of cortical dysplasia distinct from the typical clinical situation [64]. In any case, studies looking at the vulnerability of irradiated pups to FSs have, to our knowledge, not yet been done.

**2.2.3. Neonatal Freeze Lesion Model.** The freeze-lesion-induced cortical malformation in rats was developed by Dvorak and Feit [68] and closely resembles the polymicrogyrus observed in humans, in that it yields the formation of a four-layer neocortex rather than the typical six. To achieve this model, one-day-old rat pups are anaesthetized with isoflurane, their scalp cut at the midline and opened, and a frozen 2 mm large probe is placed on the soft cranium overlying the

sensorimotor cortex for a period of ten seconds [9, 17]. It should be noted however that the probe width, the lesion duration, and the number of lesions may vary from one study to another. In all cases, contact with the frozen probe causes an immediate focal necrotic lesion, followed by neuronal migration to repair the damaged region, which explains why lesions should be done at a very young age when cells are still in a migratory state [69]. Indeed, glial fibrillary acidic protein (GFAP) as well as bromodeoxyuridine (BrdU) expressing cells were found in high levels within the dysplastic cortex suggesting the presence of still proliferating astrocytic cells [70]. The polymicrogyrus later obtained following the freeze lesion in rat is very similar to what would be observed in a focal human neuronal migration disorder [71, 72]. Fiber reorganization occurs within the cortical and subcortical layers of lesion rats as thalamocortical and corticothalamic projections are shown to be affected, possibly implicated in the process of epileptogenesis [73]. Disorganized projections were also seen by Brill and Huguenard who noted more inputs coming from infra- and supragranular cortical layers synapsing onto layer V pyramidal cells than in controls [74].

On top of the macroscopic modifications taking place in the dysplastic cortex, other changes at the molecular level occur and seem to unbalance the excitation/inhibition equilibrium favoring excitation. Looking at the expression of excitatory glutamate receptors, an autoradiography study showed that NMDA, AMPA, and KA receptor levels were elevated within the dysplastic cortex [75, 76], while they were unchanged when measures were taken in the surrounding normal cortex [77], suggesting the presence of a spatial gradient of ionotropic glutamate receptors with a greater concentration within the polymicrogyrus. Amongst the NMDA receptors, the NR2B subunit seems to be of great importance to the epileptogenicity of the lesion as the NR2B currents are functionally enhanced, and specific NR2B antagonists limit the spread of the epileptiform activity [71, 78], although it was shown that an AMPAR antagonist may block more widespread epileptiform activity measured extracellularly [79]. On the other hand, looking at inhibitory activity, the same autoradiography study showed lowered GABA<sub>A</sub> and GABA<sub>B</sub> binding within the dysplastic cortex [76] and a downregulation of GABA<sub>A</sub> inhibition has been shown electrophysiologically in the freeze model [75]. However, no interneuron cell loss was reported near or far from the lesion [80, 81]. This widespread modification in various GABA<sub>A</sub> subunits can be the cause of the decrease in inhibitory activity [82]. It is, however, also plausible that the GABA<sub>A</sub> inhibition downregulation may not be directly involved in the hyperexcitability observed, as the somatostatin-positive interneuron loss occurred after the onset of epileptiform activity in their model [83]. The freeze lesion model of TLE is relatively easy to generate with reproducible results [69]. However, despite the hyperexcitability observed in brain slices from lesion animals, there are in this model no recurrent seizures occurring spontaneously *in vivo* [72] which is an important prerequisite to a good experimental model of human mTLE. We have therefore developed in our laboratory a two-hit model.

**2.3. Two-Hit Rat Model of TLE.** When the cortical polymicrogyrus model precedes another insult, this represents a two-hit model and mimics the human condition described in our clinical series [59]. A few models, having in common a cortical polymicrogyrus as a first hit followed by another insult [17, 60, 84–86], may lead to TLE development at a later age.

**2.3.1. Freeze Lesion + Hyperthermia-Induced Seizure Model.** In the case of the freeze lesion and HSs model, the FSs constitute the “second hit” occurring postnatally while the “first hit” is thought to occur at an early stage of brain development. Therefore, in this model, the freeze lesion is performed at P1, while the HSs are induced at P10 [17] (Figure 1).

At the time of HSs induction, the temperature necessary to induce a generalized convulsion during hyperthermia was diminished in rats with a cortical lesion compared to rats without lesion, and the latency to attain the generalized convulsion was also shorter [17]. More importantly, only the lesioned pups developed status epilepticus following a brief exposure to hyperthermia. This model therefore reproduces the selective vulnerability of some individuals to a common insult. Furthermore, a brain and ipsilateral hippocampal atrophy was already measurable ten days following HSs at P20 [12]. This suggests that the lesion alone seems to predispose the brain and the hippocampus to prolonged FSs and their consequences.

At P80, the hippocampal atrophy is more severe than at P20; however, it may be prevented by limiting seizure duration with diazepam at P10 [2]. Furthermore, using *in vitro* electrophysiological recordings, CA1 pyramidal cell hyperexcitability has been shown, yielding greater evoked excitatory postsynaptic potentials (EPSPs) and more frequent spontaneous excitatory postsynaptic currents (sEPSCs) specifically in the double-hit group onto pyramidal cells [87] and onto CA1 interneurons [88]. As the excitatory activity, the inhibitory activity is also altered with greater amplitude GABA<sub>A</sub> and GABA<sub>B</sub> inhibitory postsynaptic potentials (IPSPs) and evoked inhibitory postsynaptic currents (eIPSCs) on CA1 pyramidal cells in the double-hit group [87]. This would suggest an excitatory/inhibitory imbalance favoring excitation already at P20, prior to the occurrence of spontaneous recurrent seizures at P80.

In adulthood, we have found that the double hit results in the occurrence of spontaneous seizures occurring in 86–100% of male rats with the seizures arising ipsilateral to the lesion [2, 9, 12], numbers similar to the MAM model and more significant than the 33% observed in naive rats exposed to prolonged FSs [11]. Ipsilateral hippocampal atrophy persists in the double-hit group and is associated in adults with neuronal loss and memory deficits in performance of a hippocampus-dependent task [9].

**2.3.2. Putative Mechanisms Implicated in TLE Generation in the Dual Pathology Model.** Our data indicate that ionotropic glutamate receptor expression, especially the NMDA subtype, is upregulated in the double-hit animals: NR2B subtype being overexpressed at approximately P20 and NR2A at P80

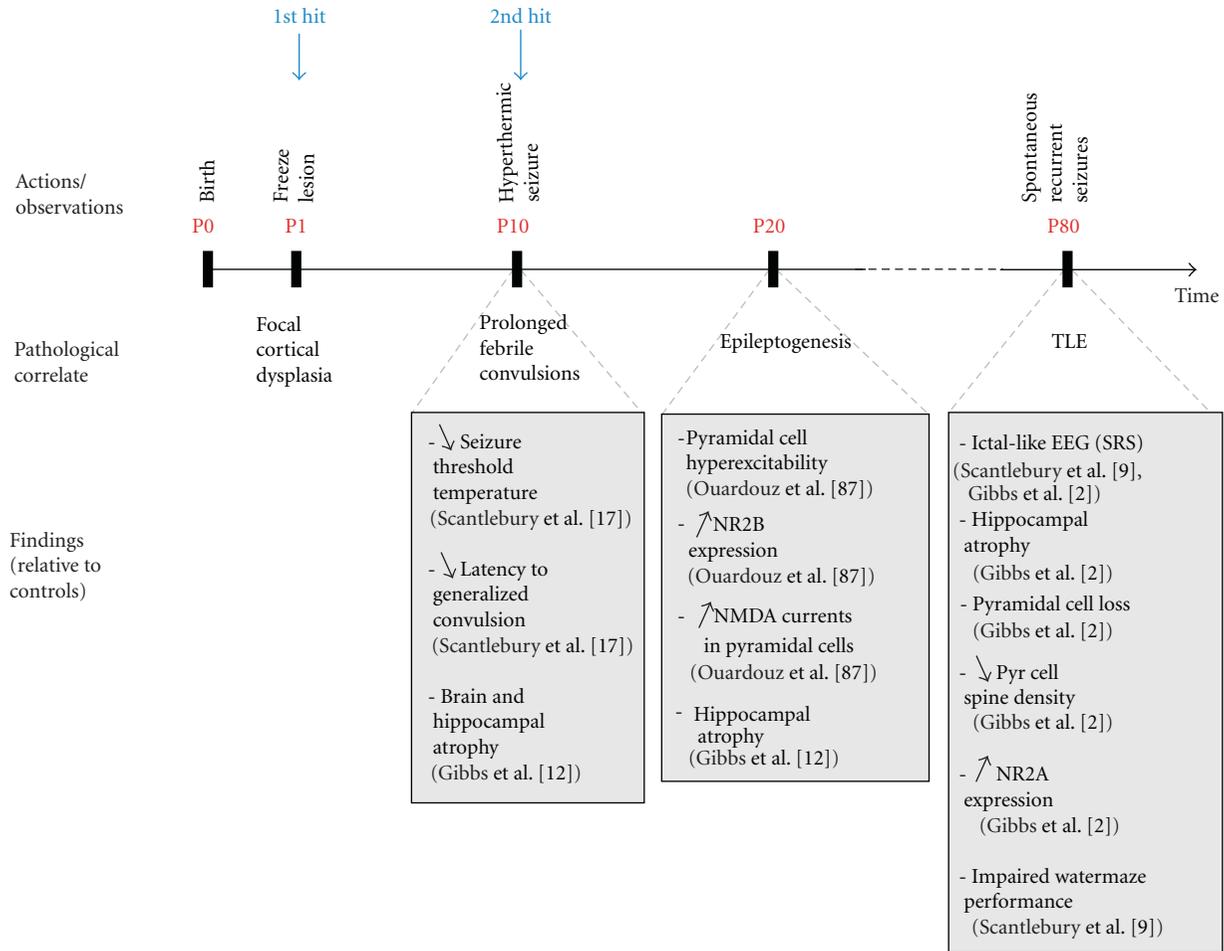


FIGURE 1: Lesion and hyperthermia model of TLE. Timeline and description of the different steps of the model, their pathological correlates, and the findings at various ages in the literature.

[87]. This is in accordance with findings from other two-hit models where high levels of NR2B expression are also found: such as in the MAM + pilocarpine model [84] or in the prenatal freeze lesion + electrical kindling [85]. The fact that lesion-only animals show higher NR2B levels and greater NMDA currents at P20 suggests that the lesion itself may underlie the hyperexcitability at P20 and may be a predisposing factor to prolonged HSs susceptibility at P10 [87], which is supported by a study in the freeze-lesion-only model [78]. Furthermore, it is possible that the IL-1 $\beta$  expression during hyperthermia, as earlier stated, further exacerbates the effect of the lesion on NMDAR.

In parallel with the excitatory changes, the inhibitory activity is also altered in the model. In this case, HSs appear to be the key event in modifying inhibitory currents and potentials [87]. The findings of this study are similar to those in naive animals [89]. Whether the changes in inhibitory circuits reduce or increase the risk of recurrent seizures remains to be determined. In summary, the lesion alone and the hyperthermia alone appear to each leave the developing brain more vulnerable, but the presence of two hits strongly promotes epileptogenesis.

### 3. Clinical Relevance of the Two-Hit Models

In humans, development of mTLE is more and more thought to be a multistage process taking place in early life and including a history of childhood prolonged febrile seizures. A retrospective study from our group demonstrated that 66% of children affected with mTLE and a history of FSs had dual pathology with the coexistence of hippocampal sclerosis and of a cortical malformation on pathology [59]. More recently, the FEBSTAT study group was able to distinguish two sub-populations of FSs with those experiencing prolonged FSs being younger and with developmental delay [90]. In an earlier publication, they had demonstrated that these same children were more likely (OR = 4.3) to have imaging abnormalities on MRI including cortical malformations [91]. Although the models described here involve disorders of neuronal migration, other predisposing factors such as genetic susceptibility can represent the first hit. Indeed, it has been shown that, in familial mTLE, mesial temporal sclerosis develops in those who have experienced prolonged FSs in early life [92]. More so, prospective studies suggest that FS duration is a key factor in leading to hippocampal injury and that

developmental abnormalities are indeed also present in children with febrile status and mTLE [93]. Therefore, we believe that any child who presents with a febrile status epilepticus could benefit from a thorough imaging evaluation, including high-resolution MRI. Up to now, a true antiepileptogenic treatment is not available. However, experimental evidence suggests a potential role for NR2B antagonists as not only a good seizure medication but also a potential antiepileptogenic treatment in the developing brain.

The role of other potential first hits such as early-life stress in the development of mTLE remains to be properly studied. Only few animal models of mTLE models implying early-life stress paradigms exist in the present literature [94–98]. Both corticotropin releasing factor (CRF) and the glucocorticoid cortisol (or corticosterone in rodents) appear to exert potent proconvulsive or hyperexcitable effects on limbic structures in the developing brain [96, 99–107]. Although there is no clear evidence that isolated early-life stressors can induce epileptogenesis, the anatomical and physiological changes produced by these hormones could predispose the developing brain to a second hit.

In conclusion, a better understanding of the pathophysiology of mTLE in the developing brain will help us develop age-specific treatments not only to control the seizures but also to prevent their occurrence altogether, an important step toward our ultimate goal of no seizure, no side effect.

## Disclosure

Dr. Nathalie T. Sanon and Dr. Sébastien Desgent shared the cofirst authorship.

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## Review Article

# Neuropathology of Temporal Lobe Epilepsy

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Received 1 September 2011; Revised 20 January 2012; Accepted 7 February 2012

Academic Editor: Seyed M. Mirsattari

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Pathologic findings in surgical resections from patients with temporal lobe epilepsy include a wide range of diagnostic possibilities that can be categorized into different groups on the basis of etiology. This paper outlines the various pathologic entities described in temporal lobe epilepsy, including some newly recognized epilepsy-associated tumors, and briefly touch on the recent classification of focal cortical dysplasia. This classification takes into account coexistent pathologic lesions in focal cortical dysplasia.

## 1. Introduction

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy [1]. In medical centers where epilepsy surgery is performed, neuropathologists often encounter temporal lobe resection specimens. Most patients scheduled for surgical resection present with intractable focal epilepsy and are selected for surgery based on clinical, electrophysiology, and neuroimaging criteria. The pathologic findings in these resected specimens represent different groups of conditions such as hippocampal sclerosis (HS), malformative lesions, tumors, ischemic lesions, old traumatic injuries, and inflammatory lesions. The objective of this paper is to outline the pathologic entities associated with TLE, while highlighting the recent classification of focal cortical dysplasia (FCD) and some recently described neoplastic entities.

## 2. Hippocampal Sclerosis, Temporal Lobe Sclerosis, and Amygdaloid Sclerosis

Hippocampal sclerosis, also known as Ammon horn sclerosis, is a common pathologic finding in surgical specimens from patients with TLE [2]. Although often used interchangeably with HS, the term “mesial temporal sclerosis” (MTS) is more appropriate for cases in which significant pathologic changes involve not only the hippocampus but

also the amygdala and entorhinal cortex. The incidence of HS is variable in different studies, ranging from 48% to 73% [2–4]. Whereas the pathogenesis of HS is unknown, its occurrence after prolonged febrile seizures in early life has been implicated [5]. According to the International League Against Epilepsy (ILAE) Commission Report, HS is defined as neuronal loss and gliosis in hippocampal area CA1 (Sommer sector) and area CA4 (endplate/hilus/end folium) [6]. Histologically, the segmental loss of pyramidal neurons in area CA1 is severe, with less prominent neuronal loss in areas CA3 and CA4 (Figures 1(a) and 1(b)). The term “end folium sclerosis” is reserved for cases with neuronal loss and gliosis restricted mainly to area CA4. In approximately 50% of HS cases, granule cell dispersion in the dentate gyrus is demonstrated [6]. In addition to routine stains, such as hematoxylin-eosin (HE) and luxol fast blue/HE, immunohistochemistry for neuronal nuclei (NeuN) has proven valuable in delineating neuronal loss in area CA1 (Figure 1(a)) [7]. Immunohistochemistry for glial fibrillary acidic protein (GFAP) frequently highlights gliosis associated with neuronal loss (Figure 1(b)). Glial proliferation, particularly astrocytic, is believed to play a role in the glutamate excess linked to seizure generation in TLE [3, 8]. Various semiquantitative methods have been devised to classify HS and MTS based on pathology findings [9, 10]. Reviewing 178 cases of mesial temporal lobe epilepsy, Blümcke and associates [10]

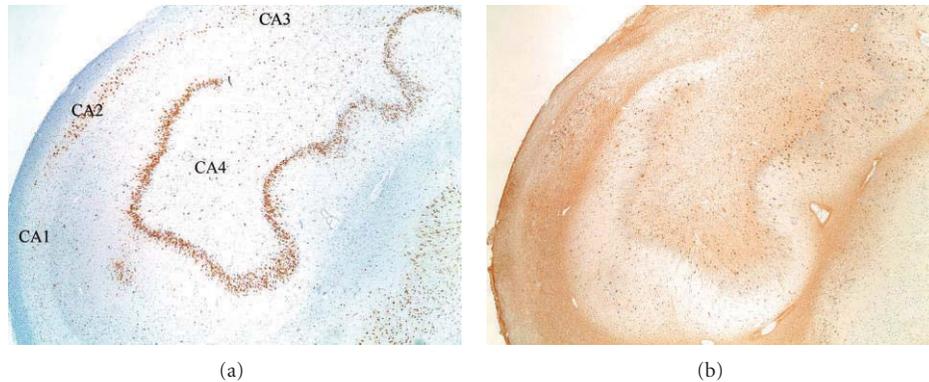


FIGURE 1: Hippocampal sclerosis. Neuronal loss in areas CA1, CA3, and CA4, with gliosis, (a) NeuN immunoreactivity. (b) glial fibrillary acidic protein immunoreactivity. Original magnification  $\times 20$ .

suggested that the patterns of MTS be categorized into (1) no MTS, (2) MTS type 1 (neuronal loss predominantly in areas CA1 and CA4), (3) MTS type 2 (CA1 sclerosis), and (4) MTS type 3 (end folium sclerosis). Cases categorized as MTS types 2 and 3 were noted to have worse postoperative seizure outcome (Engel classification) compared to MTS type 1 [10].

Thom and associates [11] used the term “temporal lobe sclerosis” to describe HS cases with definite neuronal loss and laminar gliosis in layers II/III of the temporal neocortex. Temporal lobe sclerosis has little influence on postsurgical seizure outcome and, therefore, has been regarded as an extension of HS rather than a separate entity [11]. Although a milder degree of neuronal loss in the amygdala is often observed in HS [12], “amygdaloid” or “amygdalar” sclerosis applies to severe neuronal loss with gliosis in the amygdala (especially in the lateral nucleus). Cases of amygdaloid sclerosis have also been identified without HS [13]. Such cases are believed to form a distinct group, with no clinical history of early brain insult such as febrile convulsion [13]. Given that interpretation of the degree of neuronal loss in the amygdala is often subjective, the incidence of amygdaloid sclerosis reported is highly variable, ranging from 6% to 100% [13–15].

The coexistence of an additional extrahippocampal brain pathology (excluding temporal lobe sclerosis and amygdaloid sclerosis) in HS cases, referred to as “dual pathology,” has a reported prevalence of 5% to 34% [2, 16–19]. In a study of TLE by Tassi and associates [2], only 34 cases (29%) of 117 HS cases were without dual pathology [2]. The rest were cases of dual pathology with additional lesions such as FCD and tumors. There are rare cases in the literature of HS coexisting with intrahippocampal pathology such as FCD involving only the end folium [20].

### 3. Malformations of Cortical Development and Focal Cortical Dysplasia

The term “malformations of cortical development” (MCD) encompasses developmental abnormalities of the cortex representing the broad spectrum of clinicopathologic changes attributable to various pathogenetic mechanisms during

prenatal and postnatal development [21]. These mechanisms can influence different developmental processes such as cell proliferation/apoptosis, neuronal migration, and cortical organization. Although numerous neuronal malformations have been attributed to genetic mutations or inborn metabolic errors (e.g., peroxisomal or mitochondrial disorders), other acquired causal factors affecting embryonic and fetal development have to be considered [22]. Focal cortical dysplasia is a subtype of MCD that is cited as a common cause of medically intractable, chronic epilepsy in children and young adults [21]. It includes a wide range of lesions, including cortical dyslamination, cytoarchitectural abnormalities, and underlying white matter disturbance. In our study of focal epilepsy patients with pathological diagnosis of FCD, the electrophysiology data, medical imaging features, and neuropsychology data identified the temporal lobe as the origin of epileptogenesis in 50% of the cases [23]. The prevalence of FCD reported in various studies of focal epilepsy involving TLE ranges from 9% to 45% [2, 17, 24–26]. Focal cortical dysplasia can be present alone or in association with other pathologic entities such as glioneuronal tumors or HS [27]. Other examples of MCD include agyria, pachygyria, porencephaly, grey matter heterotopia, and polymicrogyria, which can be multifocal or more diffuse [10, 28] (Figures 2(a), 2(b), and 2(c)).

Similar to HS, a history of febrile seizure has been statistically linked to patients with MCD, particularly FCD [2]. Some authors have proposed the following explanations for the association between febrile seizure, MCD, and HS: (a) MCDs have a predisposition for prolonged childhood febrile seizure, which can lead to HS, (b) MCDs are responsible for repeated seizures that cause secondary hippocampal damage, and (c) MCDs and HS stem from common embryonic damage [2, 17, 29]. The findings of Tassi and associates [2] support the notion that MCD can predispose to febrile seizure and that repeated seizures result in HS.

Resected FCD specimens may be normal on macroscopic observation. However, in some cases, the cortex appears thickened, with poor demarcation from the underlying white matter. Careful gross examination, with generous sampling and correlation with clinical (including electroencephalography and operative findings) and neuroimaging data, is

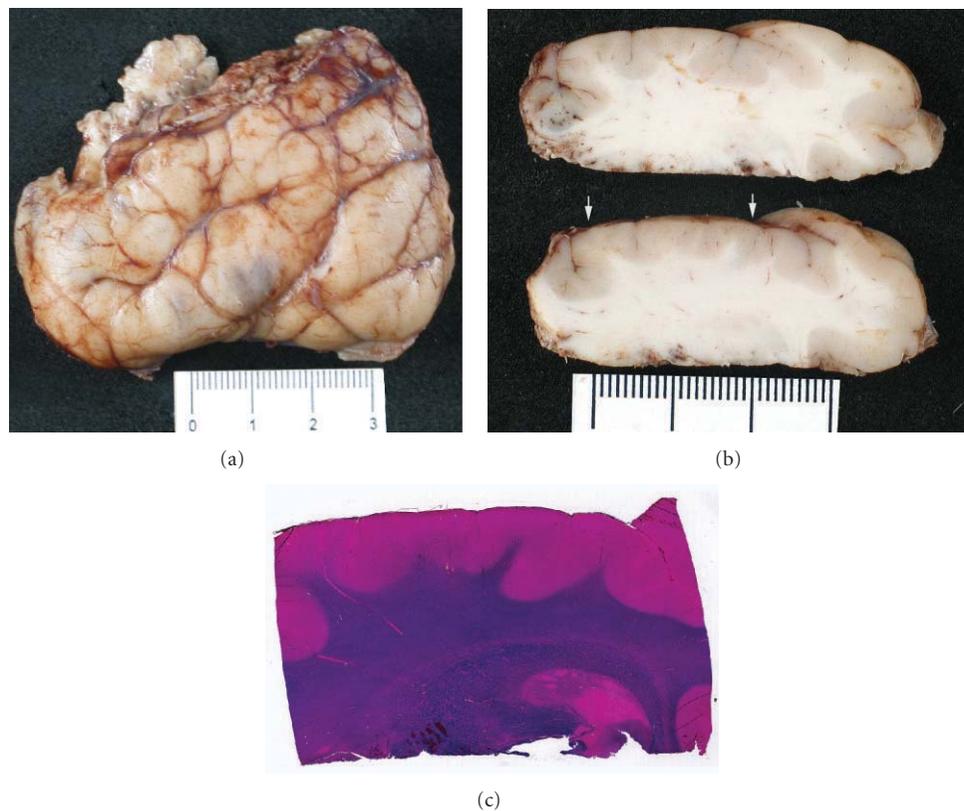


FIGURE 2: A cortical resection specimen from a child with hemimegalencephaly shows polymicrogyria. (a) external surface. (b) coronal sections, excessive convolution of cortical ribbon with shallow fused sulci (area between arrows). (c) micrograph (luxol fast blue-hematoxylin and eosin stain), several small wisps of subcortical white matter extending up to the cortical ribbon.

considered a reasonable standard of practice. Recently, a standardized protocol has been developed for the pathologic workup of FCD [30]. Samples are snap-frozen for molecular biology or genetic analysis when necessary, and the remaining (majority) resected specimen is fixed in 10% formalin. The specimen is then cut into thin slices oriented perpendicular to the cortical surface. Slices are carefully examined, photographed, and sampled before embedding in paraffin. The 4 to 7  $\mu\text{m}$ -thick paraffin sections are routinely stained with hematoxylin-eosin. Additional staining or immunohistochemistry is performed on selected sections to assess cortical architecture (cresyl violet, NeuN), myelination (luxol fast blue), and cytologic features (microtubule-associated protein 2 [MAP2], phosphorylated/nonphosphorylated neurofilament protein).

Focal cortical dysplasia is categorized into FCD type I (cortical dyslamination) and FCD type II (with the addition of dysmorphic neurons and/or balloon cells) according to the Palmini classification [31]. An analysis of inter- and intra-observer agreement using the Palmini classification found that the overall agreement was moderate and less reproducible for FCD type I, even among experienced neuropathologists [32]. The greatest concordance was observed for FCD type II, in which dysmorphic neurons and/or balloon cells were identified. There are often difficulties in drawing a clear distinction between normal and dyslaminated cortex,

owing to the cytoarchitectural heterogeneity of different subregions of the temporal lobe (e.g., Brodmann areas 21, 38, 28, 27, 35, 20, 30, and 37), thus making differentiation between normal cytoarchitectural variation and mild cortical disorganization quite subjective. For example, according to Ding and associates, the granular layer of the temporal cortex is quite variable in the different Brodmann areas, and it diminishes towards the temporo-polar area (Brodmann 38) [33]. In most studies on TLE, however, the Brodmann areas have not been specified in the surgical resections and the subsequent histological examination. The ILAE Task Force has recently introduced a consensus classification system based on correlations between neuropathology findings, imaging data, electrophysiology features, and postsurgical seizure control [34]. The ILAE classification highlights a group of FCDs with coexistent pathology (FCD type III) that demonstrates favorable postsurgical outcomes. This classification divides FCD into three clinicopathologic types (see Table 1) [35]. In FCD type I, there is isolated neocortical dyslamination (Figure 3(a)), that may be either radial (type Ia), tangential (type Ib), or a combination of both (type Ic). In FCD type II (Figure 3(b)), there is isolated neocortical dyslamination, but in addition, dysmorphic neurons (type IIa) or balloon cells, with or without dysmorphic neurons (type IIb), are identified. Whereas FCD types I and II are largely alluded to in the Palmini classification, the ILAE Task Force introduced

TABLE 1: International league against epilepsy consensus classification system for focal cortical dysplasia (FCD) [34].

FCD type I: isolated	FCD Ia: abnormal radial cortical lamination	FCD Ib: abnormal tangential cortical lamination	FCD Ic: abnormal radial and tangential cortical lamination
FCD type II: isolated	FCD IIa: dysmorphic neurons	FCD IIb: dysmorphic neurons and balloon cells	FCD IIId: cortical lamination abnormalities adjacent to any other lesion acquired during early life (e.g., trauma, ischemic injury, and encephalitis)
FCD type III: associated with principal lesion	FCD IIIa: cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis	FCD IIIb: cortical lamination abnormalities adjacent to a glial or glioneuronal tumor	FCD IIIc: cortical lamination abnormalities adjacent to vascular malformation

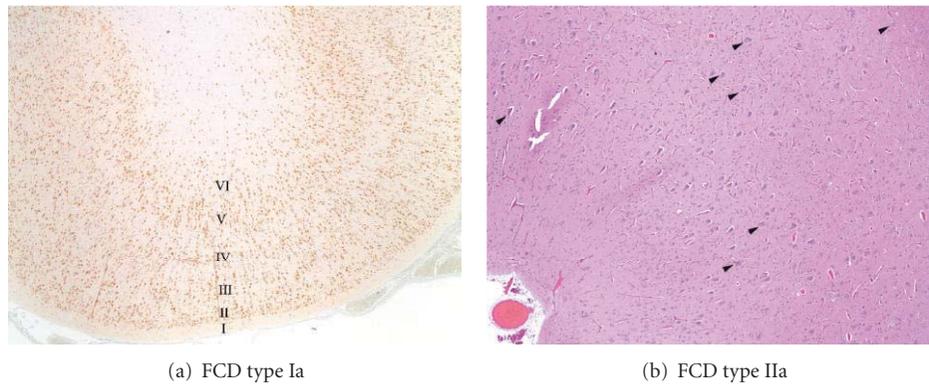


FIGURE 3: Focal cortical dysplasia (FCD). (a) FCD type Ia shows microcolumnar arrangements of cortical neurons with a preservation of cortical layering. NeuN immunoreactivity. Original magnification  $\times 20$ . (b) FCD type IIa, cortical laminar disorganization and dysmorphic neurons (arrowhead), distributed throughout the entire cortical thickness (sparing the molecular layer) and subjacent white matter. Hematoxylin-eosin stain. Original magnification  $\times 40$ .

the classification of FCD type III, which takes into account the presence of other epileptogenic lesions in association with FCD type I, such as HS (type IIIa), epileptogenic tumors (type IIIb), vascular malformation (type IIIc), or lesions acquired during early life, for example, as a result of trauma, ischemic injury, or encephalitis (type IIId) [34].

The ILAE Task Force consensus classification also provides standardized descriptions for abnormal cell types such as dysmorphic neurons, balloon cells, and hypertrophic neurons, among others [34]. Histologically, dysmorphic neurons show a large soma and nucleus, with abnormally aggregated Nissl substance displaced toward the cell membrane and cytoplasmic accumulation of phosphorylated and nonphosphorylated neurofilament protein (Figures 4(a) and 4(b)). Balloon cells show a large soma with an eccentric nucleus and abundant, eosinophilic, glassy cytoplasm on HE staining (Figure 5). These cells are considered to be indeterminate or transitional cell types because they often express both neuronal and glial markers [36]. In addition, descriptive and diagnostic terms, such as dysplasia, heterotopia, hamartoma, ectopia, dyslamination, dual pathology, double pathology, and principal lesions have been further defined to ensure standardized pathologic reporting of FCD.

From the cases of our previous FCD study [23], we selected 57 surgical resections from the temporal lobe in

which microscopic slides were available for pathology review. The histologic subtypes for these FCD cases were assigned based on the Palmi classification and then reassigned according to the ILAE classification. Isolated FCD was observed in 70% of the cases, and the rest were associated with other lesions. With one exception, lesions in all cases with other associated lesions were localized to the temporal lobe. Using the Palmi classification, type IIB was the most common subtype (21 cases, 37%). There were 16 cases (28%) associated with other pathologic lesions such as hippocampal sclerosis, low-grade neuroepithelial tumors, hamartomas, and destructive lesions. With the ILAE classification, FCD type IIB remained the most common subtype, but seven cases of FCD type I were reclassified as type III because of the presence of another principal lesion. There were nine cases (16%) of FCD type II with coexistence of other principal lesions. Three FCD type II cases (dual pathology) were associated with hippocampal sclerosis, and the other six cases (double pathology) were associated with either low-grade glioneuronal tumor, hamartomas, or destructive lesions. The major difference with the ILAE classification is that it recognizes the coexistence of other principal lesions in FCD, which were present in 28% of our cases [37].

Microdysgenesis constitutes a form of microscopic malformation in cortical development characterized mainly by

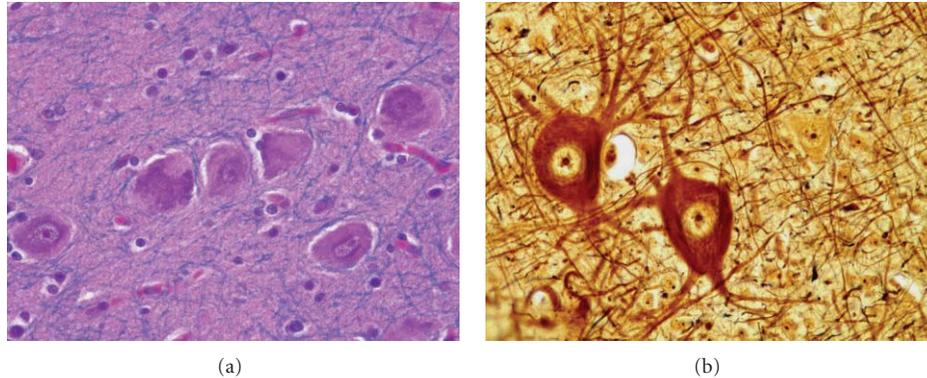


FIGURE 4: Dysmorphic neurons. (a) hematoxylin-eosin stain. Original magnification  $\times 400$ . (b) Bielschowsky stain. Original magnification  $\times 400$ .

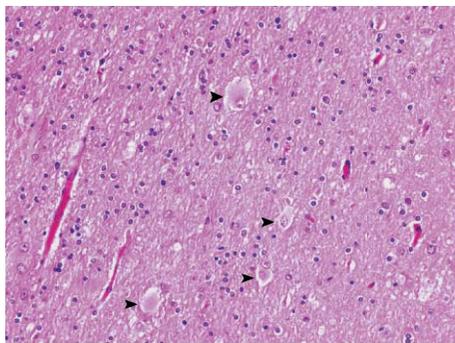


FIGURE 5: Balloon cells. Hematoxylin-eosin stain. Original magnification  $\times 200$ .

mild cortical cytoarchitectural abnormalities and an increase in heterotopic neurons in both cortical layer I and the subcortical white matter [38, 39]. Of all of the histologic features in microdysgenesis, the increase in heterotopic neurons in subcortical white matter appears to be the most consistent finding [39]. The actual quantitative data for subcortical neuronal counts remain highly variable between studies, depending on the different cortical regions evaluated, and the processing techniques and morphometric methods applied [40, 41]. However, Kasper and associates [42] reported that a count of more than 10 white matter neurons per high-power field applied to temporal lobe sections can be useful in differentiating TLE cases from normal autopsy control cases [42]. In the ILAE classification, the term microdysgenesis has been omitted, owing to the lack of a precise definition, and instead “mild forms of cortical malformations” are used to define an excess of neurons in the white matter [43].

#### 4. Meningioangiomas, Vascular Malformation, and Hamartomas

Meningioangiomas (MA) is a hamartomatous lesion that can occur sporadically or in association with neurofibromatosis type 2. Sporadic MA commonly presents as a plaque-like mass in the setting of chronic epilepsy [44].



FIGURE 6: Arteriovenous malformation comprises of mixture of arteries, veins, and abnormal vessels of variable wall thickness and caliber (arterialized veins) with intervening gliotic brain tissue. Extensive perilesional gliosis, calcification, and microhemorrhages, with hemosiderin deposition (not shown) are common features in vascular malformation. Movat stain. Original magnification  $\times 100$ .

Interestingly, MA associated with neurofibromatosis type 2 is usually asymptomatic and rarely associated with seizures. On microscopy, MA shows the proliferation of meningotheelial and fibroblastic cells arranged around cortical blood vessels, with occasional extension into the white matter [45]. Psammomatous calcification is frequent, and the intervening cortical tissue often shows gliosis. When the vascular component predominates, it mimics a vascular malformation. One report documented an overlying meningioma in 42% of MA cases, and in this setting, the authors considered the MA component to be neoplastic in nature [46]. Surgical excision of the lesion, including the adjacent cortex, is regarded as curative, even though seizures can persist in a number of patients [44].

In surgical series of focal epilepsy, vascular malformation, consisting mostly of arteriovenous malformations (Figure 6) and cavernous hemangioma, is less common than expected. However, studies on vascular malformation report that approximately 25% of patients present with epilepsy [47]. Cavernous hemangioma in the temporal lobe can be treated by extended lesionectomy, with excellent postoperative seizure control, and in cases with concurrent hippocampal

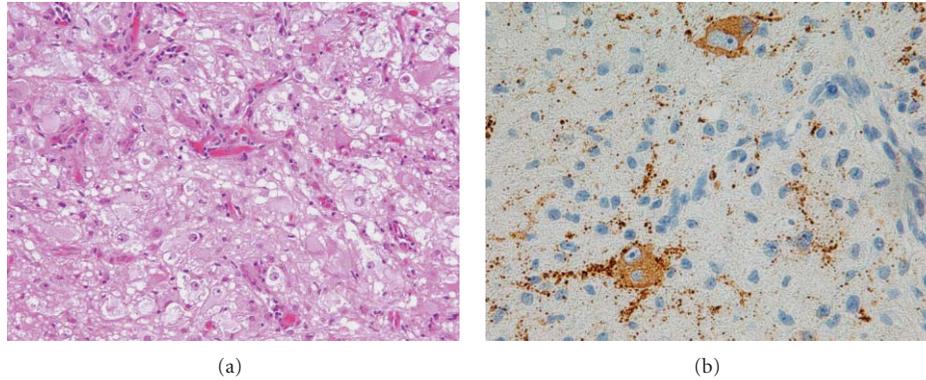


FIGURE 7: Ganglioglioma. (a) mixed population of neoplastic glial and ganglion (neuronal) cells. Hematoxylin-eosin stain. Original magnification  $\times 200$ . (b) examples of neoplastic, binucleated neurons immunoreactive for synaptophysin. Original magnification  $\times 400$ .

sclerosis (dual pathology), the resection should also include the mesial temporal structures [48].

Hamartoma is a nonneoplastic, nodular proliferation of disorganized mature tissues that are native to the site of origin. In the central nervous system, this usually refers to glioneuronal hamartomas, which have rarely been described in TLE [49]. The lesion is usually well circumscribed, with a bland, nonproliferative glial component, and a neuronal component showing minimal cellular atypia. Occasionally, it is difficult to distinguish the less cellular variants of ganglioglioma (GG) or dysembryoplastic neuroepithelial tumor (DNT) from hamartomas, suggesting that some of these entities may fall within the same histogenetic spectrum [50]. Focal cortical dysplasia has been identified in the adjacent cortex in some hamartomas [49]. Interestingly, rare cases of hypothalamic hamartoma have been reported to manifest with a syndrome similar to TLE [51].

## 5. Tumors

In general, tumor-induced epilepsy of the temporal lobe tends to present earlier in life (i.e., childhood and young adulthood). The prevalence of tumors reported in epileptic patients is variable, and may be as high as 30% [2, 52]. Whereas any slow-growing tumor (e.g., meningioma and glioma) can be associated with focal epilepsy, glioneuronal tumors have been identified as the most common epilepsy-inducing tumor [52]. However, in one study of pediatric tumor-related TLE, pilocytic astrocytoma was identified as most common tumor (41%), followed by GG (25%) [53]. Given that TLE-associated tumors are frequently of low grade, general and seizure outcomes after surgical resection are good for most patients.

Occasionally, two tumor types can form a composite tumor such as in the case of DNT and GG, or GG with pleomorphic xanthoastrocytoma (PXA) [54, 55]. A recent study revealed that the most common pathology coexisting with tumor-related epilepsy is FCD, followed by hamartia and hippocampal sclerosis [56]. Ganglioglioma and DNT are the tumors most frequently associated with FCD [2, 52].

The glioneuronal tumors associated with TLE include GG, gangliocytoma, DNT, and the novel entity of papillary glioneuronal tumor.

Ganglioglioma (World Health Organization (WHO) grade I) is the most common tumor identified in chronic epilepsy and is frequently located in the temporal lobe, although it may arise elsewhere in the central nervous system [52, 56]. This is a slow-growing tumor, mostly affecting children and young adults. Gangliogliomas may appear solid, cystic, or a combination of the two. Calcification may be observed macroscopically but is more likely to be visible only at the microscopic level. Histologically, this tumor is composed of neoplastic glial and neuronal (ganglion) cells [57]. Glial and neuronal components may be evenly admixed throughout the tumor or may be unevenly distributed, resulting in significant tumor heterogeneity (Figure 7(a)). Neoplastic ganglion cells in the neuronal component are usually large, often bi- or multi-nucleated, and dysplastic in appearance, with an abnormal distribution of Nissl substance. The glial component of this tumor is quite variable and usually forms the proliferative fraction of the tumor. Morphologically, the glial component can resemble fibrillary astrocytoma, oligodendroglioma, or pilocytic astrocytoma. Perivascular lymphocytosis, focal calcification, and eosinophilic granular bodies are common findings. Mitoses are rare, and necrosis is predominantly absent. Although neuronal markers such as MAP2, NeuN, neurofilaments, and synaptophysin are useful for identification of the neuronal component, these markers cannot differentiate neoplastic neurons from native, nonneoplastic ones (Figure 7(b)). Immunohistochemistry for CD34 could be helpful in distinguishing neoplastic ganglion cells from entrapped, nonneoplastic neurons [58]. Ganglioglioma is usually associated with a good prognosis, but occasional anaplastic GG with malignant transformation of the glial component has been reported (e.g., 5% in a study by Blümcke and Wiestler) [59, 60].

Dysembryoplastic neuroepithelial tumor (WHO grade I) is a supratentorial, heterogeneous, and glioneuronal neoplasm in children and young adults, with a predilection for the temporal lobe and often associated with drug-resistant

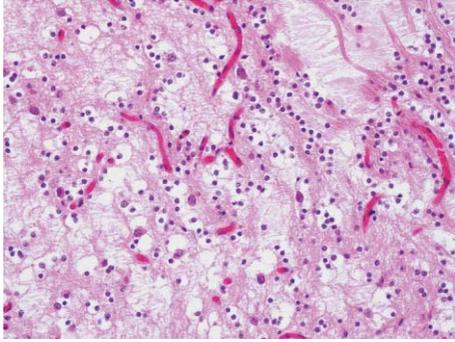


FIGURE 8: Dysembryoplastic neuroepithelial tumor. Oligodendroglia-like cells arranged in columns with occasional mature neurons and myxoid background. Hematoxylin-eosin stain. Original magnification  $\times 200$ .

partial seizures [61]. It is predominantly cortical and typically exhibits a complex columnar and multinodular architecture [62]. Grossly, there is expansion of the cortex, with isolated or multiple nodules and frequent microcystic changes. Histologically, there is a monomorphous population of round nuclei with scant cytoplasm (oligodendroglia-like cells) arranged in columns oriented perpendicular to the cortical surface. Occasional “floating” mature neurons are seen within a myxoid extracellular matrix between columns of oligodendroglia-like cells (Figure 8). These oligodendroglia-like cells express neuronal markers (e.g., synaptophysin). The complex variant of DNT displays heterogeneous astrocytoma, oligodendroglioma, and neuronal components [63]. Immunohistochemistry for CD34, nestin, and calbindin is often helpful in differentiating DNT from other gliomas, especially in small specimens [61]. The adjacent cortical tissue frequently shows cortical dysplasia [64]. Dysembryoplastic neuroepithelial tumor is a low-grade tumor with good outcome in terms of seizure-free interval and recurrence after complete surgical excision [61]. However, rare malignant transformation has been reported [65, 66].

The recently described papillary glioneuronal tumor (WHO grade I) often presents with seizures. It is reported to be rare, but we identified one case in our review of 57 FCD cases [37]. On microscopy, it consists of pseudopapillary structures with a hyalinized, vascular core enclosed by flat/cuboidal GFAP-positive glial cells (Figures 9(a) and 9(b)). The interpapillary areas show sheets of round neurocytic cells which are positive for neuronal markers (e.g., synaptophysin, NeuN) (Figure 9(c)) [67]. A favorable prognosis is expected after gross total removal [68].

A number of slow-growing, low-grade tumors, such as pilocytic astrocytoma, diffuse astrocytoma, oligodendroglioma, and ependymoma, are known to present with focal epilepsy. In this paper, however, we will discuss only three of these tumor types specifically. An often encountered tumor in children and young adults with protracted history of seizures, PXA (WHO grade II) is regarded as an astrocytic neoplasm with limited neuronal differentiation. This tumor is found mostly in the supratentorial compartment, particularly in the temporal lobe. It is typically superficial and

often involves the adjacent meninges, with occasional dural invasion. The tumor has both solid and cystic components, and on neuroimaging can appear as a “cyst with mural nodule.” The most characteristic histologic feature is the presence of large, pleomorphic, and lipidized cells (Figure 10(a)), which are often individually surrounded by a reticulin network [69]. Perivascular lymphocytosis, eosinophilic granular bodies, and Rosenthal fibers can be seen. Pleomorphic xanthoastrocytoma tumor cells are GFAP-positive, with variable immunoreactivity for neuronal markers [70] (Figure 10(b)). The prognosis for this tumor in young individuals is generally favorable [71]. However, there are rare examples of anaplastic PXA with increased mitotic activity and tumor necrosis [72–74]. Some histologic features of anaplastic PXA, including the presence of large pleomorphic cells and reticulin deposition, make differentiation from giant cell glioblastoma a diagnostic challenge [75].

Angiocentric glioma (WHO grade I), another distinctive tumor included in the recent WHO classification for central nervous system tumors, has been reported in children and young adults presenting with chronic, intractable, partial seizures [76]. This is a slow-growing, superficial, cerebral tumor that can be found in the temporal lobe (we identified one case in our review of 57 TLE cases) [37]. Angiocentric glioma is characterized histologically by an angiocentric growth pattern of monomorphous bipolar cells showing immunoreactivity for GFAP, S-100 protein, and vimentin (Figures 11(a) and 11(b)). Some of these tumors show immunoreactivity for epithelial membrane antigen and the presence of intracellular microlumens with microvilli and cilia ultrastructurally, findings which support ependymal differentiation [77] (Figure 11(c)).

While isomorphic astrocytoma is considered a variant of diffuse astrocytoma (WHO grade II), its clinical behavior is more akin to that of a WHO grade I astrocytoma [78, 79]. This tumor is mainly described in patients with chronic epilepsy who experience long survival and low recurrence rate. Histologically, this tumor shows an isomorphic, sparse population of small glial cells with rounded nuclei. Whereas tumor cells appear infiltrative, there is an absence of nuclear atypia, mitotic activity, and necrosis. This tumor shows immunoreactivity for GFAP but not for MAP2 or CD34.

## 6. Posttraumatic, Destructive, and Ischemic Lesions

Approximately 20% of symptomatic epilepsy is attributed to some kind of trauma [80]. Risk factors for posttraumatic seizures include alcoholism, age, penetrating dural injury, intracranial hemorrhage, depressed skull fracture, and focal neurologic deficits. Seizures may present beyond the first week after injury, mostly within 18 months after injury [81]. Late posttraumatic seizures are thought to result from cortical damage caused by free radicals generated by iron deposition from extravasated blood, along with increased excitotoxicity owing to glutamate accumulation [82]. In most surgical resection specimens of posttraumatic epilepsy, the tissue consists of cystic lesions that involve the crests of gyri

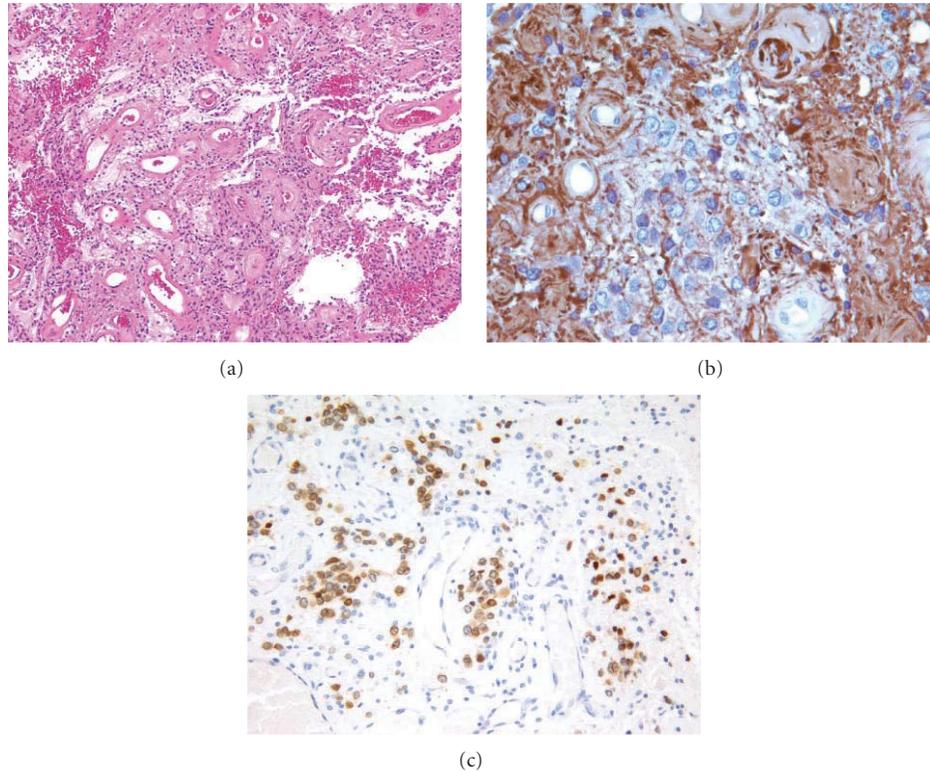


FIGURE 9: (a) pseudopapillae structures composed of hyalinized blood vessels and surrounded by glioneuronal cells. Papillary glioneuronal tumor may mimic vascular malformation. Hematoxylin-eosin stain. Original magnification  $\times 100$ . (b) the glial component around blood vessels. Glial fibrillary acidic protein (GFAP). Original magnification  $\times 400$ . (c) neuronal component in the interpapillary area. NeuN immunostain. Original magnification  $\times 200$ .

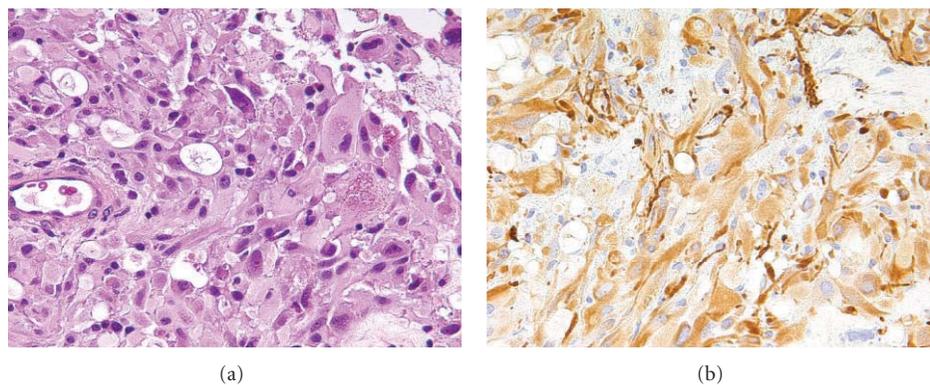


FIGURE 10: (a) pleomorphic xanthoastrocytoma with large, pleomorphic, and lipidized glial cells. Hematoxylin-eosin stain. (b) glial fibrillary acidic protein immunoreactivity (astrocyte marker). Original magnification  $\times 600$ .

with hemosiderin deposition (Figure 12). These lesions are often localized in the inferior frontal and temporal lobes, where cortical contusions are common.

The prevalence of epilepsy as a late sequela of adult stroke has been estimated at 3% to 10%, depending on the definition of epilepsy [83]. The predominant seizure type is partial and can be the result of either cerebral infarct or hemorrhage [84]. The remote ischemic infarct is cystic with central cavitation surrounded by a zone of prominent gliosis.

Hemosiderin deposition may be evident in old infarcts with a hemorrhagic component. There is no clear association between the incidence of seizures and the location of the infarct. Chronic ischemic damage of the cortex may display prominent cortical atrophy, with a loss of neurons and gliosis without cavitation. Porencephalic cysts are usually the result of infarct in the fetal brain during gestation. This type of cyst is localized on one cerebral hemisphere, connecting one ventricle to the brain surface [85]. Quite often in both

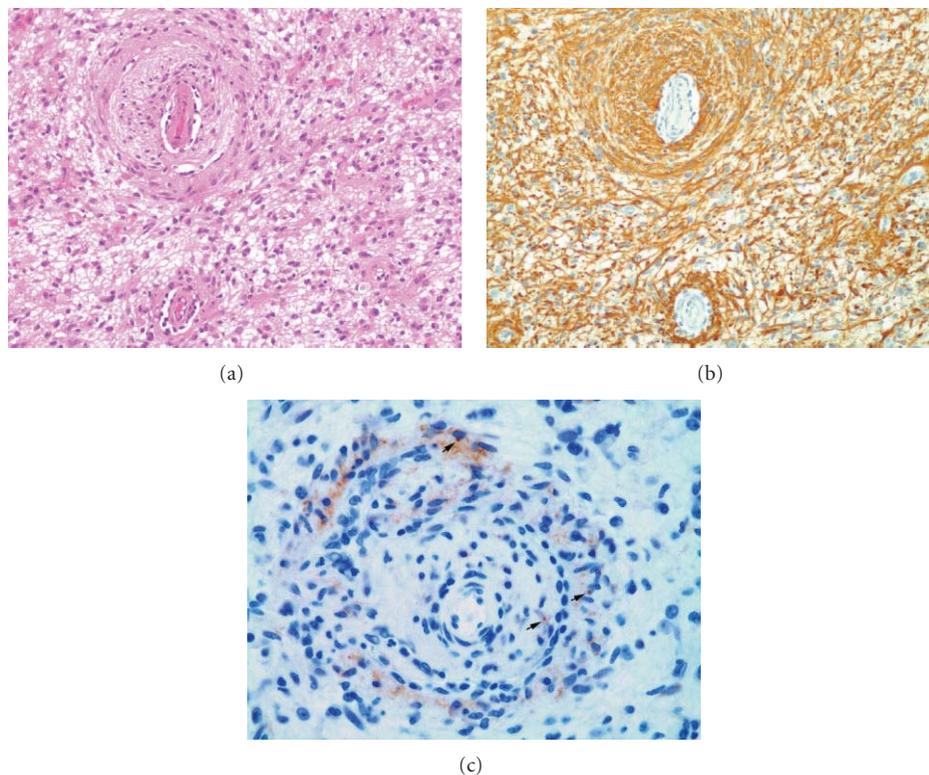


FIGURE 11: Angiocentric glioma. (a) angiocentric growth pattern of monomorphous bipolar cells. Hematoxylin-eosin stain. (b) corresponding section stained for glial fibrillary acidic protein shows cell processes wrapped around blood vessels. Original magnification  $\times 200$ . (c) epithelial membrane antigen shows a dot-like immunoreactivity (arrow). Original magnification  $\times 400$ .

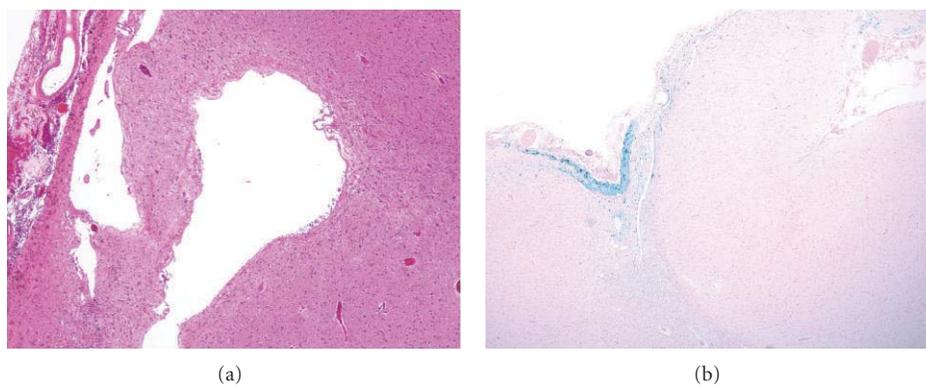


FIGURE 12: Old trauma. (a) cortical cystic lesion with hemosiderin pigments. Hematoxylin-eosin stain. Original magnification  $\times 40$ . (b) superficial iron deposit within the cortical tissue. Perl Prussian blue stain. Original magnification  $\times 20$ .

posttraumatic and postischemic injuries, the cystic and hemorrhagic components resolve, with only scar lesions remaining [25].

## 7. Inflammatory Lesions

Localized inflammatory lesions, such as brain abscesses, granulomas (tuberculosis), and parasitic cysts (neurocysticercosis and hydatid cysts) are important causes of focal epilepsy, particularly in developing countries [86, 87]

(Figure 13). Some cases of chronic encephalitis affecting the temporal lobe (limbic encephalitis) can also present with chronic seizures. Like other cases of chronic encephalitis, there are perivascular lymphocytic infiltrate and microglial nodules in the brain parenchyma (Figures 14(a) and 14(b)). The role of the inflammatory process and the immune response in epileptogenesis has been well documented in animal models and is considered to be a plausible cause of epileptogenesis in humans [88, 89]. It should be noted that some degree of chronic leptomeningeal and perivascular

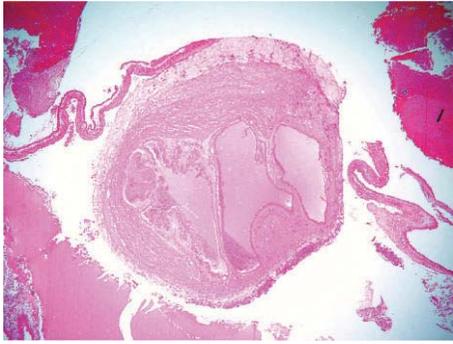
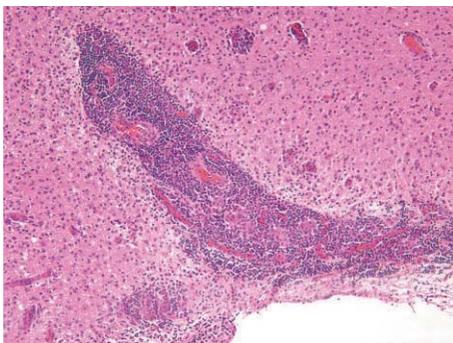
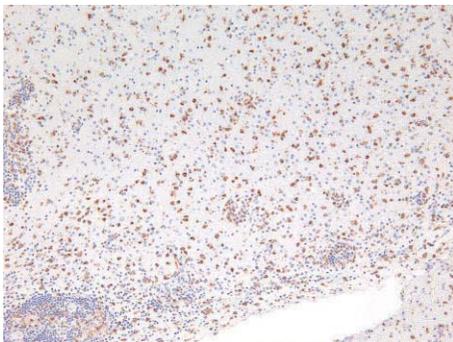


FIGURE 13: Neurocysticercosis characterized by the presence of undulating, laminated, and membranous wall of a cysticercus. Hematoxylin-eosin stain. Original magnification  $\times 40$ .



(a)



(b)

FIGURE 14: (a) perivascular lymphohistiocytic infiltrate in meningoencephalitis from a patient with temporal lobe epilepsy. Hematoxylin-eosin stain. (b) diffuse microglial infiltration with the formation of nodules. Immunostaining for CD68. Original magnification  $\times 100$ .

parenchymal inflammation may be secondary to invasive seizure monitoring and should not be mistaken for chronic encephalitis or meningitis.

Rasmussen encephalitis is a rare syndrome that exemplifies the association of chronic epilepsy and chronic encephalitis. The disease is characterized by the sudden onset of seizures (unilateral motor seizures or *epilepsia partialis continua*) in previously healthy individuals, typically within the first 2 decades of life [90, 91]. As Rasmussen encephalitis

is *unihemispheric*, the pathology is not restricted to the temporal lobe. There is usually extensive involvement of one hemisphere with active chronic inflammation in the earlier stages and scarring and atrophy in later stages [91]. Inflammatory cells in the cortex are mostly T lymphocytes with perivascular and perineuronal aggregates. There are also microglial nodules, which are pervasive in the earlier stages. In the later stages, reactive astrocytes are more predominant [92].

## 8. Conclusion

There is a wide range of pathologic findings in TLE, many of which are quite complex because more than one type of lesion is often identified in a single surgical resection specimen. The careful examination of these specimens, with the application of techniques such as immunohistochemistry, has provided improved classification of FCD and more accurate diagnosis of neoplastic and nonneoplastic conditions. This will enhance our understanding of the pathogenesis of TLE and ultimately lead to better management strategies. It is also pertinent for pathologists to understand that an accurate pathologic diagnosis cannot be attained without a correlation between pathologic and clinical findings, electrophysiologic data, and neuroimaging data. Finally, despite careful examination, there will remain a percentage of pathologic specimens that defy specific diagnosis [2, 25]. In this group, we include cases of “bizarre” or “unusual” lesions, which remain unclassifiable based on our current understanding of neuropathology as well as cases with no obvious abnormalities, which may be explained by the collection of nonrepresentative resection specimens or by the diagnosis not being attainable with current methods.

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## Review Article

# Temporal Lobe Epilepsy after Refractory Status Epilepticus: An Illustrative Case and Review of the Literature

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Received 4 October 2011; Accepted 29 January 2012

Academic Editor: Seyed M. Mirsattari

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New onset refractory status epilepticus (NORSE) is a relatively newly defined disease entity, where otherwise healthy individuals develop unrelenting seizures that do not respond to conventional anticonvulsant therapy and may require months of therapy with anesthetic drugs. We have described a case of NORSE who subsequently developed mesial temporal lobe sclerosis (MTS) and recurrent temporal lobe seizures. We discuss the possible pathophysiological mechanisms by which refractory seizures may contribute to the development of temporal lobe epilepsy (TLE).

## 1. Introduction

Temporal lobe pathology is associated with critical illness via a variety of mechanisms. Cardiac arrhythmias and asystole are known to complicate temporal lobe seizures [1]. Severe infections of the nervous system, such as herpes simplex virus infection, can cause hemorrhagic destruction of the temporal lobe and subsequent cerebral edema and herniation. The temporal tips and mesial temporal lobe structures are also commonly affected in traumatic brain injury, often resulting in memory impairment, posttraumatic epilepsy, and other deficits [2–4]. The hippocampus is the most vulnerable structure in cases of hypoxic-ischemic insults, as with transient cardiac arrest, with profound memory deficit as a frequent outcome [5]. Perhaps one of the most common reasons that an intensivist (or neurointensivist) may come to care for patients with ultimate temporal lobe dysfunction is with seizures, particularly status epilepticus.

Status epilepticus has often been associated with temporal lobe epilepsy as being a complication of, or a cause of, temporal lobe pathology. Although there have been many studies which have evaluated the clinical outcome of patients with status epilepticus (and refractory status epilepticus) in the intensive care setting [6–11], there is relatively little data regarding temporal lobe epilepsy as a sequela of prolonged

seizure activity outside of febrile status epilepticus [10–13]. More importantly, the exact mechanisms relating an episode of status epilepticus with subsequent temporal lobe epilepsy remain largely unclear.

In this report, we provide a case illustration of a previously well patient who subsequently developed multifocal epilepsy following new-onset refractory status epilepticus (NORSE) syndrome of unclear etiology [14]. The epilepsy syndrome was characterized by independent bilateral temporal lobe epilepsy (TLE), plus multifocal interictal epileptic spikes that were also maximal in the temporal regions. We use this case to illustrate that refractory status epilepticus can be associated with subsequent temporal lobe pathology, including MTS, and as a result can lead to an ongoing temporal lobe seizure disorder. The literature linking status epilepticus with TLE is reviewed.

## 2. Case Report

This previously healthy 22-year-old right-handed woman presented with generalized tonic-clonic seizures on the background of a 3-day history of fever, malaise, and a reddish skin lesion on her posterior calf. This occurred shortly after her return from travelling to the northeastern United States. She continued to have seizures despite being treated with

midazolam and phenytoin; therefore she was intubated for airway protection, started on propofol, and placed on continuous EEG monitoring. Her antimicrobial therapy included sulfamethoxazole/trimethoprim for the skin lesion, as well as ceftriaxone and acyclovir as empiric coverage for meningoencephalitis. She continued to have breakthrough seizures, despite multiple anticonvulsant medications, including levetiracetam, ketamine, isoflurane, phenobarbital, pregabalin, and valproic acid. An exhaustive search for infectious, autoimmune, neoplastic, and paraneoplastic causes of refractory seizures did not yield any specific etiology (Table 1). She was treated with two empiric courses of intravenous immunoglobulin for a presumed autoimmune/paraneoplastic limbic encephalitis. A typical seizure during her acute illness is shown in Figure 1. The seizure originated from the left frontal/anterior temporal region and remained relatively focal. At the same time, there are independent, rhythmical, and sharply formed theta waves in the right frontal region (Figures 1(a)–1(c)).

The patient's seizures eventually ceased, and she could be weaned off the anaesthetic agents and ventilatory support. After over two months of refractory seizures, she was stable enough to be transferred to the neurology ward. At that time, she was oriented to person, place, and time and was able to follow one-step commands. She had moderate-to-severe proximal muscle weakness, likely on the basis of critical illness myopathy. She had gaze-evoked nystagmus and a symmetrical action tremor, presumably due to the effects of anticonvulsant medications. Five months after the onset of her refractory status epilepticus, she had returned home from the rehabilitation centre to live with her parents and was able to work part time. She had ongoing difficulties with frequent simple partial, complex partial (with staring and automatisms) and secondarily generalized seizures, despite being on five anticonvulsant medications (clobazam, phenytoin, levetiracetam, topiramate, and pregabalin). Followup neuropsychological testing demonstrated moderately-severely impaired verbal and visual memory, an IQ in the low average-average range, and moderately impaired language functioning. The possibility of medication effects on her neuropsychological testing could not be fully excluded.

She had serial MR imaging throughout her hospital stay and clinical followup. At the onset of status epilepticus, the MRI was completely normal (not shown). Ten days after the onset of refractory status epilepticus, her hippocampi were edematous and had increased T2 signal intensity (Figure 2(a)). Subsequent MRI studies performed at 1 (Figure 2(b)), 2 (Figure 2(c)), and 6 (Figure 2(d)) months later demonstrated progressive hippocampal atrophy and mild decrease in T2 signal intensity.

The case illustrates the potential relationship between refractory status epilepticus and TLE. This relationship can be complex and may involve ongoing focal and/or generalized seizures from a symptomatic brain lesion. Moreover, it may be associated with the development of MTS, regardless whether an underlying pathologic lesion is identified or not, as in the case presented above. In the following, we review the literature as it relates to the association between nonfebrile status epilepticus, temporal lobe pathology, and temporal lobe epilepsy.

TABLE 1

Diagnostic category	Negative laboratory tests
Infectious	<i>Blood/serology:</i> parainfluenza virus, adenovirus, rhinovirus, respiratory syncytial virus, HIV, flava cirus, west Nile virus, herpes simplex virus, cytomegalovirus, Lyme, California equine encephalitis (initially equivocal, then negative on subsequent testing) <i>Cerebrospinal fluid:</i> syphilis, St. Louis encephalopathy, Powassan, arboviruses, enterovirus, Chlamydia, mycoplasma, influenza (A and B), varicella zoster virus
Autoimmune	ANA, ENA, ANCA, antithyroperoxidase
Paraneoplastic	Antivoltage-gated potassium channels, antivoltage-gated calcium channels, anti-NMDA (NR-1)

Multiple case series have reported the mortality and morbidity of patients with status epilepticus in the intensive care setting [6–11]. For example, mortality has been reported to range between 7% and 39%, while morbidity, including ongoing seizures, is reported to range between 3–13% in patients with status epilepticus (e.g., [10]). These rates are increased if seizure activity is prolonged and refractory to medical treatment, although even in these cases long term survival and some functional recovery are possible [9].

It has been recognized that symptomatic and unprovoked epilepsy may follow as a consequence of status epilepticus, particularly if it is refractory in nature [10–13]. However, the extent to which status epilepticus itself contributes to the process of epileptogenesis remains unclear. In part, this is because the inciting cause for the episode of status epilepticus can often itself be a risk factor for ongoing seizures [15]. For example, acute symptomatic seizures may occur as a result of traumatic brain injury, central nervous system infections, cerebrovascular disease, brain tumours, neurosurgery, and neurodegenerative disorders [13]. These lesions increase the risk for the development of subsequent seizures and this risk appears to be increased if it is related to an episode of status epilepticus. This suggests a synergistic effect of epileptogenic potential in the cases of symptomatic status epilepticus with defined lesions as a precipitating etiology [13]. Moreover, symptomatic status epilepticus may be related to the development of MTS, which itself can lead to TLE. Therefore, a situation may arise where TLE associated with MTS may overlap seizure activity related to the initial lesion itself (i.e., so called dual pathology) [16]. Although there have been many reported cases suggesting that status epilepticus leads to MTS, a direct link is difficult to establish, particularly if a lesion is known to be the underlying pathology.

One of the first descriptions of progressive radiological changes in the hippocampus related to status epilepticus in an adult was by Wiesmann et al. [17]. These authors described a case report of a 30-year-old woman with status

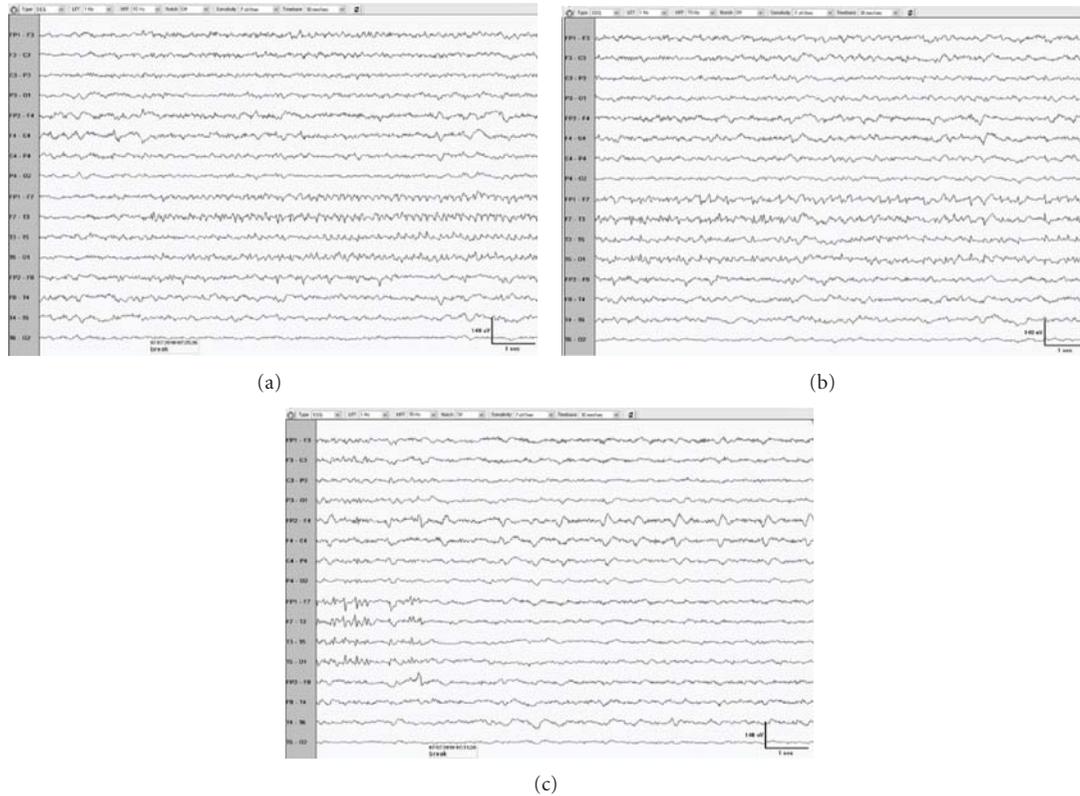


FIGURE 1: Typical electrographic seizure. This anterior-posterior bipolar montage contains an electrographic seizure which originates in the left frontal/anterior temporal region. The seizure does not generalize to the right hemisphere. Independent sharply formed slow waves are seen in the right frontal-central region. These sharply formed slow waves become semirhythmic but do not evolve into an electrographic seizure during the epoch shown. The EEG is calibrated to 7 V/mm, and the paper speed is 30 mm/second. The low frequency filter is set for 1 Hz, and the high frequency filter is set at 70 Hz. The 60 Hz notch filter is off.

epilepticus due to herpes simplex encephalitis. Although she survived the initial illness, she developed severe memory problems and recurrent focal seizures with secondary generalization, which were refractory to medical therapy. The authors clearly document progressive atrophy in both hippocampi over a 5-year period. Although the atrophy may be attributed to the initial event of status epilepticus, this hippocampal atrophy may also have been related to the herpes simplex infection or the ongoing, medically refractory seizures [17]. More recently, there have been published longitudinal assessments of hippocampal volume and progressive MTS [18, 19]. However, in these cases, the causality of MTS from status epilepticus could not be confidently defined as there was likely underlying structural pathology present prior to the onset of seizures. Likewise, in longitudinal structural imaging in patients with febrile status epilepticus [20–22], the ongoing debate regarding the development of MTS following, in these cases, febrile convulsive status epilepticus, is that there still may be preexisting structural or genetic substrates that predispose these children to developing both febrile seizures and MTS [23].

With regards to our case, while we cannot eliminate the possibility of an underlying genetic predisposition to refractory seizures, status epilepticus, and MTS, our radiological

evaluation did not reveal any underlying substrate for seizures (i.e., malformations of cortical development). We would argue that in our case much of the neuronal loss and subsequent gliosis within the hippocampus was due to a direct effect of the seizures themselves, as has been previously demonstrated in animal models of status epilepticus [24]. A similar argument was put forth following a description of an adult patient with refractory convulsive status epilepticus, also of unknown etiology. At presentation, the patient had a documented unremarkable MRI, which developed into left MTS, as demonstrated on follow-up MRI 111 days later. At that point the patient continued to require medically induced electrographic suppression of ongoing focal and generalized seizures [25]. In a comparable clinico-pathological description of refractory status epilepticus in a 3-year-old boy, initial imaging was completely normal; however, progressive T2 hyperintensity and hippocampal atrophy occurred during his 6-week course of refractory status epilepticus that occurred in the context of a febrile illness [26]. The neuropathological assessment demonstrated hippocampal neuronal loss and gliosis, in the absence of any other congenital lesion. Although these individual cases lend support to the idea that status epilepticus initiates or participates in the epileptogenesis of temporal lobe seizures, a clear definitive

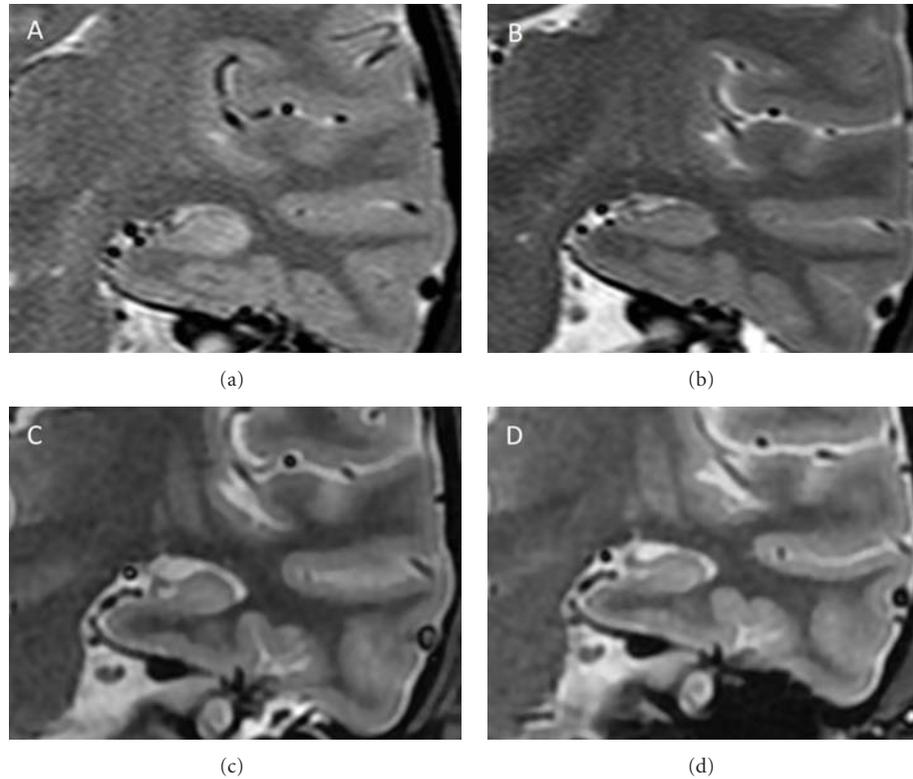


FIGURE 2: Longitudinal MRI, Coronal T2 (A, B), and fluid inversion recovery (FIR; C, D) images are shown through the hippocampus for the patient described in case number 2. While the initial imaging for this patient was normal (not shown), the hippocampus appears bright and somewhat edematous 10 days after the onset of status epilepticus (A). Thirty days after the onset of refractory status epilepticus (B), the edema has resolved, and the hippocampus appears atrophic. At 2 (C) and 6 (D) months after the onset of status epilepticus, progressive hippocampal atrophy is noted.

link has not yet been established. More importantly, the mechanism by which this could occur is still not clearly understood.

One suggestion has been that inflammation may play a key role in epileptogenesis following prolonged seizure activity. For example, in prolonged febrile seizures in children, it has been proposed that the inflammatory response during these episodes may contribute to the development of MTS, which is often associated with ongoing TLE in these patients [27]. Similarly, in adults without a previous history of epilepsy, it has become increasingly recognized that inflammation [28] and blood-brain barrier dysfunction (e.g., [29]) resulting from seizure activity might ultimately lead to cell loss and contribute to the development of hyperexcitable circuits. Indeed, inflammation within the brain can be induced by mechanisms such as trauma, infection, vascular pathology or other structural brain lesions, but the balance between the destructive and neuroprotective roles of inflammation in these scenarios is not fully understood [28]. Disorders such as lupus, vasculitis, paraneoplastic limbic encephalitis, anti-N-methyl-D-aspartate (anti-NMDA) receptor antibody syndrome, and antivoltage-gated potassium channel (anti-VGKC) antibody syndrome, all of which can lead to the manifestation of seizures and status epilepticus, are due to immune-mediated mechanisms [28] and are treated with

therapies (i.e., IVIg, plasmapheresis, and corticosteroids) targeted against the immune response.

Therefore, autoimmune processes and the inflammatory response may not only cause seizures (i.e., such as in limbic encephalitis), but may subsequently contribute to the perpetuation of seizures during status epilepticus and may participate in the epileptogenesis of future seizures from focal lesions or from the development of MTS. In a recent retrospective study of 38 patients with adult onset TLE and hippocampal sclerosis, more than half was associated with diagnosed or suspected limbic encephalitis (including paraneoplastic and anti-VGKC antibody syndrome). The remaining either had a clear precipitating lesion with subsequent hippocampal atrophy (i.e., dual pathology) or were idiopathic [16]. This highlights the relationship between new-onset seizures in the context of immune-mediated processes or discrete brain lesions and the development of TLE associated with MTS. Further work is required to help determine the exact role of the inflammatory response in the development of TLE following status epilepticus. This will help to clarify the mechanisms underlying these complex relationships, particularly since not all patients who have an episode of status epilepticus develop ongoing epilepsy and/or MTS. More importantly, it may help to define more clearly therapeutic targets in cases of refractory status epilepticus.

### 3. Summary and Conclusions

Temporal lobe pathology can be associated with critical illness in a number of ways, most commonly in the form of seizures, particularly status epilepticus and the subsequent development of TLE. The relationship between status epilepticus and TLE can be seemingly complex. This is because it may involve the development of MTS leading to seizures of temporal lobe origin. However, this can be complicated by recurrent seizures arising from the focus of initial structural pathology, if it can be identified. The case presented above illustrates the development of MTS and ongoing seizures in the context of a previously healthy young adult with a new-onset refractory status epilepticus syndrome of unknown etiology. It has been proposed that ongoing inflammation might contribute to the mechanisms that underlie complications associated with status epilepticus, including a refractory state and the development of MTS. Further work is required to demonstrate more clearly the relationship between status epilepticus and TLE. In addition, more research is necessary to help develop strategies for treating patients with status epilepticus which becomes refractory to the medications and therapeutic targets currently used in the intensive care setting.

### Acknowledgment

The authors would like to thank the EEG technologists whose role in facilitating continuous EEG monitoring cannot be underestimated.

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## Review Article

# Anatomy of the Temporal Lobe

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Received 6 October 2011; Accepted 3 December 2011

Academic Editor: Seyed M. Mirsattari

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Only primates have temporal lobes, which are largest in man, accommodating 17% of the cerebral cortex and including areas with auditory, olfactory, vestibular, visual and linguistic functions. The hippocampal formation, on the medial side of the lobe, includes the parahippocampal gyrus, subiculum, hippocampus, dentate gyrus, and associated white matter, notably the fimbria, whose fibres continue into the fornix. The hippocampus is an inrolled gyrus that bulges into the temporal horn of the lateral ventricle. Association fibres connect all parts of the cerebral cortex with the parahippocampal gyrus and subiculum, which in turn project to the dentate gyrus. The largest efferent projection of the subiculum and hippocampus is through the fornix to the hypothalamus. The choroid fissure, alongside the fimbria, separates the temporal lobe from the optic tract, hypothalamus and midbrain. The amygdala comprises several nuclei on the medial aspect of the temporal lobe, mostly anterior the hippocampus and indenting the tip of the temporal horn. The amygdala receives input from the olfactory bulb and from association cortex for other modalities of sensation. Its major projections are to the septal area and prefrontal cortex, mediating emotional responses to sensory stimuli. The temporal lobe contains much subcortical white matter, with such named bundles as the anterior commissure, arcuate fasciculus, inferior longitudinal fasciculus and uncinate fasciculus, and Meyer's loop of the geniculocalcarine tract. This article also reviews arterial supply, venous drainage, and anatomical relations of the temporal lobe to adjacent intracranial and tympanic structures.

## 1. Introduction

In this paper, I attempt to explain the positions of the parts of the normal human temporal lobe in relation to one another and to nearby structures. Some physiological and pathological correlates are mentioned, but this is primarily an anatomical account. References are provided for further reading, especially in areas where there is clinical interest or controversy or where anatomical details are not easily found in ordinary textbooks of neuroanatomy. A few historical references are included to remind readers that many of the "discoveries" made with modern imaging techniques simply confirm what has been known about the temporal lobe for many years. No attempt is made to provide references for the original descriptions of gross anatomical structures, but synonyms are mentioned to accommodate the differences in terminology used by anatomists, pathologists, and radiologists in textbooks and other literature.

Bulges on the lateral sides of the forebrain in insectivores (considered ancestral to primates) are anatomically related to the temporal bone and contain cortical areas and other

structures such as the hippocampus and amygdala that are medially located in the temporal lobes of the human brain. A true temporal lobe, delineated above (dorsally) by a lateral sulcus (sylvian fissure), and containing an extension of the lateral ventricle, occurs only in primates and is largest in man [1–3].

Approximately 17% of the volume of the human cerebral cortex, 16% in the right and 17% in the left hemisphere, forms the surfaces of the temporal lobes [4]. Temporal cortex includes areas involved with the auditory, olfactory, vestibular, and visual senses, and in the perception of spoken and written language. In addition to cortex, the temporal lobe contains white matter, part of the lateral ventricle, the tail of the caudate nucleus, the stria terminalis, the hippocampal formation, and the amygdala. The medial side of the temporal lobe includes regions concerned with olfaction (the uncus and nearby cortex) and semantic memory (the hippocampal formation). The nearby amygdala generates responses to perceived sensory stimuli that have been partly analyzed elsewhere in the brain. Such responses include largely involuntary ones, mediated by the autonomic and

somatic motor systems, and mental functions, especially those called feelings or emotions, that motivate decision and voluntary actions [5–12].

The temporal lobe can be damaged by infection, trauma, ischaemia, and neoplasia. Lesions in the temporal lobe can stimulate or inhibit the functions mentioned in the preceding paragraph. The syndrome of Kluver and Bucy [13, 14] provided an extreme example of changed behaviour following bilateral temporal lobectomy in monkeys. The animals became unnaturally docile, exhibited excessive and abnormal sexual behaviour, lost the ability to be trained, and had a condition that the authors termed “psychic blindness,” in which tactile exploration of objects with the mouth replaced their visual recognition. The equivalent human syndrome is rare and usually associated with pathology extending beyond the temporal lobes [15–17]. Fragments of the classical syndrome, such as visual field defects, visual agnosia, and inability to consolidate new memories, occur more frequently, with destructive lesions in parts of one or both temporal lobes.

## 2. Surface Features and Delimitation

Like the other lobes of the cerebral hemisphere, the temporal lobe is delineated by cortical landmarks. On the lateral surface, the stem and posterior ramus of the lateral sulcus mark the separation of the temporal lobe from the frontal and parietal lobes. The lateral sulcus or sylvian fissure is a deep cleft, but in anatomical terms it is not a fissure, because its extensive internal surfaces are all bounded by cerebral cortex. Latin *sulcus* means a furrow or trench, whereas *fissus* and related words translate to the English slit or split. A fissure separates different structures, such as the two cerebral hemispheres (longitudinal fissure), the cerebrum from the cerebellum (transverse fissure), or the fornix from the thalamus (choroid fissure). The lateral sulcus, in addition to defining the superior border of the temporal lobe, accommodates a cistern of the subarachnoid space, the middle cerebral artery, and the superficial and deep middle cerebral veins. The term perisylvian is often used when referring to cortex on both sides of the lateral sulcus, especially in neuroimaging studies of patients with aphasias [18, 19].

The lateral surface of the temporal lobe is indented by the superior and inferior temporal sulci, thus delineating superior, middle, and inferior temporal gyri. The last of these curves around onto the inferior surface of the brain and extends posteriorly into the occipital lobe; it is also called the lateral occipitotemporal gyrus. The sulci of the inferior surface of the temporal lobe are variable. Typically, the occipitotemporal sulcus separates the medial border of the inferior temporal gyrus from the lateral border of the fusiform or medial occipitotemporal gyrus. Medial to the fusiform gyrus is the collateral sulcus, and medial to the collateral sulcus, the parahippocampal gyrus forms the medial border of the inferior surface of the lobe. The anterior end of the collateral sulcus, which curves anteromedially below the temporal pole, is called the rhinal sulcus. The uncus is a small projection of the medial surface of the anterior end of

the parahippocampal gyrus, a region that will be discussed in more detail in connection with the hippocampal formation.

The superior surface of the temporal lobe, which forms the floor of the lateral sulcus, is continuous with the superior temporal gyrus. It is marked by two obliquely oriented ridges, the transverse temporal gyri, which constitute the primary auditory cortex, posterior to which is the planum temporale, a cortical area that is usually larger on the left than on the right side in men, but not in women [20]. The superior surface of the temporal lobe is bounded medially by the circular sulcus, which surrounds the insula, a lobe of the cortex that forms the expanded floor of the lateral sulcus. The anterior end of the insula, the limen insulae, is continuous, in the stem of the lateral sulcus, with cortices of the anteromedial part of the parahippocampal gyrus, the anterior perforated substance, and the medial frontal cortex (subcallosal or paraterminal gyrus) below the rostrum of the corpus callosum [21].

The posterior part of the temporal lobe blends into the parietal lobe above and the occipital lobe behind. The limits of the lobes are arbitrary straight lines connecting anatomical landmarks. The preoccipital notch is an indentation in the inferior temporal gyrus, about 3 cm anterior to the occipital pole, formed by the petrous part of the temporal bone. A straight line drawn from the parietooccipital sulcus to the preoccipital notch defines the anterior border of the occipital lobe on the lateral aspect of the hemisphere. From the midpoint of this line, a horizontal line passing forward to the lateral sulcus separates the temporal from the parietal lobe. On the inferior surface, a line connecting the preoccipital notch with the cortex immediately behind the splenium of the corpus callosum separates temporal from occipital cortex. The sulci gyri and boundaries of the temporal lobe are illustrated in Figures 1 and 2.

## 3. Hippocampal Formation

In comparative anatomy, the word pallium (Latin for cloak) is often applied to the cerebral cortex of mammals and homologous parts of the forebrain in submammalian vertebrates. A cloak has a continuous edge. The edge of the cerebral cortex around the base of each cerebral hemisphere forms a ring, often called the limbic lobe (from Latin *limbus*, a hem or fringe), a name bestowed by Broca in 1877 [22]. In the human brain the most conspicuous components of this ring of cortex are the parahippocampal gyrus and the cingulate gyrus. These gyri are continuous behind the splenium of the corpus callosum as the isthmus or retrosplenial cortex. Anteriorly, the continuity includes cortical areas that extend from the uncus and cortex overlying the amygdala (periamygdaloid cortex) across the stem of the lateral sulcus (the limen insulae) and the anterior perforated substance to the medial surface of the frontal lobe, below the rostrum of the corpus callosum (the subcallosal gyrus), which is continuous around the genu with the anterior end of the cingulate gyrus. The components of the hippocampal formation are the hippocampus, an enrolled gyrus adjacent to the parahippocampal gyrus, the dentate gyrus, which

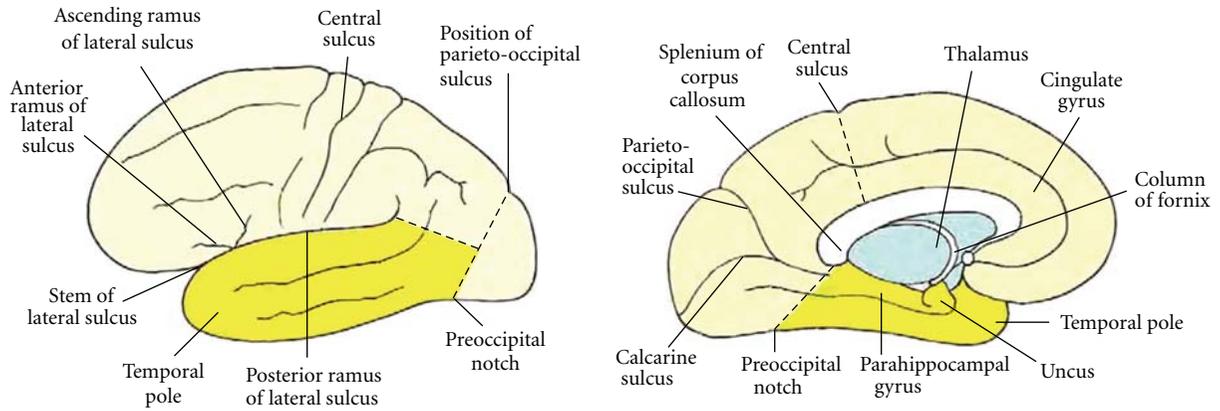


FIGURE 1: Boundaries of the temporal lobe and positions of major sulci and gyri and other anatomical landmarks of the lateral and medial surfaces of the left cerebral hemisphere.

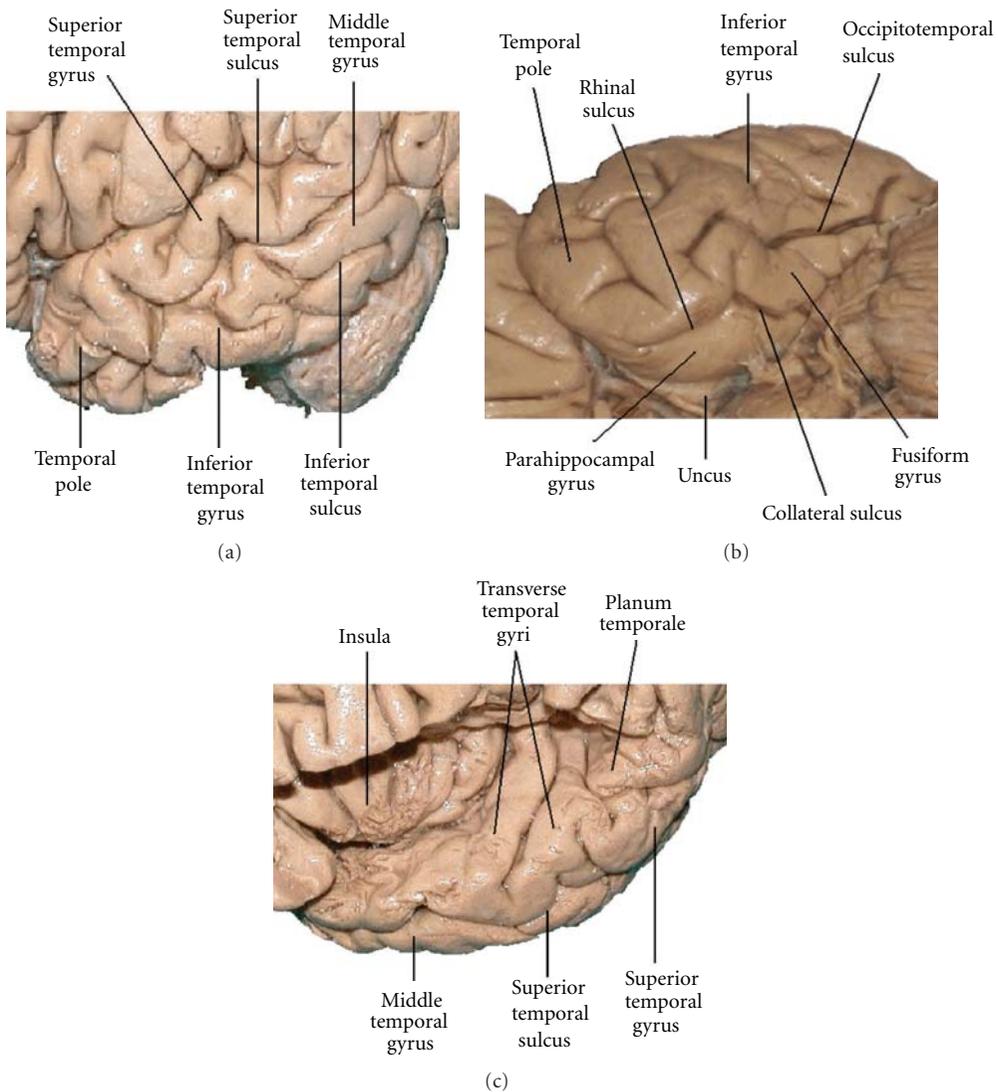


FIGURE 2: Anatomical landmarks of the cortex of the left temporal lobe. Photographs are of the lateral (a), inferior (b), and superior (c) surfaces. The superior surface, along with the insula, was exposed by removal of parts of the frontal and parietal lobes above the lateral sulcus.

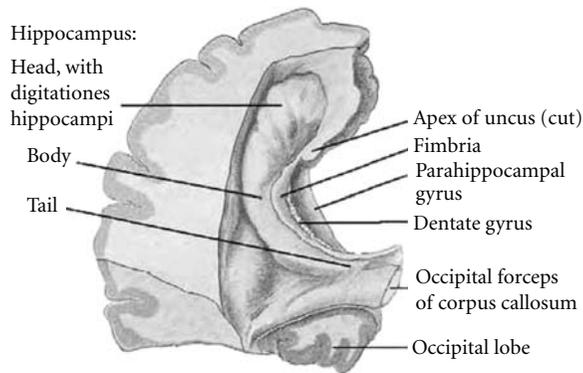


FIGURE 3: The hippocampus, dentate gyrus and fimbria as they appear after removal of the roof of the temporal horn of the lateral ventricle and of the choroid plexus (modified from Piersol, 1928 [27]). The photograph on the right (courtesy of Dr. Laszlo Seriss, University of Pecs, Hungary) shows a dissected hippocampal formation, including the reflexed intrauncal component, with a sea-horse alongside.

represents the free edge of the pallium, and the associated white matter, the alveus, fimbria, and fornix. The cortex adjacent to the hippocampus is known as the entorhinal area; it is present along the whole length of the parahippocampal gyrus [21]. The subiculum is a transitional zone between the entorhinal and hippocampal cortices. The hippocampal formation has indirect afferent connections from the whole of the cerebral cortex, funneled through the adjacent temporal cortex and the subiculum. The best understood function of the hippocampus is the consolidation of memory.

Other components of the limbic lobe, very small in the human brain, are the fasciolar gyrus, and the indusium griseum. These are continuations of the hippocampal formation, forming an inconspicuous but thin continuous ring of grey matter at the edge of the pallium. The limbic lobe includes some grossly visible bodies of white matter. Of these, the alveus and fimbria of the hippocampal formation and the crus of the fornix are within the temporal lobe. The body and column of the fornix are outside the territory of the temporal lobe, as are the longitudinal striae of Lancisi, beneath the indusium griseum. The components of the limbic lobe are also parts of the limbic system, a term that includes also the amygdala and several functionally connected nuclei in the cerebral hemisphere, diencephalon, and brain stem.

The adult anatomy of the human hippocampal formation is best understood in the context of its development. The hippocampus and dentate gyrus become recognizable late in the embryonic period of development [23], in the edge of the pallium. Growth of the cerebral cortex and associated subcortical white matter, especially the radiations of the corpus callosum, pushes the relatively small hippocampus downward and forward to become the medial surface of the developing temporal lobe. The folding that characterizes the adult hippocampal formation occurs during fetal development, from 13 to 20 weeks after fertilization [24, 25]. A shallow indentation, the hippocampal sulcus, forms on the medial surface of the temporal lobe, indenting the temporal horn of the lateral ventricle. With continued growth, the hippocampal sulcus becomes deeper and narrower, and by 18 weeks it is largely obliterated, so that the ventral surface of

the dentate gyrus is fused with the surface of the subiculum, which is the cortical area along the medial edge of the parahippocampal gyrus, adjacent to the hippocampus. The resulting bulge into the temporal horn is the hippocampus. Its surface, the alveus, is its subcortical white matter, the fibres of which converge along the edge of the hippocampus as the fimbria (from Latin *fimbriae*, fringe), which becomes progressively larger posteriorly, eventually becoming the crus of the fornix.

The hippocampus is widest at its head or anterior end, which includes a narrow reflexed prolongation into the anterior part of the uncus. The inferior surface of the uncus is crossed by an obscure transverse marking the band of Giacomini, which represents the rostral end of the dentate gyrus. Posteriorly the structure has a narrow horizontal body and a slender upwardly curved tail (Figure 3). The imaginative alternative name *cornu ammonis* (from *Amun*, an early Egyptian deity with a ram's head), dates back to the 18th century. In modern usage it excludes the dentate gyrus and is memorialized in terminology for sectors seen in transverse (coronal) sections of the hippocampus, with CA1 next to the subiculum and CA4 in the concavity (hilum) of the dentate gyrus [21, 26].

The choroid fissure is formed by invagination of the ependyma of the medial wall of the lateral ventricle and ingrowth of vascular tissue that will form the choroid plexus. In the temporal lobe, the fissure is alongside the hippocampus and fimbria, which form its inferior wall. Subcortical grey matter, the tail of the caudate nucleus, forms the opposing wall of the fissure, along with an associated fibre bundle, the stria terminalis, which contains axons from the amygdala. In the adult human brain, the amygdala is near the temporal pole and indents tip of the temporal horn of the lateral ventricle, overlapping slightly with the more conspicuous indentation due to the hippocampus. In a dissected adult brain with the lateral ventricle opened from above, the hippocampus is seen as the white floor (inferomedial surface) of the inferior horn. The ventricular surface of the human hippocampus is shallowly grooved (the *digitationes hippocampi*), with the hippocampal head

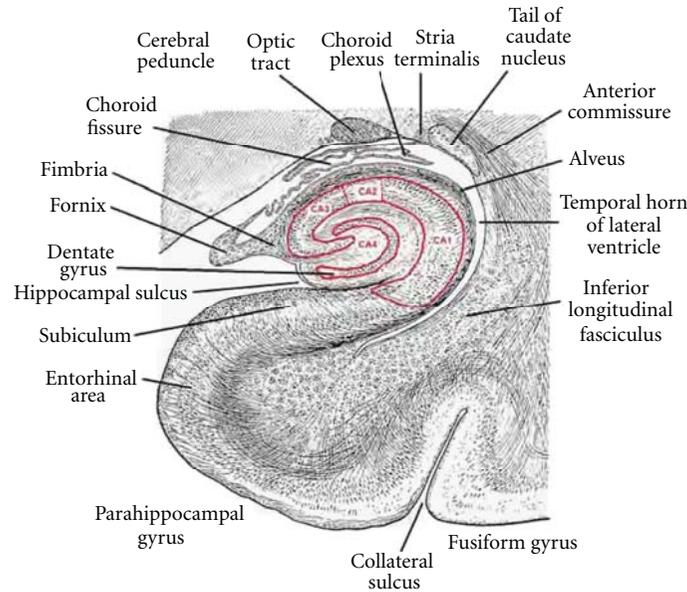


FIGURE 4: A transverse section through the body of the hippocampus and dentate gyrus, choroid fissure, and inferior horn of the lateral ventricle. The dentate gyrus and CA sectors of the hippocampus are outlined in red (modified from Edinger, 1899 [33]).

giving an impression of the dorsal surface of an animal's paw (Figure 3). The name *pes hippocampi* is still occasionally encountered for the anterior end of the hippocampus [28, 29].

The name hippocampus (Latin for sea-horse) dates from the Renaissance and a fancied resemblance to the fish (Figure 3), with its thin snout, flexed neck, plump body, and curved tail [30]. The curved shape of the hippocampus has been likened also to the horn of a ram (*cornu ammonis*), a shape that relates also to the appearance of a transverse section [31].

The architecture of the hippocampal formation is largely uniform throughout its length, as seen in transverse sections (Figure 4). Most of the human cerebral cortex (the isocortex) has 6 layers, two of which contain principal cells: neurons with axons that enter the subcortical white matter. The cortex of the hippocampal formation, however, has the principal cells in just one layer (allocortex). The molecular layer, which is continuous with the most superficial layer of the isocortex of the parahippocampal gyrus, consists largely of axodendritic synapses and is adjacent to the vestigial hippocampal sulcus. In the dentate gyrus this is quite a thin layer, but in the hippocampus it is thick, with 4 sublayers, the stratum molecular, stratum lacunosum, stratum radiatum, and stratum lucidum, which contain synapses from different groups of afferent fibres. The layer of principal cells in the hippocampus is called the stratum pyralidae; it contains neurons whose sectioned somata have triangular outlines and large apical dendrites that extend into the molecular layer. In the dentate gyrus the principal cells are small and very numerous, constituting the stratum granulosum. The axons of hippocampal pyramidal cells pass through the stratum oriens and then enter the alveus. The axons of dentate

gyrus granule cells pass through the polymorphic layer into the hilus of the gyrus (sector CA4) and then into the strata lucidum and pyralidae of sector CA3 of the hippocampus [32].

#### 4. Amygdala

In embryonic development, the origin of the amygdaloid body or complex, usually more simply called the amygdala, has been traced to populations of diencephalic and telencephalic cells that form the floor of the lateral ventricle about 3 weeks after conception [34], long before the first appearance of the developing temporal lobe at about 7 weeks [35]. The adult amygdala is a group of several nuclei located in the medial part of the temporal pole, anterior to and partly overlapping the hippocampal head. The medial part of the complex, present in the anterior part of the uncus, receives fibres of the olfactory tract. Two named gyri of the anterior end of the uncus, the ambient and semilunar gyri consist of periamygdaloid cortex that receives fibres from the olfactory tract [28, 32]. The larger lateral part of the amygdala, like the hippocampal formation, receives direct and indirect input from most of the cerebral cortex. Functional imaging confirms experimental studies involving stimulation or destructive lesions, indicating that the amygdala extracts affective content from multiple sensory inputs [36, 37].

The posterior pole of the amygdala is prolonged for a short distance around the stria terminalis, which is one of the two major efferent tracts of this nuclear group. The stria terminalis runs in the roof of the temporal horn of the lateral ventricle alongside the tail of the caudate nucleus, which ends close to but not in contiguity with the amygdala [4, 37, 38]. At the junction of the temporal horn with the central part

(“body”) of the lateral ventricle, the stria terminalis turns upward and forward into the frontal horn, in the sulcus between the head of the caudate nucleus and the superior surface of the thalamus. At the anterior tubercle of the thalamus the stria terminalis converges with a minority of the fibres of the fornix that descend anterior to the anterior commissure into the septal area. Grey matter surrounding the stria terminalis in this region constitutes the bed nucleus of the stria terminalis, which, in the human brain, has 7 named divisions [4]. The bed nucleus of the stria terminalis is currently described as part of the “extended amygdala”, located in the frontal rather than the temporal lobe [37, 39]. Dorsomedially the posterior part of the amygdala is bounded by the substantia innominata, a region contiguous with the lateral hypothalamus that includes several cell groups, notably the large cholinergic neurons of the basal nucleus of Meynert, whose much branched axons innervate the whole cerebral cortex. The second major group of efferent amygdalar fibres, the ventral amygdalofugal pathway, passes through the substantia innominata before distributing axons to extensive areas of the cerebral cortex, the mediodorsal nucleus of the thalamus, the hypothalamus, and all levels of the brain stem. Laterally the amygdala is bounded by white matter of the temporal lobe, through which afferent fibres are received principally from sensory association areas of the cerebral cortex.

On the basis of cytoarchitectonics and comparison with experiments tracing neuronal connectivity in animals, 24 nuclei are recognized in the human amygdala [4], though some authorities [40] recognize only 12. The nuclei are organized in three groups: corticomедial nuclei in the anterior part of the uncus, basolateral nuclei comprising the inferolateral two-thirds of the amygdala, and a central group, which receives afferent fibers from the other two groups of nuclei. The corticomедial nuclei blend into the thin overlying cortical layer (periamygdaloid cortex), and like that cortex they receive afferent fibres from the olfactory tract. The basolateral nuclei receive indirect olfactory input from the primary olfactory areas [37, 41], but most of the afferents to the basolateral nuclei are from association cortex of the visual, auditory, and somatosensory systems. There are also reciprocal connections with the prefrontal and anterior cingulate cortex but few or no connections with the parietal lobe [37, 39–42]. Fibres leaving the amygdala originate mainly in the basolateral and central nuclei. The position and relations of the amygdala are shown in Figure 5.

Electrical stimulation of the human amygdala causes feelings of fear. In laboratory animals, such stimulation leads to autonomic and other behavioural responses associated with fear [43, 44]. The extensive connections with sensory association cortex support a more general role of the amygdala in mediating emotional responses to sensations [45, 46]. Electrical stimulation and recording in patients prior to surgery for temporal lobe epilepsy show that a dreamy state or *déjà vu* is associated with activity in the amygdala as well as with the hippocampus and both medially and laterally located isocortex of the temporal lobe [47], indicating that the amygdala is part of a system of memory recall [48].

In fMRI studies, activity in the amygdala, bilaterally, has been associated with emotionally significant word pairs [49] and with feared aversive sensory stimuli [50].

## 5. White Matter

Subcortical white matter comprises three populations of axons. Association fibres connect cortical areas within the same cerebral hemisphere. Commissural fibres connect mainly but not exclusively [51] symmetrical cortical areas. Projection fibres connect cortical areas with subcortical nuclei of grey matter. The three types of fibre intersect extensively, but certain bundles can be demonstrated by dissection. The same bundles also can be imaged in the living brain by diffusion tensor (DT) imaging, a nuclear magnetic resonance technique. The production of DT images of fibre tracts is, however, heavily dependent on knowledge of axonal orientation gained by traditional dissection [52], and the method has not yet contributed new information about the white matter of the temporal lobe.

The temporal cortex is connected by association fibres with all the other lobes of the forebrain. The largest named bundle is the arcuate fasciculus, whose anterior end is in the frontal lobe. The arcuate fasciculus passes above the insula and lentiform nucleus, where it is also named the superior longitudinal fasciculus and follows a curved course into the temporal lobe, thus providing two-way communication between frontal cortex, including Broca’s expressive speech area, and Wernicke’s receptive language area in the posterior part of the superior temporal gyrus. The condition of conduction aphasia is traditionally attributed to a destructive lesion that interrupts the arcuate fasciculus [18, 19, 53]. Another frontotemporal association bundle is the uncinate fasciculus, named for its hooklike shape, which passes around the stem of the lateral sulcus and connects the cortex of the temporal pole with the prefrontal cortex. The ventral amygdalofugal pathway is more dorsally and posteriorly located, above the anterior perforated substance. Visual association cortex extends from the occipital lobe to the middle and inferior temporal and fusiform gyri. The inferior longitudinal fasciculus, which is in the white matter inferolateral to the temporal horn (Figure 4) connects these visual areas with one another and with the temporal polar cortex, an important source of fibres afferent to the amygdala. The fornix and stria terminalis, already discussed in connection with the hippocampal formation and amygdala, respectively, can also be considered association fasciculi.

The largest group of commissural fibres is the corpus callosum. Degeneration studies indicate that axons from the middle and posterior parts of the temporal cortex cross the midline in the central part of the body of the corpus callosum [54]. The temporal poles, transverse temporal gyri, and amygdalae may be interconnected mainly by fibers of the anterior commissure [55].

Projection fibres afferent to the temporal cortex include those from the medial geniculate body to the primary auditory area of the transverse temporal gyri. These travel in the sublenticular limb of the internal capsule, where they

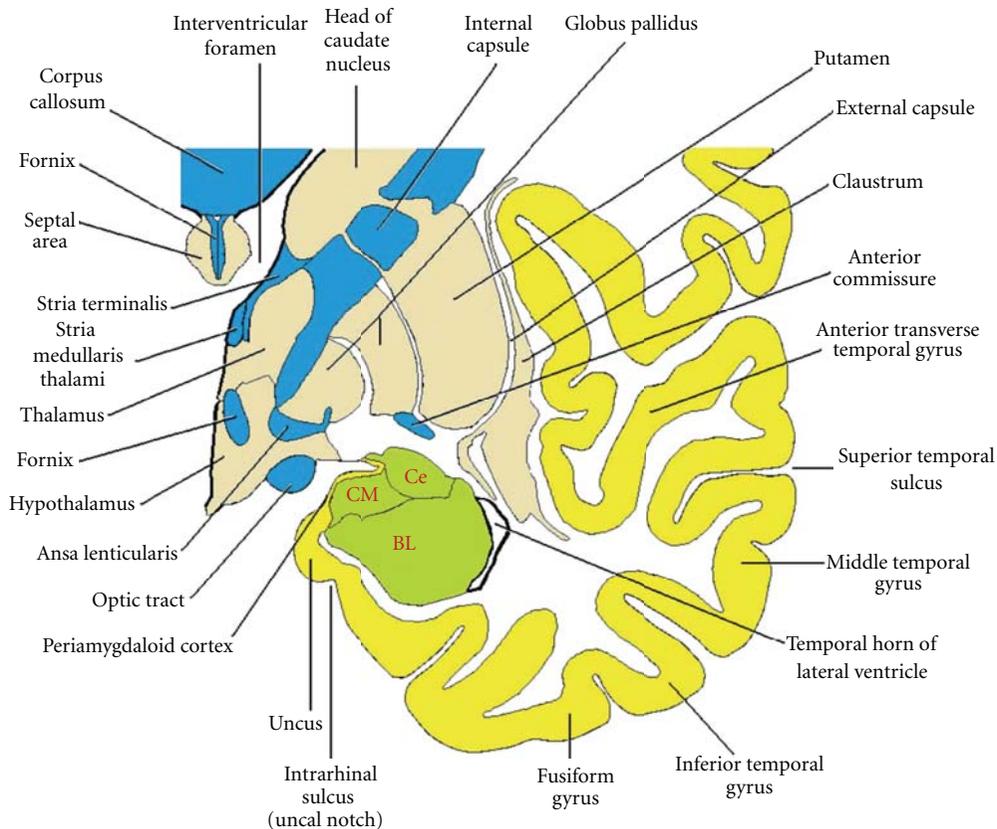


FIGURE 5: Drawing of a coronal section through the temporal lobe and adjacent structures, at a level anterior to the hippocampal head. The amygdala is coloured green, with the positions of its three nuclear groups indicated: corticomedial (CM), basolateral (BL), and central (Ce). Selected bodies of white matter are coloured blue.

probably are accompanied by fibres from the medioventral thalamic nucleus, which is connected with the amygdala, hypothalamus, hippocampal formation, and parahippocampal gyrus. For much of the temporal cortex, the sources of thalamic afferents have not been determined [40, 42]. All thalamocortical projections are accompanied by reciprocal corticothalamic fibres. An important thalamocortical pathway that passes through the temporal lobe is Meyer's loop of the geniculocalcarine tract, which is drawn into the anterior temporal white matter with the growth of the nearby temporal horn of the lateral ventricle. This loop carries signals derived from the upper quadrants of the contralateral visual fields to the corresponding primary visual cortex of the anterior half of the inferior bank of the calcarine sulcus. Some efferent temporal cortical projection fibres go to the amygdala and hippocampus and are thus confined to the temporal lobe. Corticothalamic fibres have already been mentioned. Most textbooks of neuroanatomy show a large temporopontine or temporoparietopontine tract occupying the lateral quarter of the basis pedunculi in the midbrain. Degeneration studies following temporal lobe lesions in monkeys, however, show only a small temporopontine projection, originating in the superior temporal gyrus and

ending in the most lateral of the pontine nuclei [56]. In the absence of comparable information for the human brain, we must guess that the projection is similar to that of the monkey, and that the temporal cortex does not have a large, direct influence on the workings of the cerebellum.

## 6. Anatomical Relations of the Temporal Lobe

The locations of structures close to the temporal lobe are summarized in Figures 6, 7, 8, and 9. The temporal lobe occupies the middle cranial fossa, which is bounded anteriorly by the greater wing of the sphenoid bone, inferiorly by the superior surface of the petrous part of the temporal bone, and laterally by the squamous part of the temporal bone and the adjoining parietal bone. The dura mater adheres closely to these bones and is separated from the surface of the brain by the arachnoid, subarachnoid space and pia mater. The inner surfaces of the sphenoid, parietal, and squamous temporal bones are grooved by branches of the middle meningeal artery, which enters the cranial cavity by way of the foramen spinosum, beneath the fusiform gyrus. The tentorium cerebelli lies beneath the posterior and medial

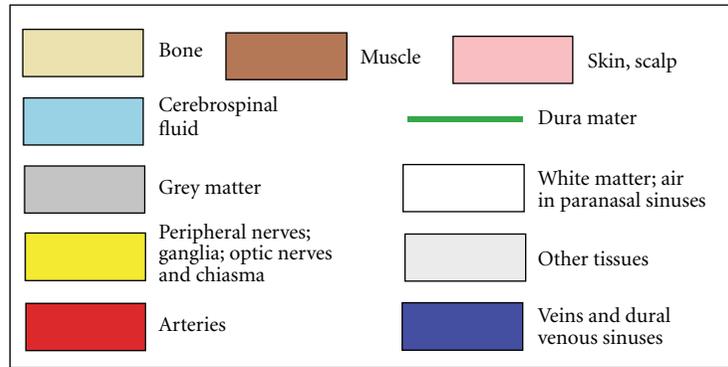


FIGURE 6: Colour scheme used in Figures 7, 8, and 9.

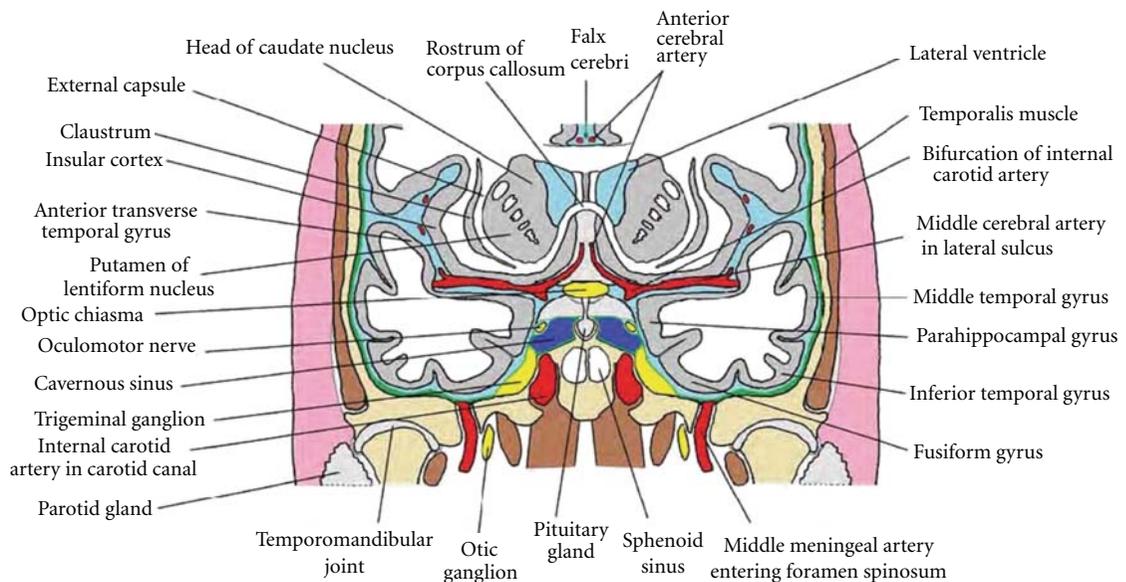


FIGURE 7: Anatomical relations of the temporal lobe, as seen in a schematic coronal section passing through the temporal pole, anterior to the amygdala, hippocampus, and temporal horn.

parts of the temporal lobe, with the free edge of the tentorial incisura being beneath the rostral end of the parahippocampal gyrus, lateral to the uncus and posterior to the rhinal sulcus, causing a shallow indentation, the intrarhinal sulcus [21] or uncal notch (Figure 5). This is a normal feature, not to be confused with the much deeper indentations that result from transtentorial herniation of the temporal lobe. The attachment of the tentorium splits to include the transverse sinus medially and the sphenoparietal sinus anterolaterally.

The petrous part of the temporal bone contains the structures of the inner ear and also the mastoid air cells, which are in continuity with the middle ear and the nasopharynx. Although the name “petrous” indicates that this bone looks like a rock, the layer of bone between the

mastoid air cells and the dura of the middle cranial fossa (the tegmen tympani) is quite thin and is susceptible to erosion by bacterial infections arising in the middle ear. Septic lesions can extend through the tegmen tympani and the dura mater and arachnoid. Meningitis can follow such an invasion, but the defensive formation of fibrous connective tissue around the lesion often protects the subarachnoid space from the bacteria, which move upward into the temporal lobe, evoking the formation of an abscess that typically involves the inferior temporal gyrus and the white matter around the temporal horn of the lateral ventricle [57, 58].

The internal carotid artery enters the cranium below and medial to the anterior end of the parahippocampal gyrus, passing through the cavernous sinus and then coming between the optic chiasma and the anterior part of the

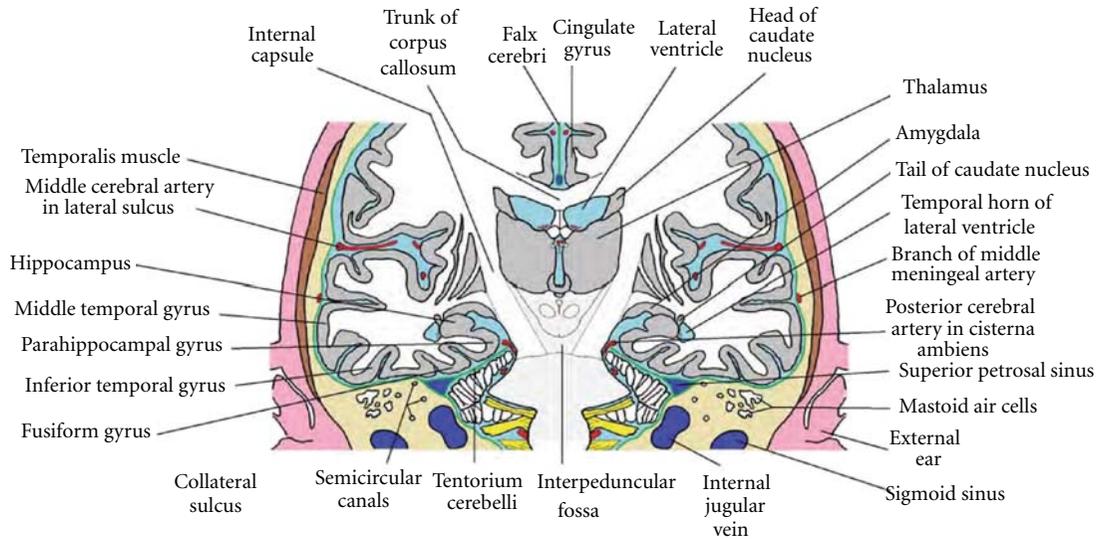


FIGURE 8: Anatomical relations of the temporal lobe, as seen in a schematic coronal section passing through the amygdala and the head of the hippocampus. This section is in a plane anterior to that shown in Figure 4.

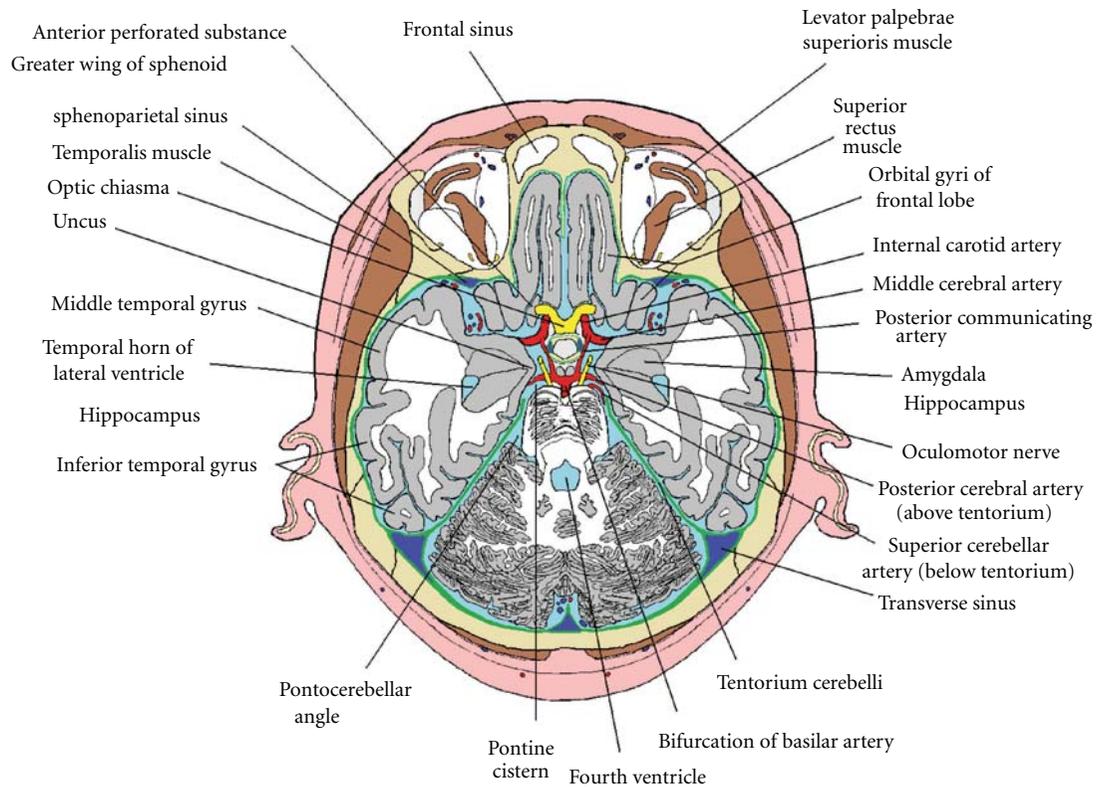


FIGURE 9: Anatomical relations of the temporal lobe, shown in a schematic horizontal section in the plane of the pituitary gland.

temporal lobe before dividing into the anterior and middle cerebral arteries. The middle cerebral artery (MCA) enters the lateral sulcus from below, giving off frontal, parietal, and temporal branches that supply the cortex of the lateral surfaces of the lobes for which they are named. The MCA

also gives rise to the anterolateral group of central arteries (lateral striate arteries), which enter the brain through the anterior perforated substance and supply much of the corpus striatum and external and internal capsules. The posterior cerebral artery, as it ascends through the tentorial notch,

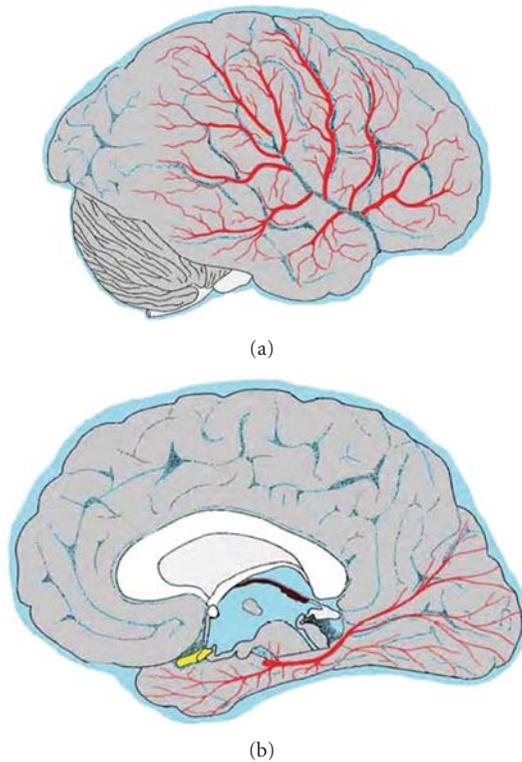


FIGURE 10: Arteries supplying the temporal lobe. The colour scheme is explained in Figure 6. (a) Three frontal, two parietal, and three temporal branches of the middle cerebral artery emerging from the lateral sulcus. (b) Hemisected brain with the pons, medulla, and cerebellum removed. The posterior cerebral artery is shown, with anterior and posterior temporal branches to the inferior temporal gyrus, and calcarine and other branches supplying the occipital lobe. Central branches to the midbrain and thalamus are represented by two small upwardly directed vessels. The medial temporal structures, supplied by the anterior choroidal artery, are hidden from view by the optic chiasma, hypothalamus and midbrain.

and its first branch, the posterior communicating artery, are also close to the medial surface of the temporal lobe, lying between the uncus and the oculomotor nerve.

The oculomotor nerve, which arises from the medial surface of the cerebral peduncle, passes through the subarachnoid space, just below the uncus, on its way to the cavernous sinus and superior orbital fissure. If the temporal lobe is displaced medially and downward into the tentorial notch by a space-occupying lesion, especially an extradural or subdural haemorrhage, the uncus is pushed medially against the oculomotor nerve, compressing first that nerve's preganglionic parasympathetic fibres, which are located superficially in the upper sector of the nerve [59], cause ipsilateral pupillary dilation [60].

## 7. Arterial Blood Supply and Venous Drainage

The temporal lobe receives blood from both the carotid and the vertebrobasilar systems. The anterior choroidal artery,

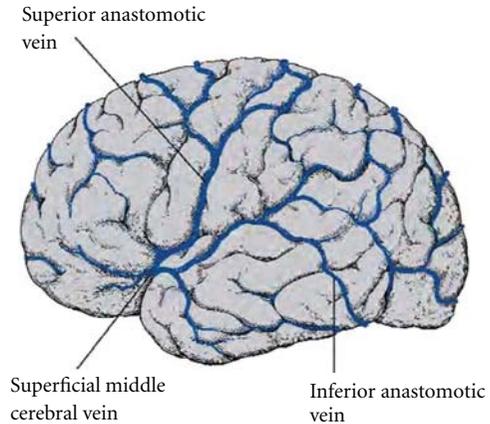


FIGURE 11: The larger superficial cerebral veins, including those draining the cortex of the temporal lobe.

which is the preterminal branch of the internal carotid, runs alongside the optic tract and then along the choroid fissure, which at this level indents the medial surface of the temporal lobe, separating the fimbria of the hippocampus from the stria terminalis and tail of the caudate nucleus (Figure 4). Structures in the temporal lobe supplied by the anterior choroidal artery are the anterior end of the parahippocampal gyrus, the uncus, the amygdala, and the choroid plexus in the temporal horn of the lateral ventricle.

The middle cerebral artery, a terminal branch of the internal carotid, crosses the insula in the floor of the lateral sulcus, giving off branches that supply the cortex of the superior and middle temporal gyri and the temporal pole. The posterior cerebral artery gives off two to four temporal branches, before it divides into the calcarine and parieto-occipital arteries, which supply the occipital lobe. The temporal branches of the posterior cerebral artery supply the inferior surface of most of the temporal lobe, but not the temporal pole.

The arteries supplying the temporal lobe are illustrated in Figure 10. Detailed anatomical accounts with photographs of serial slices of injected specimens are available [4, 61], and neuroradiology textbooks and atlases identify the vessels as they appear in angiograms.

The venous drainage of the temporal cortex and underlying white matter goes anteriorly into the superficial middle cerebral vein, in the cistern of the lateral sulcus and also into the inferior anastomotic vein (vein of Labbé), which connects the superficial middle cerebral vein with the transverse sinus (Figure 11). Blood from interior of the lobe, including the amygdala, hippocampus, and fornix, flows into the posterior choroidal vein. This vessel lies alongside the choroid plexus of the lateral ventricle, passing upward and then forward, joining the thalamostriate vein immediately behind the interventricular foramen to form the internal cerebral vein. The left and right internal cerebral veins run posteriorly in the transverse fissure between the crura of the fornix and below the splenium of the corpus callosum, where they are joined by the basal veins and unite to form the great cerebral vein, a midline structure that continues

into the straight sinus. The basal vein (vein of Rosenthal), which carries blood from the cortex and the interior of the frontal lobe, traverses the subarachnoid space in the cisterna ambiens, medial to the temporal lobe.

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## Review Article

# Natural History of Temporal Lobe Epilepsy: Antecedents and Progression

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Received 21 September 2011; Revised 20 December 2011; Accepted 29 December 2011

Academic Editor: Seyed M. Mirsattari

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Temporal lobe epilepsy represents the largest group of patients with treatment resistant/medically intractable epilepsy undergoing epilepsy surgery. The underpinnings of common forms of TLE in many instances begin in early life with the occurrence of an initial precipitating event. The first epileptic seizure often occurs after a variable latency period following this event. The precise natural history and progression following the first seizure to the development of TLE, its subsequent resolution through spontaneous remission or the development of treatment resistant epilepsy remain poorly understood. Our present understanding of the role played by these initial events, the subsequent latency to development of temporal lobe epilepsy, and the emergence of treatment resistance remains incomplete. A critical analysis of published data suggest that TLE is a heterogeneous condition, where the age of onset, presence or absence of a lesion on neuroimaging, the initial precipitating event, association with febrile seizures, febrile status epilepticus, and neurotropic viral infections influence the natural history and outcome. The pathways and processes through which these variables coalesce into a framework will provide the basis for an understanding of the natural history of TLE. The questions raised need to be addressed in future prospective and longitudinal observational studies.

## 1. Introduction

Amongst adult patients with medically intractable epilepsy, focal epilepsy from a temporal lobe focus represents the largest single etiology [1–4]. While only a small percentage (<25%) among patients operated for temporal lobe epilepsy (TLE) are in the pediatric age group [5], it is well documented that most adults in surgical series have had a childhood onset of epilepsy. It has been suggested that a significant proportion of children with refractory epilepsy on the other hand may have TLE and, more specifically, may have hippocampal sclerosis (HS) on MRI (magnetic resonance imaging) [6]. There exist gaps in our understanding of the natural history of TLE and its progression, from its antecedents in fetal life and childhood, eventually culminating in a stage of medical refractoriness that is reached in adult life. Current understanding of the natural history of TLE identifies the need for well-designed prospective studies

to elucidate risk factors and triggers [7, 8]. Clinical information of this nature might provide additional avenues for interventional strategies to be investigated and developed.

In this paper we present a brief outline and review of prior published data on TLE and identify critical areas where additional information on the evolution of TLE can be prospectively derived. For the purpose of clarification, the term TLE used is inclusive of more common mesial temporal lobe epilepsy (mTLE), as well as other forms of neocortical temporal lobe epilepsy (nTLE), unless otherwise specified.

## 2. Methods

A Pubmed search strategy using the following terms “TLE and natural history; TLE and antecedents; TLE and benign; TLE and clinical and outcome” was adopted for the purpose of this review. The search yielded a total of 678 publications

when the limits of “Human” and “English” were applied. Studies were selected on the basis of (1) whether patient selection criteria clearly defined TLE. We ascertained that each of the definitions used clearly either carried “mention of detailed semiological features of habitual seizures and latent period” or “resection of the temporal lobe for refractory epilepsy with outcome details” and (2) if the study mentioned any clinical details of antecedents or precipitating events that includes FS or FSE, age at onset, and time to refractoriness of epilepsy. After reviewing 89 abstracts and 23 full text articles reporting large series of patients with TLE, many of which were outcome studies of surgery for TLE we identified nine studies that documented details of past history obtained preoperatively.

A summary of key findings in the studies critical to this review is introduced in Table 1.

### 3. Results and Discussion

*3.1. Evidence for Role of “Initial Precipitating Events” IPEs.* The significance of early IPEs among patients with TLE has been long recognized. The participants of Group 1 (for definition and natural history of mTLE) of the ILAE (International League Against Epilepsy) Commission on Neurosurgery observed that most surgical series reported “a high incidence of “IPEs” in the form of FS, trauma, hypoxia or intracranial infection”. However the authors felt that these studies were “not definitive”, since the detailed and exhaustive case histories that are required to determine frequency of the IPEs (antecedents) and time to onset as well as time to intractability of epilepsy might not be available from these retrospective series [9].

In an elegant study, French et al. presented a comparative analysis of data obtained from 193 patients with predefined clinical and EEG criteria to define TLE and that obtained from 164 “normal” individuals [10]. The authors identified reasonably “definite” or “probable” etiological factors in the past histories of 77.2% patients with TLE, compared with only 7.3% among the control population reporting birth abnormalities or other significant past history.

Clinical data regarding IPEs in childhood have been identified in surgical series that include patients with HS on MRI (magnetic resonance imaging) and underwent temporal lobectomy (TLY) for the same. The data presented by Harvey et al. however evaluated patients who did not undergo surgery [12]. In this group nearly 40% of patients with TLE confirmed the occurrence of an IPE, in the form of simple or complicated FS. A history of perinatal problems was reported in only a small proportion of patients (<1%) by several investigators [10, 12, 13, 17] with the exception of the study by Ozkara et al. [14]. In the latter, the authors reported an antecedent history suggestive of birth asphyxia in 21 out of 62 patients (33.9%), a significantly higher proportion. A history of FS was also noted in a majority of patients (70%) among their group of postoperative patients with mTLE and MRI evidence of HS. In a study by Rathore et al., a similar proportion, that is, (68.5%) of postoperative patients were found to have a documented history of FS, while only 2

out of 124 patients (1.6%) had history of perinatal hypoxia [17]. In the largest series among the selected studies that were reviewed, Uijl et al. found history of FS in 37% of the patients, while details of other IPEs were not described [15]. In a study of factors determining the development of treatment resistance among patients undergoing epilepsy surgery, Berg et al. are only able to provide data on history of febrile seizures, while information on other IPEs is lacking [8].

An analysis of these selected as well as other studies on surgical outcomes in TLE [18] leads one to the conclusion that there is little prospective data or agreement regarding IPEs amongst most published series. It is clear from these studies that there is a considerable variation encountered when comparing results from different studies even when similar clinical variables are considered. Differences in the documentation of historical details, different selection criteria for surgery, and the lack of prospectively collected information surrounding IPEs may serve as plausible reasons for the variation in information available. Thus, while perinatal critical events and febrile seizures appear to be known variables, no definitive conclusions other than a speculative inference regarding the potential role for IPEs can be drawn from these published studies.

*3.2. What Is the Latency to Development of Epilepsy in TLE Following IPE?* Janszky et al. studied the age at onset of a homogenous group of 118 patients with mTLE and history of childhood febrile convulsions (CFCs) and reported the age at epilepsy onset to be a trimodal pattern with peaks at ages of 5.5, 15.3, and 26.7 years. These authors observed that the “latent/silent” period between occurrence of CFCs and epilepsy onset was significantly longer in patients with childhood onset, when compared to patients with an adolescent onset of mTLE [19]. Harvey et al. reported a bimodal pattern of the age at onset in a much smaller group of TLE patients with HS on MRI. The mean age observed was  $5.1 \pm 3.8$  years with two peaks identified, the first occurring early (second year) and the second, late (ninth year) during childhood years [12]. A younger age of onset of epilepsy also appears to bear a strong correlation with MRI findings of HS, even controlling for disease duration and history of FS [8, 20]. In a study aimed at evaluating predictive prognostic factors for a cohort of patients with sporadic TLE associated with either HS or a nonlesional TLE Aguglia et al. observed an older average age at onset (among 100 seizure free) patients to be  $33.5 \pm 19.9$  years in comparison to an average age of  $17.2 \pm 14.4$  years (in 90 non-seizure-free) patients on univariate analysis. Furthermore, an older age at onset was found to be the single independent prognostic factor for good seizure outcome, even on multivariate analysis [21]. Heuser and colleagues propose the occurrence of mTLE among patients with history of FS (mTLE-FS) as a separate entity based on the observation that the age at epilepsy onset is significantly lower in this group as compared to those mTLE patients who do not have prior history of FS [22].

It is evident from these studies that TLE, dominantly represented by patients with HS on MRI, has a variable

TABLE 1: Summary of selected studies on TLE and relationship to IPE.

Study	N	Criteria for diagnosis of TLE	IPE reported	Patients with TLE with positive history (%)
French [10]	67	Mesial temporal onset on depth EEG Nonlesional MRI Seizure freedom since unilateral TLX, at least 2 years	Seizures in infancy/early childhood	54 [81]
			~ FS	52 [78]
			~ Afebrile-Head	02
			Head trauma	10
			Birth trauma	02
Tassi [11]	243	Surgery confined to temporal lobe, with histopathological data on neocortex and hippocampus	Other maternal factors	02
			Febrile seizures [FS]	
			FS in patients with HS	61 [25]
			FS in patients with HS only	15/34 [44]
			FS in patients with MCD	50/110 [45]
Harvey [12]	63 [new onset TLE-age of onset <15 years]	Agreement among 3 neurologists from clinical and investigational data; ictal EEG "gold standard"	Perinatal problems	
			Head injury	24 [38]
			Bacterial meningitis	1
			Viral encephalitis	1
			FS	4
			Simple	1
			Complicated	
			Respiratory arrest	6
			Hypertensive	7
			Encephalopathy	2
Sztriha [13]	30 [new onset TLE-age of onset <14years]	Agreement amongst 2 investigators based on clinical and investigational data; no alternative diagnosis likely	Prolonged focal FS	1
			Infantile spasms	1
			Antecedent illness	5 [16.6]
			Perinatal HIE	1
			Encephalitis	1
Ozkara [14]	165	Mesial TLE with HS on MRI; postoperative follow-up data for >1 year available	Traumatic brain injury	2
			Complex FS	1
			FS	116 [70.3]
			Risk factors [antecedents]	27
			Head trauma	21
			Birth asphyxia	11
			Neonatal infections	1
			Kernicterus	1
			Near drowning	1
			Heat stroke	
Ujl et al. [15]	484	Epilepsy surgery patients who underwent TLX	FS	180 [37]
Jeong et al. [16]	227	mTLE With HS on MRI and anterior temporal onset on ictal EEG; with normal MRI but clear mesial temporal onset on invasive electrode ictal recordings	FS	99 [43.6]

TABLE 1: Continued.

Study	N	Criteria for diagnosis of TLE	IPE reported	Patients with TLE with positive history (%)
Rathore et al. [17]	124	Postoperative mTLE with histopathologically proven HS	Typical FS	85 [68.5]
			Atypical IPE	19
			Meningoencephalitis	10
			Febrile status	6
			Epilepticus	
			Perinatal hypoxia	2
		Neonatal seizures	1	
Berg et al. [8]	215 [Total patients analyzed = 333]	Refractory partial epilepsy and HS on MRI, having undergone resective surgery for same	FS	95 [44.2]

FS: febrile seizures, mTLE: mesial temporal lobe sclerosis, HS: hippocampal sclerosis, HIE: hypoxic ischemic encephalopathy, FSE: febrile status epilepticus, TLY: temporal lobectomy, MCD: malformations of cortical development, and IPE: Initial precipitating event.

age at onset. Despite suggestions that a prior cerebral insult predisposes an individual to development of TLE, at least among a subgroup of patients, the latency to the onset of epilepsy remains variable. In addition, the latency to the development of the more commonly encountered refractory form of epilepsy remains largely unpredictable in the individual setting.

Thus, the evidence from published case series suggests a role for the duration of epilepsy from the time of occurrence of the IPE in determining development of HS and prospects for a remission. Prospective cohort studies among subgroups of patients with perinatal brain injury and those with FS and FSE will be necessary to determine whether distinct subtypes of TLE can be delineated based on the age of onset of epilepsy and the occurrence of FS/FSE.

**3.3. When Does TLE Become Refractory to Medications?** It is well known that among patients with TLE as well as other focal epilepsies, treatment resistance or refractoriness to antiepileptic drugs (AEDs) appears after a significant time lapse or latency from onset of first seizure, at least in a subset of patients. The mechanisms underlying this “latent period” remain largely unidentified.

In a study analyzing information obtained from 333 patients with medically refractory partial epilepsy, Berg et al. could identify the average time to intractability as 9.1 years (median 5 and range 0–46 years) in 282 patients. The authors defined “time to intractability” as “time between occurrence of second seizure and failure of second AED”. On multivariate logistic regression analysis, the authors found that the age at onset provided the most significant correlation of this latency period; that is, earlier the age at onset, longer the latency period to intractability [8]. In another retrospective study of 162 patients fulfilling the inclusion criteria of TLE followed up for at least 2 years, the best model to predict refractoriness to medication included the variable “failure of first AED trial,” with a positive predictive value of 0.89 (95% CI 0.76, 0.96) and negative predictive value of 0.95 (95% CI 0.87, 0.99) [23].

It has been suggested that the time to establish failure to respond to an adequate trial of a second AED (or even the first AED) does not necessarily imply “latency to intractability”, as intractability may have been present long before the current standard of “proof” is attained [24]. Any direct study of human TLE, suggesting that it is a progressive condition, is not yet available. Confounding factors like the genetic profile of the individual (susceptibility genes, genetic polymorphisms), epigenetic modifiers, underlying systemic disease, effect of epileptic discharges on human brain, neuropathological effects of seizure-related systemic perturbations, trauma, AED effects (including inappropriate drugs), and multiple drug-resistant transporters will no doubt influence any estimate [24].

**3.4. What Is the Role of Febrile Seizures, Febrile Status Epilepticus, Human Herpes Virus Infection, and TLE—The Associations?** FS have long been known to be associated with the future development of epilepsy, especially mTLE [25, 26]. While retrospective studies have favored this association, prospective studies thus far have failed to confirm a causal association between the two [27–29]. In the retrospective study by Abou-Khalil et al., amongst 47 patients operated for temporal resection, a subgroup of 19 patients with history of FS showed excellent surgical outcome (85% seizure-free) in comparison to the remaining 28 patients (32%) who did not have prior history of FS [25]. Importantly, almost all patients had prolonged FS (mean duration 4 hours, range 20 minutes to 24 hours). This group also had a significantly lower age at surgery. A major selection bias could potentially have contributed to this difference, as the history of FS may have well influenced the decision to take up those patients with HS for TLY, resulting in an expectedly good surgical outcome.

It is then interesting to note the findings of a large prospective study on patients with a history of FS obtained through questionnaires administered to parents of infants born over a week in the UK. The questionnaires were administered when the children were 5 years of age (82%

responses obtained) and when they were 10 years of age (93% responses obtained) [30]. The investigators found that information was available for 14,676 children in the cohort. Nearly 382 (2.7%) children experienced at least one FS. Thirteen of these 382 (3.4%) experienced one or more afebrile seizures, nine of whom developed epilepsy. A higher proportion of children with complex FS (6/95) rather than simple FS (3/287) developed epilepsy, the risk being highest for those who had had focal FS (5/17;  $\chi^2 = 399$ ,  $P < 0.001$ ). Three of the 32 children who had prolonged FS also developed afebrile complex partial seizures (CPSs). The authors concluded that epilepsy developing after FS in childhood is not as common as expected from hospital studies, rather rare.

A systematic review of 63 studies on the outcome of pediatric status epilepticus found that the risk of sequelae in unprovoked and febrile convulsive status epilepticus (CSE) is low. The same review finds evidence that CSE, especially febrile CSE, might cause hippocampal injury, although its role in the development of MTS is unknown [31].

Additional lines of evidence favor a role for human herpes virus 6 (HHV 6) in the causation of mTLE based on the detection of the viral antigen in resected temporal lobe tissues at surgery, and exposure to the virus in the early childhood is exceedingly common. Detection of the virus or viral antigen in body fluids of children with febrile seizures has ranged from 8 to 40% in different studies [32]. The rate of HHV6 detection in resected temporal lobe tissue from surgical specimens in patients undergoing temporal lobectomy has varied greatly [33, 34]. Recently, Niehusmann et al. carried out molecular and histochemical analysis of excised pathological specimens in patients undergoing temporal lobectomy for pharmacoresistant epilepsy. They reported a 55% positivity for HHV 6 on nested PCR experiments in surgically excised temporal lobe tissue in a group of 9 TLE patients who met strict criteria of a well-defined history of encephalitis in childhood, compared to *none* among 26 others with TLE without IPEs, TLE with history of complex FS, and lesional TLE with 10 autopsy controls [35]. The authors suggest that while their findings argue against a causative role for HHV6 in TLE with a history of complex FS, the viral infection may play an important role in TLE with a history of encephalitis, despite the obvious heterogeneity of postencephalitic patients in their series. They suggest that, in patients with encephalitis of different cause, the presence of HHV6 may facilitate the development of TLE; however, they caution that it may “neither be sufficient or necessary” factor. It is also interesting to note that the presence of HHV6 was associated with significant gliosis in the temporal lobe tissue being examined, a feature which points to a role for inflammation in TLE [35, 36].

Interval data analysis from the FEBSTAT study, a multicenter prospective study on children 1 month to 5 year in age, designed to study the consequences of FSE, indicates that primary HHV-6B may be an important cause of FSE [37].

The evidence thus far offers weak associations between the occurrence of FS, FSE, and viral infections (in particular HHV-6) in childhood and subsequent development of TLE. It is also suggested that age and coexistent neuropathology

may be added as contributory factors in the variable rates of detection of herpesvirus DNA in surgically resected tissue [38].

*3.5. Are All Forms of TLE Medically Intractable? Spontaneous Remission and the Development of Treatment Resistance.* An “older age at onset” is the only independent predictor of 2-year seizure freedom or “remission” among patients with nonlesional TLE [21]. Studying 190 patients with clinically diagnosed TLE, with a mean followup of 11 years, the authors found that more than half of the patients underwent spontaneous remissions. Although occurrence of FS and HS on MRI was found to be predictors of poor prognosis on univariate analysis, these did not attain significance on multivariate analysis.

Spooner et al., in a prospective study on 64 patients with TLE followed up for a median of 13 years, found 19 (31%) to have attained 5–15-year remission and successfully remained off treatment while the remainder (69%) continued to have seizures and had to be considered for epilepsy surgery evaluation, the only predictor of significance for continued seizures, being a lesion on MRI [39].

Both these studies published nearly 15 years apart suggest similar facts about remissions in TLE that a sizeable proportion of patients with an older age of onset do remit, and that the presence of lesions on MRI and a younger age at onset predict lower chance of remission.

*3.6. Are There Different Subtypes of TLE?* A review of the literature surrounding TLE clearly suggests that the etiology varies depending on age of onset. The maximal information regarding etiology has been obtained from pathological studies on surgically resected tissue in individuals undergoing anterior temporal lobectomy (ATL). The existence of other forms of TLE where the outcome is better than the more common form of pharmacoresistant TLE is also being recognized (Benign TLE and Familial TLE).

*3.7. TLE in Infants and Children.* The findings of a recently published study suggest that the most frequently reported pathology in childhood onset TLE who develop medically refractory epilepsy consists of dual pathology in the form of a neocortical lesion associated with HS (80% of cases accounted for by cortical dysplasia or tumors such as gangliogliomas with HS). Isolated malformations of cortical development (MCD), gangliogliomas without hippocampal pathology, accounted for the remainder [40]. In infants, HS tends to be even less frequent, with the majority of the pathology reported consisting of nonprogressive lesions such as MCD, hamartomas, and low grade tumors such as dysembryoplastic neuroepithelial tumors (DNET) [41].

*3.8. Temporal Lobe Epilepsy in Adults.* The etiologies in adult onset TLE differ from those of childhood onset. While the epidemiological studies of late onset TLE point to infective, vascular (arteriovenous malformation, cavernous hemangioma, meningioangiomas), tumoral, traumatic, and in older individuals (>64 years of age) neurodegenerative

etiologies, the most frequently observed and reported pathology is HS. The causes leading to adult TLE have been less frequently reported [42, 43]. It is of interest that the etiologies in those individuals who developed TLE with an age of onset beyond 20 years differ further from those individuals developing TLE in late adulthood (often >60–65 years). In a recent study, Soeder et al. identified limbic encephalitis (LE) associated with paraneoplastic and nonparaneoplastic (autoimmune) conditions (25%) as constituting the largest group, followed by HS that was preceded by an IPE (22%). Tumors (DNET, ganglioglioma, and other low-grade tumors) and amygdalar lesions made up constituted (14% and 135), respectively. Finally, a miscellaneous group (24%) was made of patients with posttraumatic lesions, cavernomas, chronic herpes simplex encephalitis, and progressive tumors (anaplastic oligodendroglioma, glioblastoma multiforme, and astrocytomas) [43].

**3.9. Benign TLE.** The Italian group of Labate, Gambardella, Aguglia, and colleagues have addressed various issues related to “benign mTLE” in great detail [44–46]. They described this entity for patients, who were “seizure free or had auras or not more than 2 disabling (CPSs and/or secondarily generalized) seizures in 24 months, with or without appropriate medications” [44].

In a study of 101 patients diagnosed as benign TLE, they found MRI evidence of unilateral MTS in 39 (38.6%) patients. The antecedent history of febrile seizures alone predicted the association with MTS in this group of patients with benign TLE [46].

It has, thus, been clearly demonstrated that neither clinical presentation with features of TLE nor MRI evidence of MTS is determinant of future refractoriness of epilepsy in a large proportion of patients with TLE.

**3.10. Familial TLE.** First described by Berkovic and colleagues in 38 patients from 13 families in Australia, familial TLE has been recognized as a benign syndrome with typical temporal lobe seizures and good prognosis [47]. In a recent report by the same group, data from 20 new mTLE families (51 affected individuals) were presented. The epilepsies in these families were found to be generally benign, and history of febrile seizures was infrequent (9.8%). No evidence of HS or MCD was present on brain imaging. A single individual underwent ATL, with subsequent seizure freedom and histopathological evidence of HS was not found [48]. Santos and colleagues reported 15 families with TLE, 14 of which manifested with features of mTLE and one family with nTLE. The authors found marked genetic heterogeneity among the families. This study is published in abstract format and no data on course of the epilepsy has been presented [49]. Within this group of patients with a relatively benign outcome, pathogenic mutations in the LGI 1 (leucine-rich glioma-inactivated 1) gene have been identified in patients with a partial epilepsy syndrome with auditory features (both autosomal dominant and sporadic forms). The existence of genetic heterogeneity in this group is well documented [50, 51].

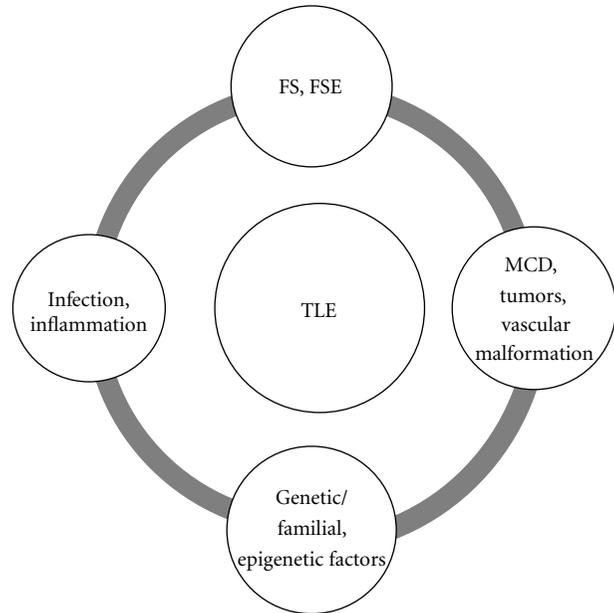


FIGURE 1: The figure summarizes the key antecedents whose interplay determines the evolution and progression to temporal lobe epilepsy (TLE). TLE: temporal lobe epilepsy, FS: febrile seizures, FSE: febrile status epilepticus, and MCD = malformations of cortical development.

#### 4. Conclusions and Future Directions

A critical look at the evidence thus far published on TLE offers conflicting conclusions. While no definitive causal associations can be established, there does not appear strong evidence to support the existence of a single common pathway to the development of TLE and medical intractability. The most important conclusion that one can draw is that TLE is not a homogeneous entity. Rather, there may be several subsets that could be characterized on the basis of the following features: (1) age of onset of epilepsy (early versus late) (2) the presence or absence of a lesion on imaging (lesional versus nonlesional), (3) the nature of the IPE, (4) the occurrence of FS and FSE, (5) genetic and familial predisposition, and finally (6) response to treatment and outcome. These subsets clearly differ in the occurrence of spontaneous remission and progression to intractability. Any combination and interaction within different factors probably confer susceptibility as well as development and progression to TLE (Figure 1).

The current body of literature on the subject is vast and confusing at times. The limitations of most studies include the retrospective nature, the lack of longitudinal and observational studies, and weaknesses in study design. Single-center studies with poorly defined criteria for selection and inherent biases in patient selection further add to the challenges in interpretation of results. Several important questions that have been raised need to be addressed in carefully designed studies. These questions could be addressed through careful assessment of patients from the index event of the first seizure by epileptologists. In

this context first seizure clinics at tertiary care centers will prove to be useful. Longitudinal observation of selected cohorts of patients sharing IPE's etiologies will form the groups where specialized high-resolution imaging and genetic studies should be considered. Tracking the patients to emergence of treatment resistance and eventual surgery in some will be important in identifying benign versus poor outcomes. Postsurgical evaluation of pathological material and specialized studies will further clarify role of infection and inflammation. Animal models could be developed to clarify questions pertaining to epileptogenesis, establish, and explore the usefulness of treatment interventions.

Future prospective studies will need to be multicenter and prospective in nature, perhaps undertaken by teams of investigators, with attention to study design. Such studies should take into account not only the factors discussed, but additionally be prepared to take a multipronged approach in investigating genetic and epigenetic factors that influence the development of an epileptogenic network that eventually leads to the development of different forms of TLE.

## Acknowledgment

The authors wish to acknowledge and thank Shauna Konrad, Clinical Librarian, J. C. Rathbun Library/Stevens Health Sciences Library for her help in obtaining access to several articles in the preparation of this paper.

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## Review Article

# Surgical Techniques for the Treatment of Temporal Lobe Epilepsy

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Received 21 September 2011; Revised 7 December 2011; Accepted 26 December 2011

Academic Editor: Seyed M. Mirsattari

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Temporal lobe epilepsy (TLE) is the most common form of medically intractable epilepsy. Advances in electrophysiology and neuroimaging have led to a more precise localization of the epileptogenic zone within the temporal lobe. Resective surgery is the most effective treatment for TLE. Despite the variability in surgical techniques and in the extent of resection, the overall outcomes of different TLE surgeries are similar. Here, we review different surgical interventions for the management of TLE.

## 1. Introduction

The first surgical intervention for the amelioration of epilepsy was performed by Horsley and involved a cortical resection in a patient suffering from posttraumatic epilepsy [1]. Cortical resection to treat epilepsy has since been performed by other surgeons [2–4]. Following the first human application of electroencephalography (EEG) by Berger in 1929 [5], EEG and electrocorticography (ECOG) were used by Penfield and Jasper to tailor resective surgeries for epilepsy [6, 7]; they modified cortical resections based on an extensive mapping of different cortical regions. Early in the practice of temporal lobe surgery to treat epilepsy, hippocampal preservation was advocated to avoid memory disruption [8–11]; however, Penfield observed that the failure to resect mesial temporal structures was associated with poor epilepsy control [7, 12]. Subsequently, surgery for temporal lobe epilepsy (TLE) has come to constitute the majority of resective epileptic surgical interventions.

Several modifications have been made to the surgical techniques and methods used to treat epilepsy over the last 50 years. Modifications to temporal lobe resective surgery have been based either on resection of the epileptogenic zone, assisted by the use of ECOG and cortical mapping to avoid functional deficits, or on resection of the seizure onset zone,

as with selective amygdalohippocampectomy (SAH). Functional deficits following temporal resection surgeries were identified early by Penfield and Scoville [9, 13]. Since that time, neuropsychological assessment has become a standard part of the multidisciplinary approach for the treatment of epilepsy. The primary goal of temporal lobe surgery is to achieve freedom from seizures without causing neurological or cognitive dysfunction. In turn, the achievement of this goal should improve psychosocial adjustment, education and employment status, and quality of life, as well as significantly reducing the overall treatment cost for patients [14, 15]. Although surgery is effective in the majority of patients with TLE, not all show improvements. Wiebe et al. demonstrated the effectiveness of temporal resective surgery compared to medical therapy [14]. TLE can be classified as either mesial temporal lobe epilepsy (mTLE) or neocortical temporal lobe epilepsy (nTLE). It can be also classified based on the presence or absence of lesions. The term “temporal lobe epilepsy” describes numerous underlying pathological substrates and their clinical features. The term “TLE” is also nonspecific and comprises several surgical techniques and procedures. In this paper, we describe temporal lobe surgical techniques. A detailed discussion of preoperative investigations or the ECOG-based tailored approach is beyond the scope of this paper.

## 2. Surgical Anatomy

The temporal lobe comprises three heterogeneous cortices: a six-layered neocortex (with superior, middle, inferior, transverse, temporal, and fusiform gyri), a three-layered archicortex that includes the hippocampus, the prepiriform area, the uncus semilunar gyrus, and the parahippocampus, a transitional region between the neocortex and the archicortex [16, 17]. The lateral upper surface of the temporal lobe is separated from the frontal and parietal lobes by the sylvian fissure. Posteriorly, the temporal lobe is separated from the occipital and parietal lobes by imaginary lines. The parietotemporal line extends from the parietooccipital fissure impression to the preoccipital notch on the lateral surface. The temporooccipital line runs perpendicular to the parietooccipital line, starting at the posterior end of the sylvian fissure. The basal surface of the temporal lobe is separated from the occipital lobe by the basal parietooccipital line, which connects the preoccipital notch to the inferior end of the parietooccipital fissure. The temporal lobe is connected superiorly and medially to the insula by the temporal stem, anteromedially to the globus pallidus via the amygdala, and anterolaterally to the frontal base by the limen insulae.

The following five gyri are located on different temporal lobe surfaces: the superior (T1), middle (T2), and inferior (T3) gyri, the fusiform gyrus (T4), and the parahippocampal gyrus (T5), Figure 1. The above gyri are separated by multiple sulci, including S1, S2, S3, and S4. S1 is a deep sulcus that extends toward the temporal horn and serves as an important landmark for the identification of the temporal horn. S4 is a collateral fissure located at the edge of the lateral temporal horn wall that forms the collateral eminence. Medial to the superior surface of T1, the transverse temporal gyri, also known as Heschl's convolutions, extend to the depth of the sylvian fissure and mark the location of the primary auditory cortex. The posterior region of T1 is the planum temporale. This structure is larger on the left side in males (but not females) and is involved in the receptive language function.

The parahippocampus ends anteriorly at the level of the posterior uncus, approximately 2 cm from the temporal pole [18]. The anterior calcarine sulcus is located at the posterior aspect of the parahippocampus gyrus and divides the parahippocampus into superior and inferior regions. The superior parahippocampus continues along the isthmus of the cingulate gyrus, whereas the inferior region merges with the lingual gyrus near the occipital lobe.

The uncus is a conical structure partially formed by the anterior parahippocampal gyrus. The uncus extends medially and then curves posteriorly to form the uncus notch sulcus; this path inspired the name "uncus," which means "hook." The other region of the uncus is formed by the medial extension of the hippocampus and the dentate gyrus. There are several gyri at the surface of the uncus, including the intralimbic gyrus (posteriorly), the band of Giacomini, the uncinatus gyrus, the ambient gyrus, and the semilunar gyrus (superiorly). The uncus continues along the globus pallidus at its superior surface.

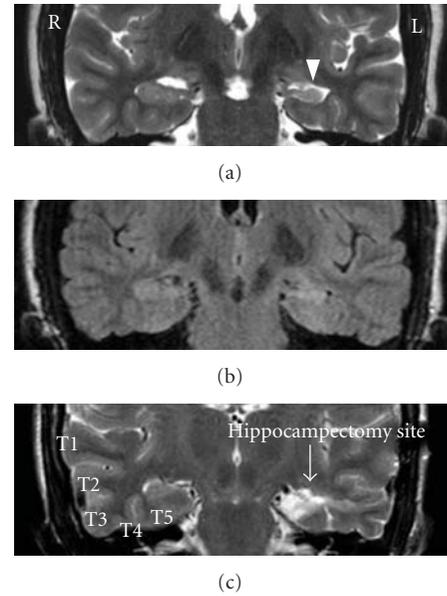


FIGURE 1: ((a) and (b)) Coronal T2 and FLAIR magnetic resonance image (MRI) respectively depicting a left mesial temporal sclerosis. (c) Coronal T2 MRI depicting hippocampectomy site after selective amygdalohippocampectomy on left and temporal gyri (superior (T1), middle (T2), and inferior (T3) gyri, the fusiform gyrus (T4), and the parahippocampal gyrus (T5)) on right side.

Rostral to the uncus, the amygdala is occupying the depth of the medial temporal lobe. It is connected to the striatum superiorly without clear border, Figure 2 [18]. The posterior inferior border of the amygdala is bounded by the anterior temporal horn, while the anterior inferior border is related to the entorhinal area. The medial side is bounded by the uncus and the mesial cistern. From structural standpoint, the amygdala is composed of 13 nuclei divided into three main groups: central, corticomедial, and basolateral groups. Grossly, the amygdala is recognized with its relatively brownish color or the hazelnut tissue appearance, Figure 3.

The hippocampus is an intraventricular structure. It has a C shape that resembles a seahorse and occupies the medial surface and the floor of the temporal horn. The hippocampus proper covers both surfaces of the hippocampal sulcus, which contains the hippocampal feeding vessels. The hippocampus is divided into three regions: the head, the body, and the tail. The head contains the largest area and extends anteriorly and medially toward the uncus recess, which is a continuation of the lateral eminence, Figure 3. The head is the only region of the hippocampus that has no choroid plexus coverage. Posteriorly, the head ends at the choroidal fissure and the beginning of the fimbria, Figure 4(a). The presence of several digitations usually characterizes the head of the hippocampus. The hippocampal body begins at the junction of the choroidal fissure and the fimbria, extending posteriorly and superiorly toward the atrium of the lateral ventricle. At the medial hippocampal body, the choroidal fissure communicates with the ambient cistern below the pulvinar of the thalamus. The tail of the hippocampus is

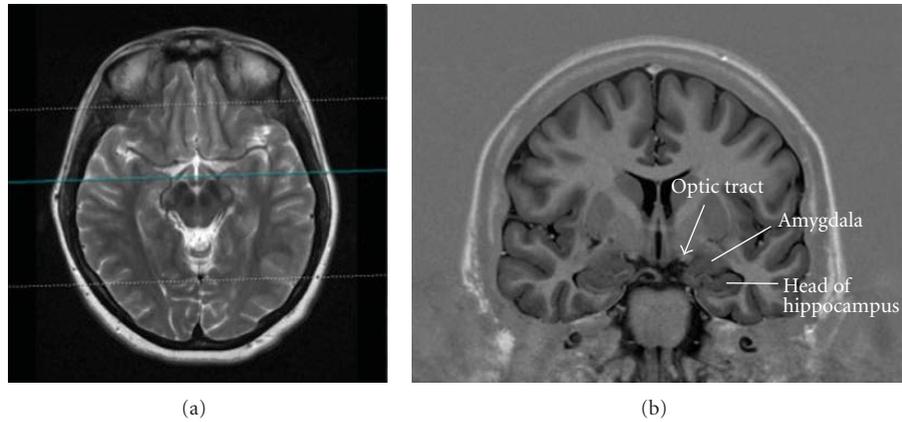


FIGURE 2: MRI coronal inversion recovery image (right) at the level of optic tract ((a), blue line) depicting the anatomical relationship of the amygdala to the optic tract (b).

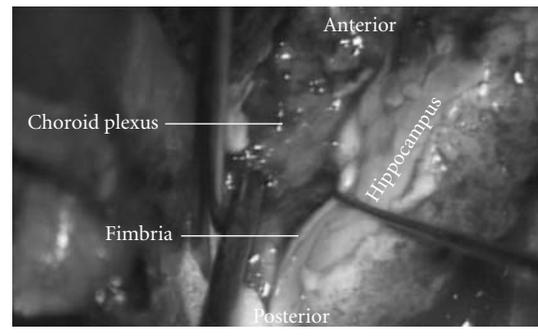


FIGURE 3: Surgical specimen photographs of the hippocampus and amygdala. The brownish color of the amygdala tissue is noted.

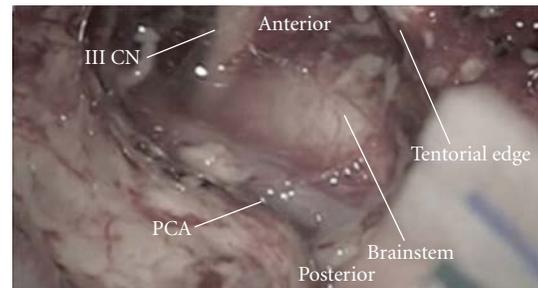
formed at the pulvinar level of the posterior intraventricular region and fuses medially with the calcar avis, the inferior bulge on the medial wall of the atrium.

The alveus, a thin layer of white matter, forms the fimbria, a structure that runs horizontally along the medial hippocampus. The fimbria is separated from the dentate gyrus by the shallow fimbriodentate sulcus. The dentate gyrus continues anteriorly along the band of Giacomini and posteriorly along the fasciolar gyrus. Above the corpus callosum, the dentate gyrus becomes the indusium griseum [16].

The entorhinal cortex is formed by the anterior portion of the parahippocampal gyrus and connects the hippocampus to the neocortex. The hippocampal efferent pathway projects through the fornix and the entorhinal cortex. Internally, the hippocampus is composed of a pyramidal cell layer called the cornu ammon (CA). The CA is divided into 4 regions: CA1–CA4. The trisynaptic circuit connects the entorhinal cortex, the dentate gyrus, and CA3 through mossy fibers. Shaffer collaterals then connect CA1 back to the entorhinal cortex. These structures are important for the pathophysiology of mTLE. Pathological findings in patients with mesial temporal sclerosis (MTS) have suggested that



(a)



(b)

FIGURE 4: Intraoperative photographs showing (a) the dissection of the fimbria to expose the choroidal point. (b) Postresection of the uncus and amygdala showing the third cranial nerve, brainstem, PCA (posterior cerebral artery), and the tentorial edge.

pyramidal cell loss occurs primarily in the CA1 region and, to a lesser extent, the CA3 and CA4 regions. There is little cell loss in the CA2 region.

### 3. Overview of Surgical Procedures

Surgical treatment for TLE mainly targets the mesial structures, employing a variable degree of lateral neocortical

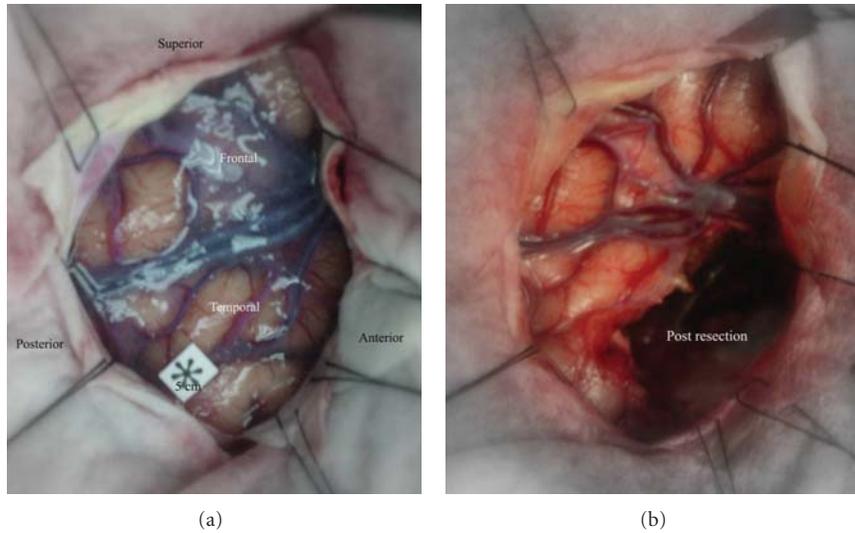


FIGURE 5: Intraoperative photographs demonstrating pre and post resection for right anterior temporal lobectomy.

TABLE 1: Summary of different surgical approaches and techniques for TLE surgery.

Standard anterior temporal lobectomy
Electrocorticography tailored temporal lobectomy
Anteromedial temporal lobectomy
Transcortical selective amygdalohippocampectomy
Transsylvian selective amygdalohippocampectomy
Subtemporal selective amygdalohippocampectomy
Temporal lobe disconnection
Hippocampal transection

resection. This section summarizes the different temporal lobectomy surgical (TLY) techniques (Table 1).

#### 4. Standard Anterior Temporal Lobectomy

Performing a standard anterior temporal lobectomy (ATL) consists of resecting the lateral temporal and mesial temporal structures, either en bloc or separately. Removal of the lateral temporal structures allows better visualization of the mesial structures, allowing en bloc removal of the hippocampus. The procedure is usually performed with the patient in the supine position, elevating the ipsilateral shoulder with a roll and rotating the head to the contralateral side. The head is tilted slightly laterally to place the zygoma at an approximately 10-degree angle from the horizontal plane of the surgical floor. There are several techniques for opening the skin and temporalis muscle. Some surgeons perform a question-mark skin incision followed by reflection of the myocutaneous flap. Others use curvilinear or straight skin incisions. To avoid injury to the frontalis branch of the facial nerve, the incision is begun 1 cm above the zygoma and 1 cm anterior to the tragus. The superficial temporal artery is dissected and preserved if possible. A subperiosteal dissection

is used to remove the muscle from the bone. Extensive cauterization is avoided to minimize the subsequent atrophy of the temporalis muscle. A craniotomy is performed on small portion of the frontal bone posterior to the pterion. Some surgeons tend to expose the pterion at the frontal bone. Venous oozing from the sphenoid ridge can usually be controlled using bone wax or gelfoam. Bleeding from the middle meningeal artery branches is controlled by bipolar coagulation. A U-shaped durotomy is often preformed with the base reflected anteriorly. A cruciate durotomy can also be used.

A posterior cortical incision at the lateral temporal gyri begins approximately 5.5 cm from the temporal tip on the nondominant hemisphere and 4.5 cm from the temporal tip on the dominant side at the level of T2, Figure 5. A number 1 Penfield dissector is used to measure the length from the temporal tip. The posterior resection is slanted anteriorly across T1 to avoid the primary auditory cortex. The pia mater at the upper border of T1 is coagulated and divided. A subpial dissection is performed to elevate T1 from the sylvian fissure using bipolar cauterization and controlled suction, an ultrasonic aspirator, or a dissector technique. The pia and middle cerebral artery (MCA) branches are protected. Oozing from the pia can be controlled using cottonoid packing or Surgicel. The insula is exposed, and dissection extending to the lateral uncus is performed. The temporal pole is reflected laterally after the coagulation and division of the anterior leptomeninges. The posterior resection line is extended from the T1 through T2 and into T3. This line is then extended medially through the fusiform gyrus to the collateral sulcus. The temporal horn is entered through the white matter above the fusiform gyrus. The wall of the temporal horn can be identified by the bluish ependyma. Subsequently, opening of the ventricle anteriorly exposes the hippocampal head. The temporal stem is resected at the inferior circular sulcus. The temporal neocortex is removed by dividing the basal leptomeninges lateral to the temporal

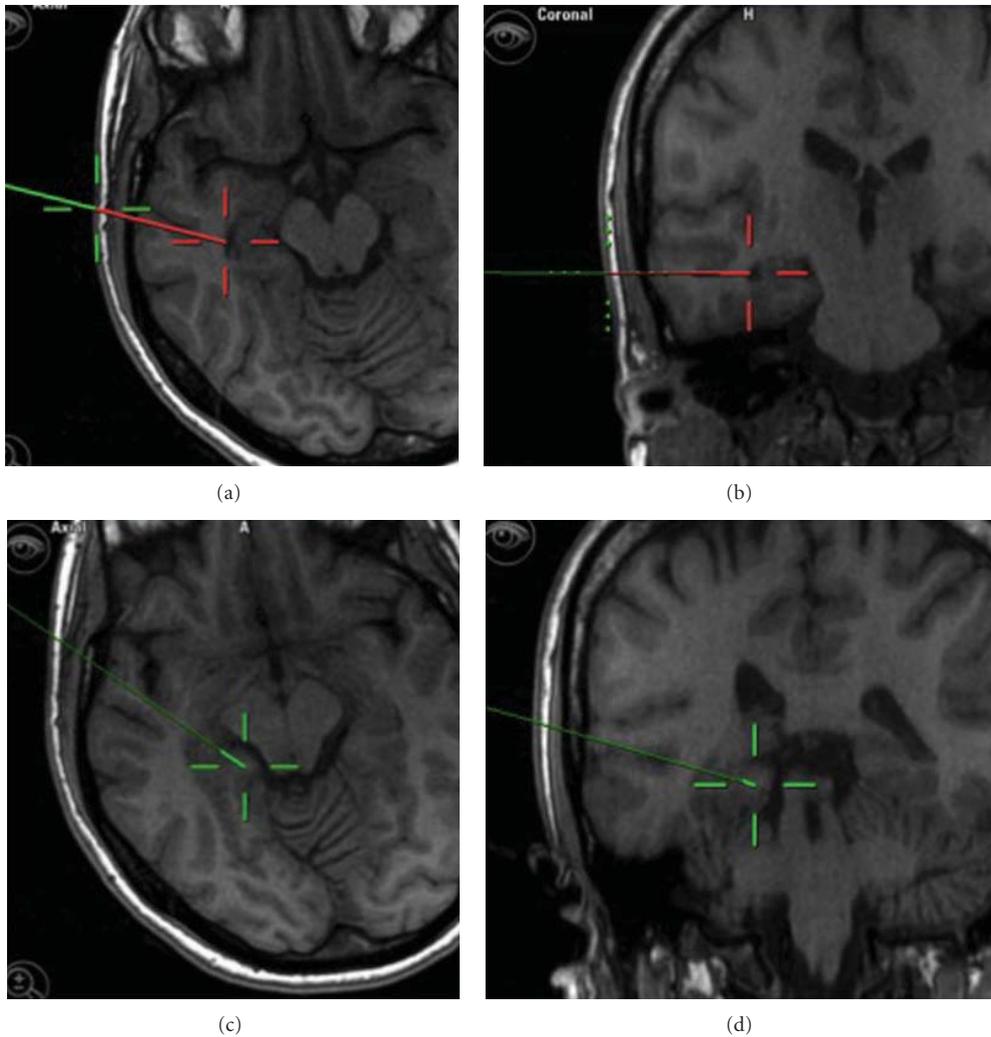


FIGURE 6: Snapshot from neuronavigation showing the entry point through the middle temporal gyrus and the trajectory toward the temporal horn ((a) and (b)). ((c) and (d)) showed the posterior extent of mesial temporal structures resection at the level of quadrigeminal plate.

horn exposure. If en bloc temporal resection is intended, further resection of the mesial structures is performed. During the resection of the mesial structures, an ultrasonic aspirator is used at a low setting to avoid injury to the arachnoid that overlay the posterior cerebral artery (PCA), the basal vein of Rosenthal, the third cranial nerve, and the midbrain.

Different surgical techniques have been used to resect the mesial temporal structures. In general, the areas of the uncus that extends to the level of the limen insulae and the parallel M1 segment of the MCA are removed with an ultrasonic aspirator. The amygdala is resected at the line that connects the choroidal point and the limen insulae, Figure 4(b). The choroidal point is located at the anterior portion of choroid plexus. Care should be taken to not extend the resection superior and medial into the globus pallidus. Due to the absence of clear demarcation between the amygdala and globus pallidus, the anatomic landmarks for amygdala resection are variable among different surgeons. Wieser and

Yazargil advocate using the insular circular sulcus and uncus to avoid entry into globus pallidus [35]. Based on anatomical dissection study, Wen et al. found that a line interconnecting the inferior choroidal point and the proximal MCA can define the superior limit of amygdalar resection [16]. Recently, Tubbs et al. examined the line connecting the anterior choroidal artery and the MCA bifurcation in 20 sides cadavers [36]. In this study, no damage to the striatum was found using this line for upper amygdala removal. The entorhinal cortex is resected to the anterior portion of the parahippocampal gyrus. At this stage, the fimbria can be dissected laterally from the arachnoid attachment, exposing the hippocampal sulcus that carries the Ammon's horn arteries, Figure 4(a). Next, the subpial dissection of the parahippocampal gyrus exposes the hippocampal sulcus. This step will allow the lateral reflection of the hippocampal body. The hippocampal feeders are coagulated and divided at the hippocampus edge, and the tissues of the hippocampus and parahippocampus are removed en bloc. The posterior

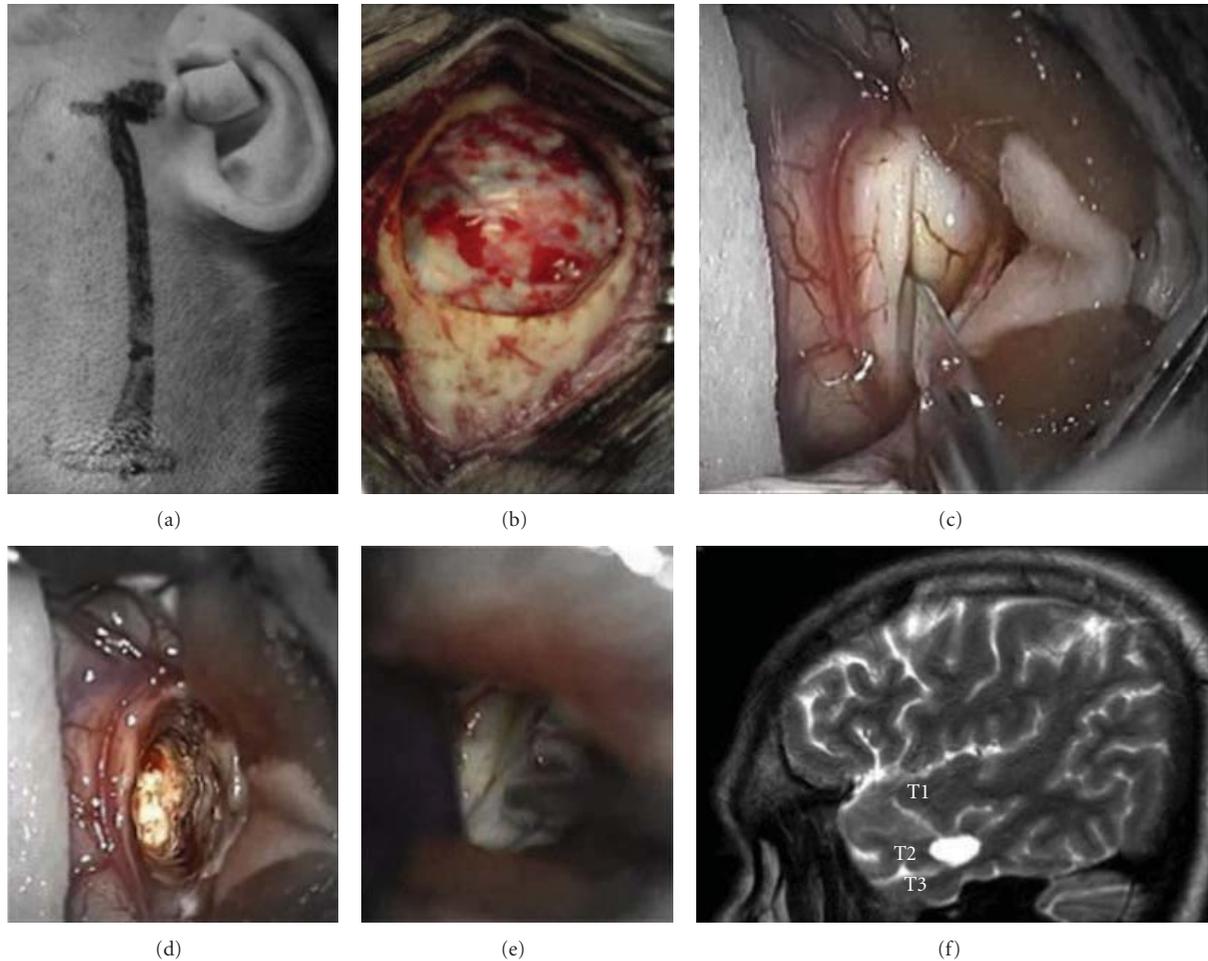


FIGURE 7: (a) Intraoperative photograph showing site of skin incision for selective amygdalohippocampectomy. (b) Minicraniotomy and dura exposure. (c) Corticectomy at middle temporal gyrus (T2). (d) Transcortical access to temporal horn. (e) Hippocampus exposure. (f) Postoperative sagittal T2 MRI depicting the transcortical access through middle temporal gyrus.

portion of the hippocampus is removed using an ultrasonic aspirator to the level of the midbrain tectum, as identified by image guidance. Next, hemostasis is secured, and wound closure is performed in a standard manner.

### 5. Anteromedial Temporal Resection

The anteromedial temporal resection technique was developed by Spencer to preserve the function of lateral temporal cortex and to access the mesial temporal structures through the temporal pole corridor [37]. Approximately 5 to 6 cm of the temporal lobe is exposed in this technique.

The cortical incision begins in the T2, 3 to 3.5 cm from the temporal tip, and curves toward T3 and temporal base. The T1 is usually spared. The temporal tip is removed lateral to the temporal horn. At this stage, the mesial temporal structures are removed using an ultrasonic aspirator. The temporal horn is entered, followed by resection of the uncus and amygdala. Resection of the hippocampus and parahippocampal gyrus is performed from anterior to posterior. The parahippocampal gyrus is removed as it curves medially

posterior to the brainstem. The hippocampus is removed posterior to the tail region. After mesial temporal resection, hemostasis is achieved, and the wound is closed in a standard manner.

### 6. Transcortical Selective Amygdalohippocampectomy

Transcortical SAH was introduced in 1958 by Niemeyer and was originally referred to as “transventricular amygdalohippocampectomy” [38]. Niemeyer used a cortical incision through the T2 to reach the mesial temporal structures. Subsequently, Olivier modified this technique to include resection of the anterior portion of T1 [33, 40].

The head position in this procedure is similar to that used for ATL. A linear or slightly curvilinear skin incision is made anterior to the tragus and above the zygoma. Neuronavigation is a helpful intraoperative tool to tailor the surgical approach, Figure 6. It is applied to navigate the optimal bony exposure over the cortical entry point. Through out

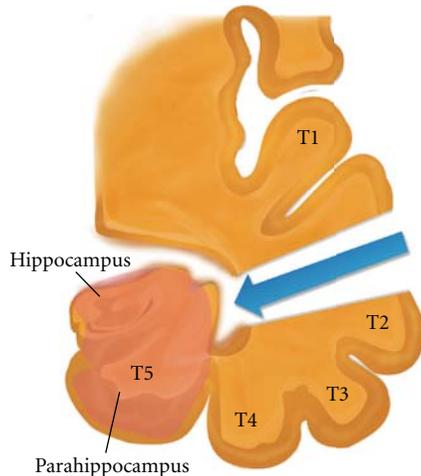


FIGURE 8: Diagram representing transcortical selective amygdalo-hippocampectomy approach.

the procedure, neuronavigation helps in guiding the surgical pathway to the temporal horn and the posterior extent of mesial temporal resection. However, van Roost et al. found that neuronavigation can overestimate the extent of posterior hippocampal resection, which is related mainly to brain shift during the procedure [41]. While neuronavigation is a useful adjunct, a thorough understanding of the anatomy is essential. On the other hand, intraoperative MRI was found to be helpful to ensure the completeness of hippocampal resection [42].

After exposure of the bone, neuronavigation can guide to center the craniotomy over the middle temporal gyrus, Figures 6 and 7. Olivier used image guidance to place the cortical incision at the T2, anterior to the central sulcus on the nondominant hemisphere and anterior to the precentral sulcus on the dominant side [33]. The pathway to the ventricle traverses the white matter. The lateral ventricular wall is usually found 2 mm above the fusiform gyrus. The white matter over the ventricle is resected from anterior to posterior in a slit-like fashion, Figure 8. Exposure of the intraventricular structures is performed by applying a retractor that elevates the upper ventricular wall and choroid plexus, Figure 7. This movement exposes the fimbrial attachment to the ambient cistern arachnoid. An ultrasonic aspirator is used at a low setting to remove the parahippocampal gyrus using the endopial technique. The hippocampus is resected at the junction between the body and tail regions, followed by dissection of the fimbria from the arachnoid to allow the lateral elevation of the hippocampus. This procedure exposes the hippocampal sulcus and allows the coagulation of the hippocampal feeders. The uncus is removed beginning with the apex and followed by the regions of the amygdala that are posterior to the M1 segment of the MCA. The residual posterior hippocampus is resected extending to the level of the tectal plate. In this approach, Meyer's loop fibers can be affected by removal of the white matter located lateral to the temporal horn.

## 7. Transylvian Selective Amygdalohippocampectomy

Wieser and Yasargil introduced the transylvian SAH approach for resecting the mesial temporal structures through the sylvian fissure corridor without compromising the adjacent temporal neocortex [35, 43]. The patient's position is different from that in other temporal procedures: the head is tilted such that the malar eminence is the highest point. A curvilinear skin incision exposes the frontal and temporal bones above and below the sylvian fissure. The sphenoid ridge is flattened to the anterior clinoid process. The dura is opened in a curvilinear fashion and reflected onto the sphenoid ridge. Next, the sylvian fissure is opened from the level of the carotid artery bifurcation through the bifurcation of the MCA, exposing the anterior insular cortex, limen insulae, mesial uncus, and temporal pole. A 15-mm incision is made in the temporal stem at the level of the limen insulae. The temporal horn is entered, and the uncus is removed using an ultrasonic aspirator. This step is followed by the removal of the amygdala, anterior parahippocampus, and entorhinal cortex. The choroid plexus and choroidal point are identified, and the hippocampus is disconnected from the lateral regions in an anterior to posterior manner using (preferably) an ultrasonic aspirator until the collateral sulcus is reached. The fimbria is dissected from the mesial arachnoid using a dissector. The hippocampus is dissected laterally, exposing the hippocampal sulcus, followed by the coagulation of the hippocampal feeders. Finally, a posterior hippocampal resection is performed to remove the hippocampal tissue, hemostasis is secured, and closure is performed.

## 8. Subtemporal Selective Amygdalohippocampectomy

Subtemporal SAH was first described in 1993 by Hori et al. [44, 45]. This technique involves removing the fusiform gyrus to access the temporal horn and cutting the tentorium to minimize retraction onto the temporal lobe. Later, the same group modified the subtemporal approach, opting for retrolabyrinthine presigmoid transpetrosal access to resect the mesial temporal structures [46]. Shimizu et al. described the removal of the zygomatic arch and the minimal resection of the T3 to access the mesial temporal structures using a zygomatic approach [47]. Park et al. reported a modification of the subtemporal approach that employed transparahippocampal access, thus preserving the fusiform gyrus [48, 49]. Miyamoto and colleagues performed an amygdalohippocampectomy using a combined subtemporal and transventricular-transchoroidal fissure approach [50]. In general, the rationale for using this approach is the avoidance of an incision into the temporal stem and the preservation of the temporal neocortex. This approach, however, risks damaging to the vein of Labbe caused by temporal retraction. Moreover, the limited exposure of the amygdala and uncus limits resection.

TABLE 2: Summary of the surgical outcome from selected studies.

Author	Year of publication	Follow-up period (years)	Number of patients	Outcome measure	Type of surgery	Percentage of best outcome
Blume and Girvin [19]	1997	5	100	2-year seizure freedom	ATL	58%
Spencer et al. [20]	2005	5	339	Seizure freedom $\pm$ auras for 2 years	AMTL	69%
Jeong et al. [21]	2005	5	227	Engel I	ATL	75%
Urbach et al. [22]	2004	2	209	Engel IA	SAH	73%
Wiebe et al. [14]	2001	1	80	Freedom from seizures that impair awareness	ATL	58%
Mihara et al. [23]	1996	5	132	Engel I	ATL or SAH	70%
Zentner et al. [24]	1995	3	178	Engel I	ATL or SAH	62%
Sperling et al. [25]	1996	5	89	Engel I	ATL	70%
Wieser et al. [26]	2001	7	369	Engel I	SAH	62% at 5-year follow-up
McIntosh et al. [27]	2004	10	325	Engel I	ATL	41%
Paglioli et al. [28]	2004	5	135	Engel IA	ATL or SAH	74% at 5-year follow-up

ATL: anterior temporal lobectomy, AMTL: anteromedial temporal lobectomy, SAH: selective amygdalohippocampectomy, Engel: Engel's classification for seizure outcome after surgery.

## 9. Other Procedures

Several other surgical procedures have been used to treat TLE. Temporal disconnection has been advocated as an alternative surgical procedure to avoid certain complications while providing a level of seizure control comparable to that of traditional surgery [51]. A study by Chabardes et al. described 47 patients with nonlesional TLE who underwent the temporal disconnection procedure [51]. Of those, 85% were seizure-free 2 years after surgery. Hippocampal transection has been advocated to minimize memory dysfunction following hippocampectomy [52, 53]. Stereotactic ablation and resection of the hippocampus have been reported by several authors [54–60]. Stereotactic radiosurgery has also been used and may be useful for the treatment of MTS related to epilepsy [61, 62]. Neuromodulation, another treatment, involves a combination of neurostimulation, drug delivery, neuronal tissue transplants, and gene therapy. The FDA has approved neurostimulation of the vagus nerve for the treatment of refractory epilepsy; however, the only effective use of this technique in temporal lobe epilepsy remains palliative [63]. Recently, anterior thalamic stimulation was shown to be promising for the treatment of TLE [64]. Hippocampal stimulation performed by the London Ontario group also showed some long-term benefits with no significant negative impact on memory [65, 66]. Recently, responsive cortical stimulation was shown to provide a reduction in seizure frequency in a multicenter, double blind, randomized controlled trial [67].

## 10. Outcomes and Complications of Resective Surgery

It is difficult to compare the success of various surgical techniques because of the lack of standardized outcome

criteria. Overall, 50–70% of patients report no seizures 5 years after surgery [14, 35, 38, 39, 68]. Table 2 summarizes the outcomes of selected studies that have utilized different surgical techniques. It has been suggested that the amount of mesial temporal tissue resected is correlated with successful surgery [69–73]. Residual tissue is a known risk factor for seizure recurrence, and a second operation should be considered in patients who continue to experience seizures. The success in achieving a seizure-free state after a second operation is approximately 50% [74–77]. The effectiveness of residual hippocampal resection and the positive outcomes following SAH suggest that a thorough resection of the hippocampus may be necessary for optimal seizure control. The neuropsychological state and quality of life of patients are most improved when a seizure-free state is achieved [14].

Operative complications from temporal lobe resective procedures are variable but uncommon. These complications include the following: death (<1%) [78]; infection [79]; mild contralateral superior quadrantanopsia caused by the resection of Meyer's loop fibers in the roof of the temporal horn [78]; hemianopsia caused by injuries to the optic tract or by posterior extension of the white matter (optic radiation fibers) dissection during ATL [80]; postsurgical hematoma [79, 81]; oculomotor and trochlear nerve palsy [82]; rarely, facial nerve palsy [83]. Hemiparesis can occur as the result of the manipulation or thrombosis of the anterior choroidal, MCA or perforators of the PCA. Moreover, hemiparesis can occur from direct injury to the cerebral peduncle and brain stem, or neuroparalytic edema, as described by Penfield et al. [79, 84–86]. Girvin described only one postoperative hemiplegia caused by an internal capsule infarction in a series of 300 cases of ATL [87]. Resection of the dominant temporal lobe rarely produces permanent dysphasia; however, it more frequently causes transient dysphasia [78]. Postoperative dysnomia

TABLE 3: Summary of reported temporal lobe surgery complications from selected studies.

Author (year)	Number of patients	Type of surgery (Number of procedures)	Complications (%)
Clusmann et al. (2002) <sup>ϕ</sup> [29]	321	ATL (98)	Meningitis (1.5%)
		Transsylvian SAH (138)	Subdural hematoma (0.6%)
		Lesionectomy and AH (27)	Thrombosis (1.2%)
		Lesionectomy/corticectomy (58)	Neurological complications (5.2%)
Rydenhag and Silander (2001) [30]	247	SAH (5)	One mortality (0.4%)
		ATL (168)	Hemiparesis (2%)
		Neocortical resection (74)	Trochlear nerve palsy (0.8%)
			Oculomotor nerve palsy (0.8%)
Acar et al. (2008) [31]	39	Transcortical SAH (39)	Visual field defect (10%)
			Fourth nerve palsy (2.5%)
			Hemiparesis (2.5%)
			Aphasia (2.5%)
			Hemotympanum (7.5%)
			Memory difficulty (5%)
			Frontalis nerve palsy (2.5%)
Jensen (1975)* [32]	858	All temporal lobe resective surgical procedures (858)	Persistent hemiparesis (2.4%)
			Transient hemiparesis (4.2%)
			Partial hemianopia (46%)
			Complete hemianopia (4%)
			Cranial nerve paresis (3.5%)
			Dysphasia (5%)
			Infection (1.5%)
Olivier (2000) [33]	164	Transcortical SAH (164)	Transient dysphasia (1.8%)
			Wound infection (0.6%)
			Brain swelling (0.6%)
			Subgaleal effusion (0.6%)
			Abscess (0.6%)
			Third-nerve palsy (0.6%)
			Otitis (3.6%)
Sindou et al. (2006) [34]	100	ATL (76)	Motor deficit (2%)
		TTL (18)	Hydrocephalus (2%)
		Transsylvian SAH (6)	Postsurgical hematoma (3%)
			Temporary third cranial nerve palsy (5%)
			Bacterial meningitis (3%)
			Pulmonary embolism (1%)

ATL: anterior temporal lobectomy; TTL: total temporal lobectomy; AH: amygdalohippocampotomy; SAH: selective amygdalohippocampotomy.

\*This data was taken from a survey covering 2282 temporal lobe surgeries worldwide between the period of 1928 and 1973.

<sup>ϕ</sup>No difference in the complications incidence between different surgical techniques was identified in this study.

or aphasia is observed following approximately 30% of dominant temporal lobe resective surgeries; however, most of symptoms usually disappear gradually over a few weeks [88]. Language deficits occur even after cortical language mapping [89, 90]. The causes of transient language dysfunctions are not clear; however, they are more common when resection is performed within 1-2 cm of the language area [91, 92]. Other possible causes include edema caused by brain retraction, the deafferentation of white matter pathways, and ischemia [84, 93].

Global memory deficits are rare following temporal lobe resection, but verbal memory dysfunction occurs more frequently. Postoperative de novo psychiatric disorders have been reported in some cases. A survey of various reports indicates that de novo psychosis occurs in 0.5% to 21% of patients [15, 94–96]. Affective disorders have also been described in the literature: transient mood elevation and emotional changes can occur in the first year after surgery [97, 98], whereas postoperative depression occurs in approximately 10% of patients [99, 100]. Resection of

the nondominant temporal lobe may carry a greater risk for depression [101]. Recent systemic review demonstrates that most of the studies showed improvement or no change in the psychiatric outcome after epilepsy surgery [102]. Table 3 summarizes reported complications from selected studies.

## 11. Conclusion

There are a variety of surgical techniques employed for temporal lobe epilepsy that provide an effective treatment with significant preservation of neurological function and acceptable surgical risks. Regardless, a highly localized epileptic focus predicts the best surgical outcome. Future research should evaluate the etiology and pathology of late epilepsy recurrence.

## Acknowledgment

The authors thank Monirah Albloushi, RN, MSN, for the assistance in figures and paper preparation.

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## Review Article

# Spontaneous EEG-Functional MRI in Mesial Temporal Lobe Epilepsy: Implications for the Neural Correlates of Consciousness

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Received 20 September 2011; Revised 21 November 2011; Accepted 19 December 2011

Academic Editor: Warren T. Blume

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The combination of electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) has been shown to have great potential for providing a greater understanding of normal and diseased states in both human and animal studies. Simultaneous EEG-fMRI is particularly well suited for the study of epilepsy in that it may reveal the neurobiology of ictal and interictal epileptiform discharges and noninvasively localize epileptogenic foci. Spontaneous, coherent fluctuations of neuronal activity and the coupled hemodynamic responses have also been shown to provide diagnostic markers of disease, extending our understanding of intrinsically structured ongoing brain activity. Following a short summary of the hardware and software development of simultaneous EEG-fMRI, this paper reviews a unified framework of integrating neuronal and hemodynamic processes during epileptic seizures and discusses the role and impact of spontaneous activity in the mesial temporal lobe epilepsies with particular emphasis on the neural and physiological correlates of consciousness.

## 1. Introduction

Temporal lobe epilepsy (TLE) manifests with partial seizures whose semiology can reflect a dynamic interplay among several anatomical divisions of the temporal lobe, in addition to their sites of origin [1]. Approximately 20%–30% of TLE patients are intractable to treatment with antiepileptic drugs though they may still benefit from surgical resection of the epileptogenic focus (EF) [2]. It is, therefore, essential to localize the EF in patients with focal epilepsy and to discern the large-scale cortical and subcortical networks involved in seizure generation. This is best achieved with the use of simultaneous, multimodal techniques that are able to elucidate complex functional relationships through converging or parallel operations. The development of electroencephalogram (EEG) recording of epileptic patients inside a magnetic resonance imaging (MRI) scanner was largely driven by the

necessity of localizing and delineating mesial or deeply originating EF electrically and metabolically during presurgical evaluation [3–7]. The concurrent measures allow for the monitoring of abnormal hypersynchronous events in the EF, as well as the full-brain coverage of variations in blood flow and oxygenation in response to epileptic discharges conducive to a wide range of research applications within epileptology. Simultaneous EEG-fMRI has the potential to become a routine diagnostic test, complementing the diagnostic accuracy of clinical acumen and EEG to greatly improve medical and surgical managements of patients with intractable epilepsy, a goal that was set since its first introduction [4].

Investigation of spontaneous, low-frequency, and blood-oxygenation-level-dependent (BOLD) fluctuations measured by fMRI has revealed spatially organized and distributed brain networks [8–16]. The coherent patterns of hemodynamic oscillations occur in the absence of any overt

task and as such are referred to as resting-state networks (RSNs). RSNs are believed to be the epiphenomenon of endogenous neural activity [17] and shaped by structural connections [16, 18–21] though their functional significance and neuronal correlate remain an active area of research [22, 23]. Alterations of RSNs have recently been reported in several conditions, including psychiatric and developmental disorders [24], Alzheimer’s disease [25], schizophrenia [26], coma [14], and epilepsy [27–30], revealing changes in connectivity between network nodes. By contrast, spontaneous neuronal rhythm measured using EEG evince endogenous patterns of connectivity and synchronicity underlying states of attention, perception, and consciousness [31]. A comprehensive understanding of the functional network dynamics related to the electrical activity recorded from the EF during ictal and interictal epileptiform discharges (IEDs) remains elusive [32–35]. However, empirical evidence does indicate disruption of the normal distributed networks; temporal lobe IEDs of patients with complex partial seizures secondary to TLE have been reported to affect the activity in regions comprising the default-mode RSN (discussed below) [36]. Therefore, spontaneous neural activity and its associated hemodynamic manifestation (BOLD contrast) allow not only for the noninvasive exploration of temporal and spatial patterns of the brain but can also be envisaged as early diagnostic or prognostic markers of disease states [14, 24, 37–43]. This review places an emphasis on the fundamentals of spontaneous EEG-fMRI and extends the unified framework we previously proposed to a new avenue of exploring the neuronal and physiological basis underlying intrinsic brain activity. Only studies relevant to specific aspects of simultaneous EEG-fMRI in mesial TLE (mTLE) studies in the context of resting state including seizure-induced alterations of the conscious state are discussed in here.

## 2. Emerging Issue in Simultaneous EEG-fMRI Acquisition

The prevalent strategy is to continuously sample the interictal and ictal events while measuring the BOLD signal for spontaneous EEG-fMRI study. Unfortunately, continuous-recording EEG on epileptic patients inside the magnet suffers various kinds of noise problems such as muscle contraction motions, eye movements, perspiration, 50/60 Hz power interference, and ballistocardiogram [44]. Motion-related artifacts of patients such as involuntary gross head movements, swallowing, and coughing can also impose adverse consequence on both EEG signals and MRI images. As such, these confounds make data acquisition in the high-field environment more difficult through deteriorating the shimming performance and causing unexpected susceptibility issues arising from magnetic field inhomogeneities at air-tissue interfaces. There have been a number of postprocessing methods developed to handle the epileptic electrophysiological data by focusing on the focal spike density [45], phase coherence [32–35, 46], and noise separation [47]. But, many of these artifacts including signal loss, image distortion, and poor BOLD contrast-to-noise ratio can occur both focally and globally in an unpredictable manner. They may also vary

slowly with physiological vitals, extending beyond straightforward image misregistration and invoking more advanced mathematical techniques to mitigate these confounds. Independent component analysis (ICA) has emerged as a popular data-driven method that has been used successfully to remove ballistocardiogram and other MRI-related artifacts during the past decade [47–51]. For the purposes of reliably detecting clean, discrete interictal and ictal spike events, noise components either from statistically independent decomposition or adequately sampled recording in a specific reference channel can be simply subtracted out from an unsaturated raw EEG trace [6], or in more elaborate techniques such as adaptive noise cancellation [44]. Nevertheless, ICA has been successfully utilized to reveal intrinsic functional connectivity patterns of RSNs in human and animal fMRI data sets [8, 11, 12, 52].

Besides the difficulties summarized above, the relation between the detectable anatomical abnormalities, epileptic neuronal activity (i.e., various types of epileptic seizures), and functional MRI signal remains largely unclear [53, 54]. This elusive relationship also generates a strong motivation for those seeking to improve the recording EEG inside the MRI scanner. One of many emerging issues is to detect the high-frequency oscillations with clinical instruments.

Previously BOLD changes have been reported to occur before the happening of IEDs in patients with focal epilepsies, suggesting the alteration of synchronized neuronal activity in the spike field before the generation of EEG spike [55]. Similar findings have been reported before the onset of epileptic seizures [56, 57]. In the study by Jacobs and colleagues [55], the early focal BOLD changes were localized in the mesial temporal lobe where neuronal activity might not be detectable by the scalp EEG. Scalp potentials arise from the spatial summation of synchronous dipole moments over the neocortical volume with a weighting that depends upon the anisotropic conductivity of the cranium [58, 59]. Areas that are too deep or lack a sufficient amount of synchrony are unable to produce a measurable potential difference on the scalp. The “blurring” and low-pass filtering effects of the skull and scalp can be overcome with invasive depth recordings, as only a fraction of spikes recorded intracranially in mTLE patients are detectable by the EEG [59].

More recently with small clinical contacts and clinical amplifiers, high-frequency oscillations (HFOs, referred to as ripples 80–250 Hz and fast ripples 250–500 Hz) have been recorded in animal and human subjects [60–62], suggesting a possible relation with ictogenesis [61, 63, 64] and epileptogenesis [65]. Moreover, Châtillon and colleagues demonstrated that the contact size did not significantly affect HFO detection in intracerebral EEG recordings in a rat epilepsy model [60]. They have shown that the optimal size of a recording electrode should be dependent on the potential generation, distribution, amplitude, and frequency of the targeted signal, even though it was conventionally deemed that the contact size may influence HFO recording ability by affecting impedance and sampling volume. Specifically, they suggested there should be no difference in HFO detection in human recordings using contact from 0.036 mm<sup>2</sup> to 1.698 mm<sup>2</sup>. The generation of the HFO varies in anatomical

structures and pathological conditions that could lead to the difference in its detectability reported by different groups. Further research with regard to synchrony in large neuronal circuitry is needed for detailed and complete understanding of the underlying mechanism from a global network perspective. Note that analysis of changes in phase synchronization, frequency bands, and rhythmicity was not conducted by Jacobs and colleagues and presents an exciting avenue for future study.

### 3. Correspondence between Spontaneous EEG and fMRI

**3.1. Methodological Consideration.** The challenges of concurrent EEG-fMRI are not solely limited to noise removal, but also arise when developing the framework of analysis. This represents a fundamental issue which can influence the seeking of the correspondence between the measured spontaneous EEG and resting-state fMRI signals (see Figure 1 for a unified framework). Since little is known about the BOLD response to epileptic discharges prior to the analysis, two fundamental assumptions must be made to establish the link between neural activity and hemodynamic modulations. The first is that the shape and time course of the hemodynamic response function (HRF) derived from the normal human or animal subjects is also appropriate for epileptic brains [3, 27, 66]. The second is that the nature of neural hemodynamic coupling derived from an epileptic subject is homogenous across different brain regions regardless of the location inside or outside the epileptogenic focus. Judicious selection of an HRF and experimentally based assumptions about the nature of the cortical electrical activity are important first steps in the general linear model analysis of fMRI data sets [27, 49, 50]. Many of the published epilepsy studies using fMRI have been bound by these two underlying assumptions.

A growing body of evidence is challenging the validity of these two working hypotheses and suggest that the HRF and its uniformity of epilepsy patients deviate from the normal population [55, 66, 68–70]. The result has been a greater preference for the utilization of data-driven or exploratory methods such as ICA and temporal clustering analysis [71, 72]. A major advantage of data-driven analyses is the flexibility to circumvent a priori hypothesized HRF while simultaneously deducing the activated fMRI response [73]. However, it suffers an inherent deficit: the lack of statistical measure to assess the intended hypothesis. To be considered clinically useful, the epileptogenic zones defined by hemodynamic and metabolic modulation through ICA analysis must be spatially consistent and statistically robust across individuals and scanning sessions. Consequently, one has to rely on comparison of the results with the linear model method for validation [49, 50]. McKeown has proposed a hybrid method which can gracefully navigate from a fully data-driven approach to a fully model-driven approach [74]. Building on this early work, we further improved it by replacing a vital priori hypothesis (presumed neuronal response) used in McKeown's work with the actual EEG signal and obtained statistically robust BOLD activation in an animal model of

focal epilepsy [71]. With regard to the framework of EEG-fMRI, the integration of superior spatial information provided by MR images and temporal information of EEG can be improved by linking them with hemodynamic transfer functions as we previously proposed. In our framework, the variation of the HRF can be estimated rather than simply assuming a fixed canonical response. Another advantage is that intermodal, interregional, and interindividual variability can be explicitly taken into account in the estimation. Thus, it becomes more straightforward to fit epileptic discharge events into continuous fMRI recordings under a spontaneous condition since this type of data does not contain sparse/blocked stimulus inputs [41].

**3.2. Neuronal and Physiological Consideration.** Paradoxical imaging changes can occur in the nonepileptogenic and epileptogenic zones that do not always accurately reflect the underlying electrical activity [57, 66]. During absence seizures, it still remains largely unknown if a decrease in fMRI signal during seizure activity has been found in those regions such as spike-wave discharges, relative silence, or some other electrophysiological phenomenon occurring [27, 49, 75–79]. From a large-scale network perspective, it is uncertain if in the complex partial seizures of temporal lobe origin that either reduced excitation or increased inhibition (or both) results in decreased activity in the frontoparietal cortex [80–82].

The characterization of the neuronal correlate of spontaneous BOLD signal still remains an open issue. Typical observations of spontaneous EEG contain a complex spectral composition including the alpha rhythm (8–12 Hz oscillations), sleep spindles (~12–14 Hz oscillations), and individual IEDs [83]. BOLD fMRI contrast should be sensitive to these and any changes in neuronal function that result in alteration (either increase or decrease) of brain metabolism [84–86]. It should be noted that failure to consider the background EEG oscillations when seeking the electrical basis of the BOLD response may cause poor correlation between these two measures [69] and confusion when attempting to explain their direct correspondence [55, 87]. For example, evidence from simultaneous fMRI and depth recordings in monkeys and individuals undergoing invasive clinical monitoring has suggested that spiking, multiunit activity, and band-limited power changes in the gamma frequency range were the primary correlate of resting state fMRI activity and connectivity [17, 88]. This is in conflict with other work in humans suggesting a direct linkage of low-frequency BOLD fluctuations and the posterior alpha rhythm [89]. Further, He and Raichle proposed that the low-frequency end of field potentials (<4 Hz, also termed as “slow cortical potential”, SCP) is also correlated with BOLD signal in its raw spontaneous fluctuations in the light of its temporal scale overlapping with that of fMRI signal [15, 90]. Correlation at or below delta band LFPs is also in agreement with a rat investigation [91]. De Munck and colleagues have further reported that power fluctuations of different EEG bands are significantly correlated and are similar to the alpha harmonics [89]. In striking contrast, other studies yield different results as to the role what other

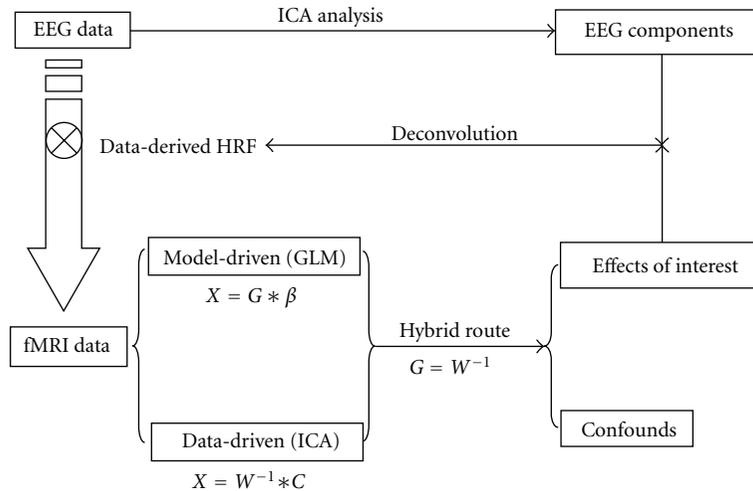


FIGURE 1: Unified framework of simultaneous EEG-fMRI analysis.

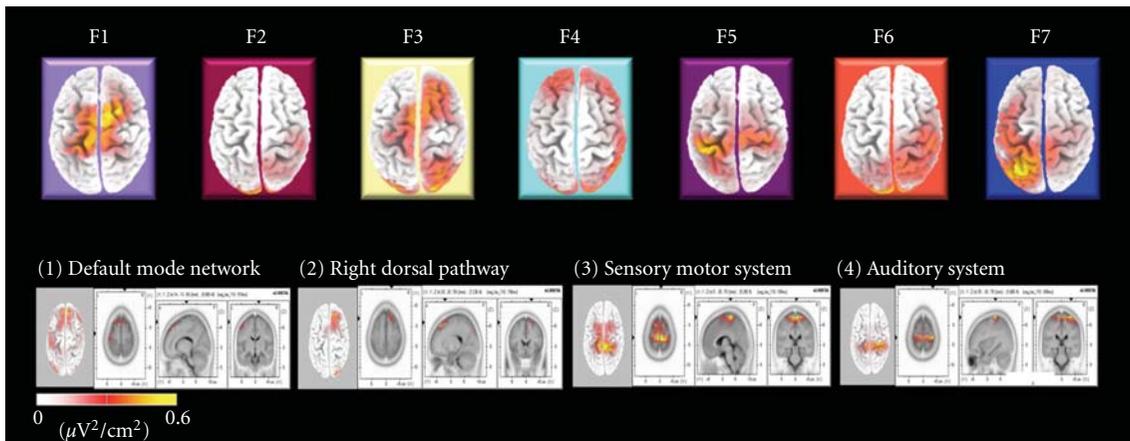


FIGURE 2: Statistical factor analysis on the microstates inferred by EEG and fMRI. The top row shows the sLORETA CSD maps ( $\mu\text{V}^2/\text{cm}^2$ ) of the specific electrophysiological landscape or microstate, which is used to inform the fMRI analysis in four selected single subject at rest (the bottom row). In each column of the bottom row, on the left, a CSD map projected onto a 3D Talairach model of the brain while on the right axial, sagittal and coronal views of a microstate CSD map is shown. Reproduced and modified with permission from Musso et al. [67].

frequency bands play [92, 93], some suggesting unique frequency profiles across multiple bands representing characteristic EEG microstates [67, 94] (see Figure 2 for the EEG microstates informed fMRI analysis). It has yet to be adequately clarified how changes in distinct bands of electrical signal are related to the hemodynamic response under different states of brain activity.

Therefore, two important caveats should be noted when one attempts to resort to a consistent interpretation of these controversial observations. One is that intrinsic synchrony of brain activity is network specific and exists at multiple spatial levels [24]. Another is that spontaneous activity not only reflects the functional architecture of the brain by forming structured spatiotemporal profiles but can also encode traces of previous behavior history (memory retrieval) and predict future decisions in view of its “ongoing” internal representations [15]. In other words, the role of the brain oscillations

within an interested frequency range could be highly contextual. Taken together, further study of humans and animal models with the use of simultaneous, spontaneous EEG-fMRI recording is necessary to elucidate the complex, dynamic, behavior of intrinsic hemodynamic oscillations, and their neuronal correlate. Revealing the underlying mechanisms of brain oscillations, coupling, and functional significance will provide a valuable measure for the assessment of both normal and pathological brain functions, especially epilepsy.

#### 4. Alterations of Spontaneous EEG-fMRI in Mesial TLE

TLE is often considered the prototype of localization-related epilepsy, even though evidence indicates a multiplicity of sources involving cortical and subcortical structures outside

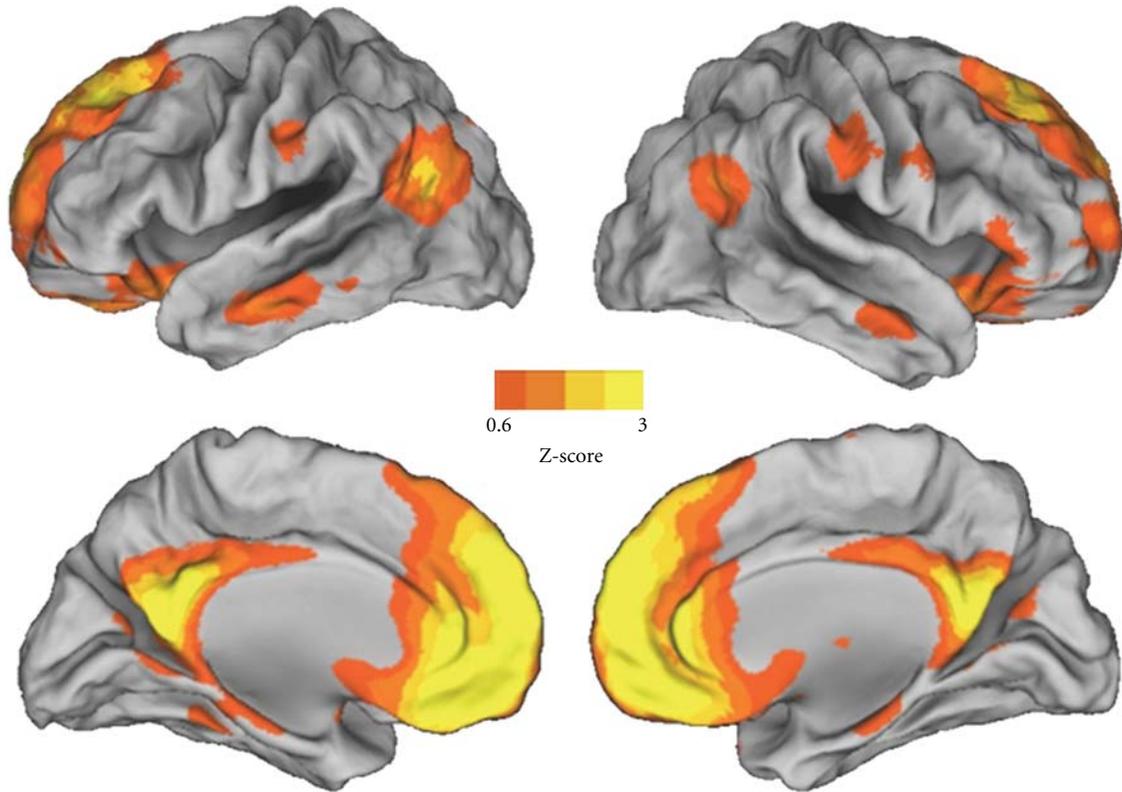


FIGURE 3: The human default-mode network represents a critical junction in the study of temporal lobe epilepsy, consciousness, and spontaneous brain activity. The resting-state network is displayed on a 3D cortical representation of the human brain. Overlaid color maps represent thresholded z scores derived using independent component analysis network of resting-state fMRI data ( $N = 13$ ).

the epileptogenic temporal lobe [28]. For instance, mTLE is the most common type of focal epilepsy in adult patients and is usually caused by hippocampal sclerosis (HS) [29]. A large number of concurrent EEG-fMRI studies have sought fMRI activations during IEDs to localize the epileptogenic focus in their presurgical evaluation of patients with medically refractory partial epilepsies [54]. Surgical outcomes in mTLE are good, but far from optimal, particularly in long-term followup studies [41, 95]. One of potential reasons of poor clinical outcome could be that hemodynamic activation and deactivation patterns are not always of localizing merit since current understanding of neurovascular regulation is limited [53]. When studying functional connectivity of the mesial temporal lobe, one must consider that the subregions within temporal lobe structures are critical components of other cortical networks [35]. TLE focal seizure onset can propagate to subcortical structures impairing the ascending reticular activating system (ARAS) which mediates arousal and in turn deactivating the cortical hierarchy, particularly the large frontal-parietal associative cortical areas [96]. This fits within the “network inhibition hypothesis” suggesting that partial complex seizures that lead to impaired consciousness affect an entire network as opposed to only the local epileptogenic focus [1, 96, 97].

Interestingly, these cortical areas are implicated in the default-mode network (DMN), a RSN, which comprises the

posterior cingulate cortex/precuneus, lateral parietal cortex, ventral anterior cingulate cortex/mesial prefrontal cortex, angular gyrus, and inferior temporal cortex, in addition to the mesial temporal lobes (see Figure 3). Mesial TLE patients show significantly increased connectivity within the mesial temporal lobes and decreased connectivity within/between the frontal and parietal lobes implicated in the DMN [28]. In addition, cerebral blood flow (CBF) has been shown to increase in the medial thalamus correlating with a reduction in activity within the DMN regions [81]. Morgan et al. [72] showed increased negative connectivity across thalamic, brainstem, frontal, and parietal brain regions, in accordance with the idea that there is inhibited function in subcortical and cortical structures during ictal propagation. These findings suggest that both thalamocortical activation and suspension or disturbance of the default state contribute to the abnormality in responsiveness of patients with medial temporal origin. They are in concordance with what Gotman and coworkers found using concurrent EEG-fMRI. The brain could temporarily suspend baseline processes and engender deactivations in this higher-order associative network [27]. The overlap of cortical between the DMN and TLE may provide some context as to why altered consciousness occurs in TLE (see Figure 4 for illustration of the network inhibition hypothesis).

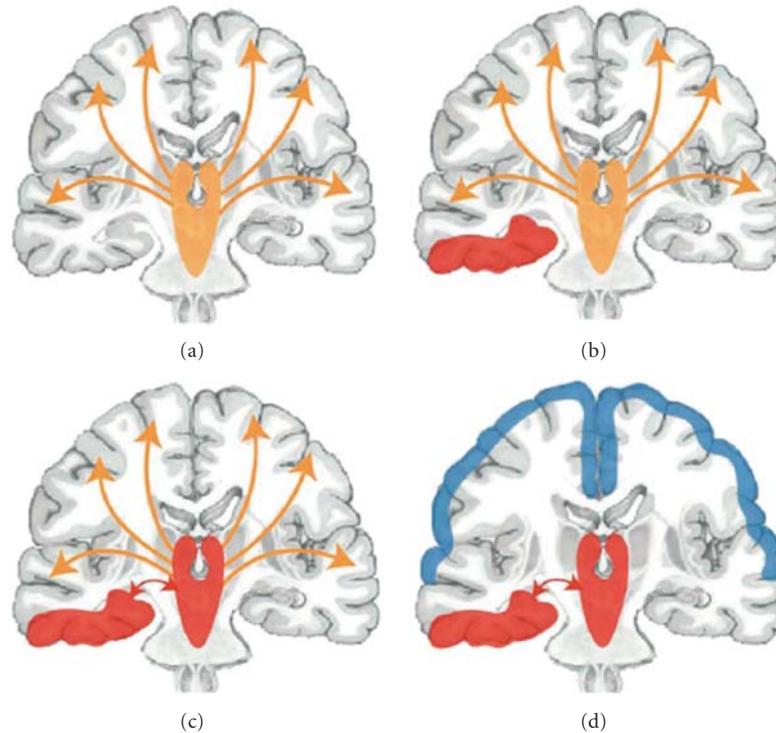


FIGURE 4: Network inhibition hypothesis for loss of consciousness during the onset and propagation of unilateral focal seizure in mesial temporal lobe. Reproduced with permission from Blumenfeld and Taylor [1].

The role of the DMN is still largely unclear, however, two hypotheses have been proposed relating to conscious awareness (for review see [98]). The DMN has been suggested to be responsible for unconstrained conscious internal mental processes such as mind wandering [99] or alternatively may involve low-level monitoring of the external environment [10, 100]. Regardless of the fact that one or both hypotheses may be correct, both relate to awareness (either of self or environment), and thus the contents of consciousness. The potential role of the DMN governing conscious awareness has been investigated through imaging in altered states of consciousness where awareness is thought to be absent including such conditions as anesthesia [16, 101], sleep [102], vegetative state [38, 42, 103], and coma [14, 37]. Under light sedation in healthy subjects, Greicius et al. [101] found significantly reduced connectivity in the posterior cingulate cortex (PCC) within the DMN suggesting that focal reductions of the PCC may reflect decreased levels of consciousness. In deep sleep, a more natural occurrence of decreased consciousness, a decoupling of the medial prefrontal cortex to the rest of the cortical regions in DMN, have been shown to occur [102]. A disruption of functional connectivity in the DMN in vegetative state (VS), a pathological disorder of consciousness whereby a patient lacks awareness while regaining arousal, has also been reported. In three VS patients, it was found that the degree of functional connectivity within the network correlated with the severity of the neurological impairment [103]. An absence of DMN has also been reported in a VS patient who was scanned 21 years after anoxic injury

[42]. Vanhaudenhuyse et al. [43] examined DMN connectivity in 14 patients with range of altered states of consciousness including locked-in syndrome, minimally conscious, vegetative states, and comatose patients and found that the DMN connectivity decreased in proportion to the degree of consciousness impairment. When taken together, the integrity of the DMN may correlate with levels of consciousness, and a fully intact DMN may be needed for normal levels of consciousness to occur.

The DMN has also been proposed to have some other intrinsic role in functional brain organization [16]. Preserved DMN connectivity has been documented in one case of VS [38], in coma [14, 37], and in a possible homologous network under isoflurane anesthesia in the monkey [16]. It has been suggested that DMN may be needed for consciousness to occur but cannot be exclusively responsible for conscious awareness [16, 37]. Possibly, DMN connectivity may be an indicator of the extent of cortical disruption and predict reversible impairments in consciousness [14].

The role of DMN in mediating consciousness is supported by known metabolic impairments in VS patients which occur in cortical areas known to be implicated in the DMN such as the prefrontal, temporoparietal association areas, and posterior cingulate cortex/precuneus [104]. In addition, the emergence from reversible vegetative state coincides with recovery-related metabolic changes in areas such as the precuneus and thalamus [40, 105]. The DMN is an attractive candidate for the neural correlate of consciousness as it has a great deal of functional and structural connectivity

across large associative cortical areas [98, 106] including long-range corticothalamic connections, in addition to its role in internal mental processes and/or involvement in gathering information about the external environment, as well as disruptions in altered states of consciousness. The DMN fits within the global workspace (GW) theory of consciousness that suggests long-distance connectivity between multiple cortical networks that usually operate separately work together in an organized fashion to enable consciousness to occur [107]. Intracerebral EEG signals in TLE seizures resulting in alterations in consciousness have been shown to cause oversynchronization in long-range corticocortical and corticothalamic connections [108]. Excessive synchrony of these connections, reported to be important in the GW, is thought to prevent the variation and complexity needed to allow for a conscious state [109]. Intracerebral EEG recordings in the thalamus and temporal lobe structures (hippocampus, entorhinal cortex, and neocortex), have shown increased neuronal synchrony with the occurrence of seizures and early loss of consciousness [35].

The concept of consciousness has long been central to epileptology since generalized seizures and complex partial seizures both can induce a variable degree of impairment in consciousness [31], as frequently observed in mTLE patients. There is a series of discussion on this theme most recently [109–115]. Besides linking the SCP to the resting BOLD fluctuations as discussed above, He and Raichle made a remarkable stride forward in arguing that this slow frequency of cortical oscillation might contribute directly to the emergence of consciousness [90]. Their work has triggered a debate in the field of whether the SCP per se in widespread cortical networks carries specific details sufficient to express our vivid daily conscious experience, as opposed to the proposed role of gamma oscillation established in higher level of cognitive experience like attention [116]. It has been well known that the contents of conscious states as well as the level of awareness are affected to varying degrees during different types of epileptic seizures [27, 31, 110, 111, 115]. Accordingly, epilepsy can be used to provide an easily accessible entry into the working mechanism of altered conscious states. In principle, carefully constructed experiments that manipulate the onset/offset and subjective level of consciousness loss could dissociate hardly defined awareness from activity of either the SCP or gamma oscillation (or both).

## 5. Conclusions

Over the past decade, simultaneous EEG-fMRI recording has become technically feasible with applications in multiple areas of basic and applied sciences. Converging evidence from fMRI and depth EEG in humans and animals has already revealed that generalized seizures do not affect all brain areas indiscriminately, whereas complex partial seizures alter functional brain activity less focally than previously thought. Spontaneous EEG-fMRI investigations into topics such as asymmetry of the background activity in the homeostatic neural networks, paroxysmal focal delta or theta

oscillations, and other nonepileptic but abnormal phenomena may provide additional clinically meaningful information, particularly relevant to impairment of conscious experience in patients. It will greatly enhance our understanding of the underlying mechanism in generation of generalized seizures, provide unique insight into the brain regions involved in the generation and/or propagation of epileptiform activity, determine the neural substrate of various forms of dyscognitive seizures, and offer clinicians neuronally validated spatial guidance for surgical planning to benefit patients with medically intractable TLE.

## Acknowledgment

This work was partly funded by The Physicians' Services Incorporated Foundation (SM).

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## Review Article

# Temporal Lobe Epilepsy Semiology

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Received 22 October 2011; Accepted 26 December 2011

Academic Editor: Seyed M. Mirsattari

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Epilepsy represents a multifaceted group of disorders divided into two broad categories, partial and generalized, based on the seizure onset zone. The identification of the neuroanatomic site of seizure onset depends on delineation of seizure semiology by a careful history together with video-EEG, and a variety of neuroimaging technologies such as MRI, fMRI, FDG-PET, MEG, or invasive intracranial EEG recording. Temporal lobe epilepsy (TLE) is the commonest form of focal epilepsy and represents almost 2/3 of cases of intractable epilepsy managed surgically. A history of febrile seizures (especially complex febrile seizures) is common in TLE and is frequently associated with mesial temporal sclerosis (the commonest form of TLE). Seizure auras occur in many TLE patients and often exhibit features that are relatively specific for TLE but few are of lateralizing value. Automatism, however, often have lateralizing significance. Careful study of seizure semiology remains invaluable in addressing the search for the seizure onset zone.

## 1. Introduction

Epilepsy has been recognized since antiquity. It affects millions of people worldwide and remains one of the most common and frightening neurological conditions. The word is derived from the Greek word which means to “seize” or “take hold of.” Epilepsy encompasses a heterogeneous group of disorders with various manifestations including seizures in addition to other signs, symptoms, and features that define a phenotype.

The taxonomy and terminology of epilepsy has undergone a number of changes over the years. An early classification system generated confusion and heated discussion over equating the term “complex partial seizures” (CPSs) and “temporal lobe epilepsy” (TLE) [1]. The 1981 classification of epileptic seizures represented a consensus at that time [2]. A further revision was the Classification of Epilepsies and Epileptic Syndromes accepted in 1989 [3]. Yet another modification and change in philosophy was initiated by the Executive Committee of the International League Against Epilepsy (ILAE) which took office in 1997. The ILAE task force published the Revised Terminology and Concepts for Organization of the Epilepsies in 2010 [4].

Temporal lobe seizures are the most frequent site of origin of partial seizures. They represent approximately two thirds of the intractable seizure population coming to surgical management. Jackson in the 19th Century [5] was the first to link seizures characterized by a “dreamy state” to lesions near the uncus in the temporal lobe (hence the term “uncinate fits”). Gibbs and Lennox suggested the term psychomotor epilepsy to describe a characteristic EEG pattern together with emotional, mental, and autonomic phenomena for seizures originating in the temporal lobe [6]. Researchers at the Montreal Neurological Institute (MNI) described the psychic phenomena as experiential hallucinations based on clinical observations and intraoperative stimulation studies [7, 8]. Gastaut proposed the term CPSs for partial onset seizures associated with loss of consciousness [3]. Videotape and computer technology has permitted careful review of captured seizures and their associated EEG telemetry thus providing detailed descriptions of the features of temporal lobe seizures [9–12]. Frontal lobe seizures (FLS) are the second most frequent site of origin of partial seizures and are often difficult to differentiate from temporal lobe seizures but some features may help (see Table 1).

TABLE 1: Temporal and frontal lobe seizures differential semiological features.

Features	Temporal	Frontal
Sz frequency	Less frequent	Often daily
Sz onset	Slower	Abrupt, explosive
Sleep activation	Less common	Characteristic
Progression	Slower	Rapid
Automatisms	Common-longer	Less common
Initial motionless stare	Common	Less common
Complex postures	Late, less frequent, less prominent	Frequent, prominent, and early
Hypermotor	Rare	Common
Bipedal automatisms	Rare	Characteristic
Somatosensory Sx	Rare	Common
Vocalization	Speech (nondominant)	Loud, nonspeech (grunt, scream, moan)
Seizure duration	Longer	Brief
Secondary generalization	Less common	Common
Postictal confusion	More prominent-longer	Less prominent, Short
Postictal aphasia	Common in dominant hemisphere	Rare unless spreads to temporal lobe

## 2. Cardinal Semiology of Temporal Lobe Seizures

**2.1. Prodrome.** Some patients experience preictal events, which may be helpful in predicting a coming seizure. Prodromes may last several minutes, hours, or, occasionally, even days. Examples of prodromes include headache, personality change, irritability, anxiety, or nervousness. These phenomena should not be confused with seizure onset. Often, prodromes are recognized by family and friends but, not by the patient (especially changes such as irritability or exhilaration).

**2.2. Aura.** Auras (from the Latin for breeze, Greek for air) are in fact simple partial seizures and can occur in isolation but occur in the majority of patients at the onset of a CPS. They can last from seconds to as long as 1-2 minutes before consciousness is lost.

The types of auras patients report may correlate with the site of seizure onset. Some authors have questioned the localizing value of the aura as a marker of ictal origin in CPSs [13–15]. Many authors, however, have noted a close association of some sensory auras with temporal lobe seizures. Examples include viscerosensory symptoms such as a rising epigastric sensation and experiential phenomena such as fear, déjà and jamais vu, visceral and auditory illusions, and complex auditory or visual hallucinations [16–20]. Gustatory and olfactory hallucinations are also relatively specific for TLE, as are elementary auditory hallucinations [21]. Although auras often have localizing value, they do not often have lateralizing significance.

Semiological seizure classifications associate the anatomical focus of seizure origin with the clinical features of seizures [22–24]. If, however, the seizure begins in an area inaccessible to scalp EEG recordings, then localization will be inaccurate. Similarly, if seizures begin in “noneloquent” cortex, the subsequent spread to “eloquent” cortex may lead

to false localization of the seizure focus. Seizure semiology in the latter case signifies seizure propagation rather than seizure origination.

**2.3. Altered Consciousness.** CPSs are associated with altered consciousness and amnesia for the event; typically, behavioural arrest and staring with a duration of 30 seconds to 1 to 2 minutes. Consciousness has several facets, including cognition, perception, affect, memory, and voluntary motility [25]. Impaired awareness should be distinguished from a temporary block of verbal or motor output or of verbal comprehension with maintained consciousness.

Loss of consciousness in CPSs (as well as in “Absence” episodes) has been shown to be associated with decreased activity in the “default mode network.” This network includes the precuneus/posterior cingulate, medial frontal, and lateral parietal cortices as detected by functional MRI (fMRI) [26]. For more detailed discussions on default mode network in TLE, the reader may refer to a dedicated article in this special issue.

**2.4. Amnesia.** Individuals with CPSs may be unaware that they had a seizure minutes earlier. They may also be unable to recall events which occurred before seizure onset. The degree of retrograde and anterograde amnesia is variable. For example, patients may have experienced an aura which prompted them to signal the onset of a seizure when they were in the epilepsy monitoring unit (EMU) but, subsequently, not recall having done so. Postictal amnesia likely results from bilateral impairment of hippocampal function. Stimulation of medial temporal lobe structures producing an after-discharge affects the formation and retrieval of long-term memories [27, 28].

**2.5. Automatisms.** Automatisms represent coordinated involuntary motor activity that is stereotyped and virtually

always accompanied by altered consciousness and subsequent amnesia. No uniform classification of this phenomenon has been developed. One system divides automatisms into *de novo* and preservative automatisms [29]. *De novo* automatisms are said to occur spontaneously at or after seizure onset. They might be classified as “release” phenomena, which include actions normally socially inhibited or “reactive” phenomena when they appear to be reactions to external stimuli. For example, the patient may drink from a cup placed in his hand or chew gum placed in his mouth. Preservative automatisms might represent continuation of complex motor acts initiated prior to seizure onset, for example, opening and closing a door repeatedly. Automatisms occur in almost two thirds of CPSs of mesial temporal lobe onset [16, 20, 30]. They often involve the hands (fumbling, picking, fidgeting) or mouth (chewing, lip smacking, swallowing).

Less common automatisms associated with temporal lobe seizures include vocalizations, ictal speech, and affective behaviours (out of context fear). Additionally, even less common behavioural, such as, crying (dacrystic), laughing (gelastic), and so-called “leaving behaviours,” for example, running out of the house or down the street during a seizure (cursive) have been reported [31–34]. A rare automatism, whistling, has also been recently reported to occur during temporal lobe seizures [35].

Temporal lobe seizures can be simple partial, complex partial, or secondarily generalized. A number of features of TLE semiology have lateralizing or localizing value (see Table 2).

### 3. Mesial Temporal Lobe Seizures and Neocortical Temporal Lobe Seizures

TLE is the most common symptomatic partial epilepsy in adolescents and adults but, extratemporal or neocortical epilepsy is more common in young children [36, 37]. Mesial temporal sclerosis (MTS), hippocampal sclerosis (HS), is the most common cause of TLE, representing greater than 80% [38]. Other causes include perinatal injury, malformations of cortical development (MCD), arteriovenous malformations (cavernous hemangiomas, meningioangiomas), infections of the central nervous system (CNS), glial tumors (e.g., ganglioglioma, dysembryoblastic neuroepithelial tumors, astrocytomas, oligodendrogliomas, meningiomas, or CNS metastasis), hamartomas, head trauma, and limbic encephalitis [38, 39]. MTS involves neuronal loss in the hilar region of the hippocampus (CA1, CA3, CA4, and the dentate gyrus, with relatively sparing of the CA2 region). It is typically bilateral but greater on one side [16]. Temporal lobe epilepsy with mesial temporal sclerosis usually presents between 6–10 years of age but can present from infancy to the 30s [16]. MTS is usually a progressive disorder and seizures initially controlled with antiepileptic drugs can later become intractable in 60–90% [16, 17].

The association between MTS and depression, anxiety, and other psychiatric comorbidities is controversial [16]. Impairment of cognition and memory may be the result of

frequent seizures and/or medication side effects. Psychiatric symptoms can occur ictally and be mistaken for primary psychiatric illness. For more details on this topic, the reader may refer to the dedicated articles in this special issue.

The semiological features of mTLE were said to include typical auras such as rising epigastric sensations, *déjà vu*, affective phenomena (fear or sadness), or experiential phenomena followed by unilateral motor signs (frequently ipsilateral contraction of face or mouth, head deviation) and bilateral motor phenomena in the face or axial muscles. Behavioural arrest and oral automatisms are common and bitemporal spread heralds alteration in consciousness, amnesia, autonomic phenomena (change in heart rate and respirations), and prominent motor automatisms (tonic and dystonic posturing) [40].

Familial mesial temporal lobe seizures are a heterogeneous syndrome characterized by predominantly psychic, autonomic auras, and dysmnestic symptoms including *déjà vu* usually evolving to CPSs and/or secondary generalization [41–44].

The semiological features of neocortical TLE are said to include auditory, vestibular and complex visual hallucinations, and aphasia and focal sensory-motor phenomena [40]. Some authors have reported that early onset unilateral motor automatisms, without dystonic posturing, can localize seizure origin to the contralateral temporal lobe neocortex [45]. nTLE-originating temporal lobe seizures are seemingly less common than mesial temporal lobe seizures and as a result are less well characterized. nTLE is associated with structural abnormalities including MCD, vascular malformations, neoplasms, and traumatic brain injuries [46–48]. For more details on this topic, the reader may refer to the dedicated paper in this special issue.

A rare hereditary syndrome, autosomal dominant partial epilepsy with auditory features (ADPEAF), has been described [49–52]. It usually begins in adolescence or early adulthood. The cause, in greater than 50% of families described, is a mutation of leucine-rich glioma inactivated gene (LGII). The most common auditory symptoms are simple unformed sounds (humming, buzzing, ringing), less frequently, complex sounds (voices, songs) or distortions (volume changes may occur). Some patients experience seizures precipitated by specific sounds (pieces of music, telephone ringing) [50]. Some also reported experiencing olfactory, visceral, vertiginous, experiential, or autonomic auras [50]. The diagnosis requires exclusion of structural lesions, in addition to a characteristic family history.

Some authors found no differences in the auras of patients with mTLE and nTLE onset [53]. Most authors, however, note that CPSs of mesial temporal origin typically begin with oroalimentary or hand automatisms in contrast to those of neocortical onset, which often begin with staring, without automatisms or epigastric phenomena.

There are reciprocal connections between mesial and neocortical temporal cortex. There is evidence that these connections are activated to produce an aura [54, 55]. This suggests that the type of aura in TLE is more indicative of the pattern of seizure spread than the site of seizure onset. Gloor’s hypothesis posits that experiential phenomena

TABLE 2: Semiological Features (TLE) - Lateralizing or Localizing Value.

Feature	Location
<i>Automatism</i>	
Unilateral limb automatism	Ipsilateral focus
Oral automatism	(m)Temporal lobe
Unilateral eye blinks	Ipsilateral to focus
Postictal cough	Temporal lobe
Postictal nose wiping	Ipsilateral temporal lobe
Ictal spitting or drinking	Temporal lobe focus (R)
Gelastic seizures	(m)Temporal, hypothalamic, frontal (cingulate)
Dacrystic seizures	(m)Temporal, hypothalamic
Unilateral limb automatisms	Ipsilateral focus
Whistling	Temporal lobe
<i>Autonomic</i>	
Ictal emeticus	Temporal lobe focus (R)
Ictal urinary urge	Temporal lobe focus (R)
Piloerection	Temporal lobe focus (L)
<i>Motor</i>	
Early nonforced head turn	Ipsilateral focus
Late version	Contralateral focus
Eye deviation	Contralateral focus
Focal clonic jerking	Contralateral perirolandic focus
Asymmetrical clonic ending	Ipsilateral focus
Fencing (M2E)	Contralateral (supplementary motor)
Figure 4	Contralateral to the extended limb (temporal)
Tonic limb posturing	Contralateral focus
Dystonic limb posturing	Contralateral focus
Unilateral ictal paresis	Contralateral focus
Postictal Todd's paresis	Contralateral focus
<i>Speech</i>	
Ictal speech arrest	Temporal lobe (usually dominant hemisphere)
Ictal speech preservation	Temporal lobe (usually nondominant)
Postictal aphasia	Temporal lobe (dominant hemisphere)

are positive expressions elicited by activation of neurons interconnected in a matrix that includes components of the hippocampal formation as well as elements of the temporal isocortex [54]. He proposed that these phenomena could be initiated by activation of different parts of the matrix and therefore did not distinguish between mesial and neocortical onset of seizures. He based his hypothesis on concepts of parallel distributed processing as applied to parallel distributed cortical networks for higher cognitive functions [56, 57].

#### 4. Lateralizing Features in Temporal Lobe Epilepsy

Unilateral upper limb automatisms are associated with an ipsilateral seizure onset [58, 59]. Some authors, however, dispute this and found no lateralizing value of upper limb automatisms in isolation [11, 60, 61]. Other authors, however, reported that early onset unilateral motor automatisms

without dystonic posturing can localize seizure origin to the contralateral temporal lobe neocortex [45]. Unilateral ictal blinking (winking) is a rare automatism and usually indicates an ipsilateral focus [62]. Postictal nose rubbing or wiping is also usually associated with an ipsilateral focus [63]. Postictal head turning or head tilt occurring early especially with preserved consciousness is usually ipsilateral to seizure onset [59]. It is most often contralateral to the seizure focus when it occurs later. It is also more forceful and appears involuntary, earning the characterization of versive [59, 64]. Eye deviation is usually associated with forced head turning and occurs in the same direction. Version occurs in both temporal and extratemporal onset seizures and is frequently followed by dystonic or tonic posturing occurring just before or concurrently with secondary generalization [60].

Unilateral tonic limb posturing is associated with a contralateral seizure focus. This was reported in an early study 3 decades ago [65]. There has been an agreement with this observation in several studies since then [59, 66]. Dystonic posturing of the arms and leg reliably predicts seizure

onset in the contralateral hemisphere [59–61]. It has been attributed to spread from the amygdale and hippocampus to the ventral striatum and pallidum through the fornix and stria terminalis [61]. The typical hand posture includes wrist flexion, finger extension at the interphalangeal joints, and flexion at the metacarpal-phalangeal joints, thumb adduction. Asymmetric tonic limb posturing (figure of 4 sign) is usually observed during the early tonic phase of a seizure, just before secondary generalization. One arm is flexed at the elbow and the other arm is extended at the elbow, hence, the appearance of a figure of 4. Seizure onset is contralateral to the extended arm [61].

Unilateral ictal paresis or “immobile limb,” [67] is an infrequent sign contralateral to the seizure focus. It involves sudden loss of tone in one upper limb while the other upper limb maintains tone and movement (automatism) [68].

Lower facial weakness (mild to severe) has been noted contralateral to a unilateral temporal lobe focus in 3/4 of a sample of 50 patients. The weakness was reportedly more prominent with mimetic movements. Facial asymmetry may, therefore, be a useful sign in temporal lobe epilepsy in combination with other semiological features [69].

Rare autonomic phenomena include ictus emeticus, ictal urinary urge, and ictal spitting or drinking localizing to a right temporal origin and piloerection to a left temporal origin [59, 70]. Ictal whistling and postictal coughing localize to a temporal lobe origin but are not lateralizing [36, 70, 71]. Postictal vomiting has no lateralizing or localizing value [70].

Language disturbances in association with temporal lobe seizures can include expressive, receptive, or global aphasia as well as dyslexia. Speech arrest at seizure onset (before altered consciousness) or ictal or postictal aphasia reliably implies dominant hemisphere seizure origin [72–74]. Speech arrest, as the origin of seizure, can occur if the patient is talking at seizure onset. It can also be confirmed if the patient is unable to speak despite clear attempts to do so and is able to recall this following termination of the clinical event. Its mechanism may be the involvement of Wernicke’s area, Broca’s area, or the dominant baso-temporal area since electrical stimulation of these areas produces speech arrest without loss of consciousness or motor impairment [73]. Postictal aphasia is a very reliable lateralizing sign (80–90%) [59, 75], but specific postictal language testing must be utilized by the EMU in order to detect this phenomenon. Anomia and paraphasic errors are easy to demonstrate during seizures [59, 72]. Paraphasic errors and alexia are clearly associated with CPSs originating in the dominant hemisphere [74]. Ictal speech preservation reliably predicts seizures of nondominant hemisphere origin [58, 72]. Seizures of nondominant hemispheric origin, however, may interfere with speech function on the basis of postictal confusion [70, 76].

## 5. Age and the Semiology of Temporal Lobe Epilepsy

Age at first seizure can influence the semiology of temporal lobe seizures. Several studies have noted a predominance

of mesial temporal foci in younger onset patients and neocortical foci in older onset patients [77, 78]. This may suggest that mesial temporal structures are more susceptible to early development of epileptogenesis. For more details on this topic, the reader may refer to the dedicated article in this special issue. Several authors have noted an association between the occurrence of auras and a mesial temporal origin [16, 79]. This correlates with a predominance of HS in patients with a younger onset of TLE. Not all studies are in agreement on this association [80]. There is also an association of epigastric auras with HS, which also favours a younger onset population with TLE [52, 77, 78].

Several studies have noted that elderly patients (>60 years) tend to have seizures that become less elaborate and shorter in duration and have a lesser tendency to go on to secondary generalization [81]. Thus, aging may have an independent effect on seizure semiology. For more details on this topic, the reader may refer to the dedicated article in this special issue.

Blinking is a rare automatism that has been noted by some to occur in patients with older onset of TLE [77]. It has been noted to have a lateralizing value when it is unilateral. It is usually ipsilateral to the side of seizure onset [82].

## 6. Semiology of Childhood Onset Temporal Lobe Epilepsy

The semiology of TLE in childhood seems to be influenced by age-related mechanisms. Ictal features in young children do not seem to provide many localizing or lateralizing clues to the ictal origin [83–85].

Young preschool children often manifest an arousal type of reaction as the initial event with eye opening, sitting up, or axial jerking [83]. Some exhibit epileptic spasms resembling “infantile spasms” [83, 86]. Most studies in young children describe initial motor features such as tonic, dystonic, and clonic movements bilaterally. They tend to be symmetrical and more typical of secondarily generalized seizures [87, 88].

Older children may exhibit semiological features similar to adults. The occurrence of initial motor features decreases parallel with age and mostly disappears in school age children. Older children exhibit auras, psychomotor arrest, and automatisms. They are mainly oral and manual and tend to be less complex than in adults [89]. Automatisms tend to become more complex in parallel with increasing age [84, 88, 90]. There also seems to be an age-dependent increase in the occurrence of lateralizing signs such as unilateral dystonic, tonic, and clonic components. Also, asymmetric epileptic spasms, ictal speech and unilateral blinking, and ictal spitting and post ictal nose wiping are more common in older patients with TLE [84].

Interestingly, auras with autonomic and emotional features seem to be unaffected by the maturational process [90].

Secondary generalization of temporal lobe seizures is uncommon in childhood [87, 91, 92]. This may be related to age-dependent cortical maturation, immature dendritic development, and myelination together with imperfect synchronization of both hemispheres [93].

There are age-dependent changes in epileptic manifestations despite a seemingly identical underlying pathophysiology. An example is the progression from West syndrome to Lennox-Gastaut Syndrome (LGS) and the development of CPSs and secondarily generalized tonic-clonic seizures (GTCs) [94].

The locus of seizure origin within the temporal lobe and the underlying etiologies vary with age. For example, epilepsy, secondary to MCD, presents at a mean age of 7 years (range 1–26 years) [10, 89]. Neoplasms and cerebrovascular disease are commonest in later life [94].

### 7. Localization Reliability of Semiological Features in Temporal Lobe Epilepsy

Semiology of temporal lobe seizures that occur during sleep or wake seem to reliably show the same lateralizing features in individual patients [92]. Secondary generalization occurs more frequently in temporal lobe seizures occurring during sleep. This is also a feature of rapid drug withdrawal in patients in an EMU before possible surgical treatment of their epilepsy. Other semiological features, however, are not substantially altered and seizures recorded under these circumstances, therefore, appear to be the same as the patient's habitual seizures [92, 95].

Localizing the onset of seizures based on ictal semiology has been reportedly accurate in the majority of patients with partial epilepsy [96]. False localizations raise the possibility of multifocal epilepsy [91]. Seizure semiology has reportedly been accurate in localizing ictal onset in only 59–67% of patients with multifocal epilepsy [97, 98].

Kotagal and associates analyzed 31 Engel class 1 patients, who had complex partial seizures of temporal lobe onset to detect symptom clusters and seizure progression. The 18 most common symptoms were found to form a tight cluster with several subclusters: (i) epigastric aura, ictal emesis, alimentary, and hand automatisms; (ii) behavioral arrest, complete loss of consciousness, staring and bilateral facial contraction; (iii) unilateral dystonic posturing of an arm, mimetic automatisms, complex gestures, ictal speech, partial loss of consciousness; (iv) looking around, agitation, vocalizations, and whole-body movements. A strong association of epigastric sensation and ictal vomiting was noted with right temporal origin foci. The commonest order or sequence of symptoms consisted of behavioral arrest followed by alimentary and hand automatisms, then random gazing and whole-body movements [99].

Frontal lobe onset is the second most common site of origin of complex partial seizures. An aura of an indescribable sensation or generalized body sensation is said to occur exclusively in frontal lobe complex partial seizures, while an orolimentary aura was more frequent and occurred earlier in mesial temporal seizures. Perseverative automatisms and emesis are said to occur only in temporal lobe seizures. Olfactory and experiential auras followed by behavioral arrest, alimentary and distal upper limb automatisms, loss of consciousness, and purposeless looking around coupled with whole-body movements were typical of mesial temporal lobe

seizures. Bicycling movements and hypermotor activity were noted to be typical of frontal lobe seizures [100].

### 8. Orgasmic Aura's Lateralizing and Localizing Semiological Features in TLE

Orgasmic auras most frequently represent a right hemispheric or nondominant hemispheric ictal onset. Some are associated with genitalia sensations but many are purely experiential. They have good lateralizing as well as localizing value when they represent the initial manifestation of the seizure [101–103].

Auras often provide valuable localization information but not useful lateralization features [104]. Orgasmic auras represent a useful exception. Most reported cases of ictal orgasm are revealed after a long epileptic history because patients are reluctant to disclose such intimate details. It is likely that many more patients have experienced orgasmic auras but never reported this feature. There are often other clinical features in reported cases that are typical of TLE such as fear, déjà vu, epigastric sensations, olfactory, and gustatory hallucinations [101]. Epileptic discharges from limbic elements of the temporal lobe commonly produce emotional phenomena such as fear, hallucinations, or illusions, and erotic feelings represent an extension of these experiential phenomena.

The occurrence of erotic ictal phenomena is more frequent in females as opposed to the more common nonerotic ictal genital sensations reported by males. This suggests that the neural organization of psychosexual behavior differs in male and female brains. This could point to anatomic as well as functional dimorphism of the limbic components of the temporal lobe in humans [101].

Physiological orgasm can occur without any physical stimulation, which points to a central neural mechanism and may be further evidence in support of a nondominant right hemispheric origin of the ictal onset.

### 9. Semiology of Benign Mesial Temporal Lobe Epilepsy

Benign mTLE (bMTLE) is defined as mTLE with at least 24 months of seizure freedom with or without AEDs. It was recognized many years ago [105]. More recent studies have attempted to establish the clinical features and prognosis of this group [106]. The epidemiological study of this entity is difficult because it can only be documented after a long period of observation. bMTLE is easily treated with one AED, such as, carbamazepine or oxcarbazepine. Most studies of TLE have focused on medically intractable patients.

In bMTLE, seizures begin in late adolescence to mid-adult life. Past histories are devoid of many risk factors, such as, head injury, stroke, or substance abuse. Some 1/3 have a family history of febrile seizures. The neurological exam is usually normal. Viscerosensory or experiential auras are the commonest ictal symptoms. Déjà vu often represents the only type of seizure for many years. Infrequent partial seizures are noted in about 2/3 of patients before treatment,

and secondarily generalized seizures are rare and tend to occur during sleep [107]. Two thirds have normal interictal EEG's, but the majority of bMTLE with MRI signs of HS have interictal EEG abnormalities [107]. Because of this mild clinical picture, many patients are misdiagnosed as panic disorders or GI disturbances. This is especially true since many experience seizures that consist of a déjà vu phenomenon only. Since a number of nonepileptic individuals experience déjà vu phenomena, many of these patients do not come to neurological attention unless they develop other seizure manifestations.

Evidence of HS may be seen in 30–40% of bMTLE patients [106, 107]. Since febrile seizures, HS, early age onset of seizures and interictal EEG abnormalities are negative prognostic factors, other factors, both genetic and environmental must play a pivotal role in causation and severity of seizures [108].

Clinical neuroimaging, EEG features, and seizure outcome of bMTLE patients are similar to familial mTLE, [109, 110] suggesting that genetic predisposition is an important causal factor in bMTLE.

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## Review Article

# Determining Surgical Candidacy in Temporal Lobe Epilepsy

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Received 26 July 2011; Revised 26 October 2011; Accepted 3 December 2011

Academic Editor: Seyed M. Mirsattari

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Temporal lobe epilepsy (TLE) is the most common form of adult epilepsy that is amenable to surgical treatment. In the carefully selected patient, excellent seizure outcome can be achieved with minimal or no side effects from surgery. This may result in improved psychosocial functioning, achieving higher education, and maintaining or gaining employment. The objective of this paper is to discuss the surgical selection process of a patient with TLE. We define what constitutes a patient that has medically refractory TLE, describe the typical history and physical examination, and distinguish between mesial TLE and neocortical TLE. We then review the role of routine (ambulatory/sleep-deprived electroencephalography (EEG), video EEG, magnetic resonance imaging (MRI), neuropsychological testing, and Wada testing) and ancillary preoperative testing (positron emission tomography, single-photon emission computed tomography (SPECT), subtraction ictal SPECT correlated to MRI (SISCOM), magnetoencephalography, magnetic resonance spectroscopy, and functional MRI) in selecting surgical candidates. We describe the surgical options for resective epilepsy surgery in TLE and its commonly associated risks while highlighting some of the controversies. Lastly, we present teaching cases to illustrate the presurgical workup of patients with medically refractory TLE.

## 1. Introduction

*1.1. History of Temporal Lobe Epilepsy Surgery.* Cerebral localization and electroencephalography (EEG) have together been two fundamental advances that have been paramount in the diagnosis and management of epilepsy. The clinical observations of Broca [1] and Jackson and Colman [2], along with the landmark observations of Fritsch and Hitzig [3], the electrical excitability of the human brain, and discrete localization of brain functions, began to be established. Through experiments of electrical stimulation on narcotized dogs, Fritsch and Hitzig were able to differentiate the *motor* from the *nonmotor* cortex [3]. Drawn to these findings, Sir Horsley was likely the first to attempt amelioration of epilepsy in a patient with posttraumatic seizures via a craniotomy [4]. Not long after this, in 1875, Caton was able to measure electrical activity from the cat brain [5], and this was followed by EEG recordings in humans by Berger in 1929 [6]. Thereafter, Bailey and Gibbs proceeded to operate on individuals with psychomotor epilepsy solely based on anterior temporal

spikes on EEG [7]. Penfield later observed that patients failing neocortical resection could benefit from resection of the mesial temporal lobe structures such as the amygdala and the hippocampus. While many new developments have occurred since, these represent the key contributions that have remained as the fundamentals building blocks of the modern-day practice of epilepsy surgery.

*1.2. Background.* With approximately 1% of the world population affected by epilepsy, it is classified by the International League Against Epilepsy (ILAE) as the most common serious neurological disorder in the world [8]. The annual incidence rate is between 40 and 70 per 1000 people in developed countries [9]. Patients with epilepsy are at a threefold higher risk of cognitive decline as compared to the general population [10]. In addition, epilepsy is associated with significant psychosocial harm including social isolation, depression, and stigmatization [11]. Patients with epilepsy are less likely to complete secondary and postsecondary education translating into higher rates of unemployment

[12]. In the United States, the direct average cost of epilepsy is \$10,000 a year for patients with medically uncontrolled epilepsy and \$2,000 a year for patients with medically controlled epilepsy [13, 14]. However, the direct medical costs comprise only 25% of the total economic impact of epilepsy [15]. For the estimated 2.3 billion people with epilepsy in the United States of America, the annual indirect cost is \$12.5 billion; costs are eightfold higher in patients with medically intractable epilepsy [13, 16].

Medical intervention is the first step in the management of epilepsy. However, this fails to achieve seizure freedom in up to one-third of patients [17]. In a subset of patients who are refractory to medical management, evaluation of surgical candidacy is appropriate [18]. Temporal lobe epilepsy (TLE) is particularly common and amenable to surgery resulting in better seizure outcomes (50–70% seizure freedom at 5 years) [19] as compared to extratemporal epilepsy [20]. In addition, patients undergoing TLE surgery may benefit from improved psychosocial functioning [21], achieving higher education, maintaining or gaining employment [22], long-term seizure freedom [23], in addition to significant monetary savings by the society [9].

*1.3. Objectives.* The objective of this paper is to discuss the surgical selection process of a patient with TLE. We will outline the definition of a medically refractory patient with TLE, distinguish between mesial TLE (mTLE) and neocortical TLE (nTLE), review the role of routine and ancillary preoperative testing, describe surgical techniques and discuss common surgical risks. We lastly present several case studies to review the rationale for surgery.

## 2. Selection of Patients for Temporal Lobe Epilepsy Surgery

*2.1. Medically-Refractory Temporal Lobe Epilepsy.* A recent consensus paper defined medically refractory epilepsy as having seizures despite being treated with 2 consecutive first-line antiepileptic medications (AEDs) over 2 years [24]. Complex partial seizures (CPSs), most commonly generated in the temporal lobe, are least likely to respond to medications [25]. Patients with CPSs, along with radiographic abnormalities in the temporal lobe or mesial temporal sclerosis (MTS), are most likely to fail medical management and are amongst the best surgical candidates [26]; hence why TLE could be considered a surgically-remediable form of epilepsy from the onset [27]. A small proportion of patients with mTLE may ultimately become seizure-free with more drug trials [20]. Furthermore, another subgroup of patients may achieve seizure freedom without treatment. This is referred to as benign mTLE in which the etiology may have an underlying genetic component [28]. There is scarce data regarding the predictors of this condition [28].

*2.2. Differentiating between Mesial and Neocortical Temporal Lobe Epilepsy.* From an electrical and clinical perspective, there are two subtypes of TLE: mTLE and nTLE. This distinction is made (although there is indeed overlap) as

it has important implications with respect to electrophysiology, neuropsychological profile, underlying pathological substrate, and response to surgery [29]. The electroclinical and diagnostic differences are presented in Table 1.

The most common pathological substrate for TLE is MTS. This is characterized by segmental loss of pyramidal cells, dispersion of granule cells, and a resultant reactive gliosis. Other pathological entities resulting in TLE include tumors (either malignant or benign, e.g., ganglioglioma, dysembryoplastic neuroepithelial tumour, oligodendroglioma, low- or high-grade glioma, and meningiomas), infections (e.g., herpes, tuberculosis, and cysticercosis), vascular malformations (arteriovenous malformations, cavernous hemangioma, and meningioangiomatosis), migrational disorders (cortical dysplasia and hamartoma), and trauma (encephalomalacia and gliosis). The differential diagnosis of nTLE is similar to mTLE with the exception of MTS.

*2.2.1. Dual Pathology.* Approximately 15% of patients with partial epilepsy that have an extratemporal lesion have associated MTS; these cases are referred to as involving dual pathology [30]. The amount of hippocampal cell loss is correlated to the specific type of extra-temporal pathology with vascular lesions, gliomas, and hamartomas resulting in the least amount of cell loss while heterotopias are associated with the greatest amount of cell loss [30, 31]. While it is not clear whether it is the hippocampus alone, the extra-temporal lesion, or both that serve as the true epileptogenic lesion, it is evident that resection of both lesions generally yields the highest likelihood of attaining seizure freedom, provided that preoperative testing demonstrates concordant localization [32].

### 2.3. Routine Diagnostic Workup

*2.3.1. Goal of Presurgical Patient Evaluation.* The main goal of surgical management of epilepsy is the removal of the epileptogenic zone: the region which, if resected completely, would result in seizure freedom [33]. Hence, the preoperative workup seeks to identify this region and determine the safety of its resection. As part of the evaluation, the ictal onset zone, the symptomatogenic zone, the irritative zone, and the functional deficit zone may also be identified. The ictal onset zone is the region from which seizures arise. The symptomatogenic zone reproduces the clinical semiology of the ictal episodes upon stimulation. The irritative zone is the region in which interictal discharges can be detected; this depends highly on the method used for measurement, the level of patient awareness, and the amount of medication they are on. The functional deficit zone is correlated to neurological deficits during the interictal period. In an ideal scenario, substantial overlap is observed between the aforementioned zones, and there is congruence with the epileptogenic lesion identified on imaging. In such cases, there is a high likelihood that the patient will attain seizure freedom postoperatively [34–36].

These concepts are simplifications, and they may not be accepted amongst all epileptologists. An alternative method of conceptualizing seizure onset and propagation is the

TABLE 1: Electroclinical and diagnostic differences between mTLE and nTLE.

	mTLE	nTLE
Clinical aspects	Auras (simple partial seizures) (i) Not present in approximately half of TLE patients (ii) Visceral sensation/fear (or both) (iii) Déjà vu (iv) Illusions/hallucinations	
	Complex partial seizures (i) Autonomic changes (ii) Arrest of behavior/motionless stare (iii) Oroalimentary automatism (iv) Contralateral dystonic posturing (v) Nose rubbing (vi) Dysphasia (if dominant hemisphere involved)	Same as mTLE
Preoperative testing	MRI (i) MTS (ii) Other structural pathologies (iii) Dual pathology (iv) No lesion ("MRI normal")	Same as mTLE
	TLE	
	Neuropsychological testing (i) Lateralized memory impairment	Neuropsychological testing (i) More likely to have naming problems Wada test (i) Less likely to have lateralized memory dysfunction on side of seizure onset, compared with mTLE
	Scalp EEG (i) "Classic" anterior temporal inter-ictal spikes	Scalp EEG (i) No unique pattern (ii) Absence/multiple types of inter-ictal spikes
Intracranial recordings	Seizures originate from mesial structures	Variable with widespread electrophysiological changes

theory of cortical and subcortical neuronal networks (NNs); these are bilateral brain regions that are interconnected functionally and anatomically [37]. Individual components within the network have the ability to influence each other and the particular clinical semiology, and electrographical seizure manifestation is dependent on the particular NN involved. A well-defined NN is the medial temporal-limbic network consisting of the hippocampus, amygdala, neocortex of the lateral temporal lobe, entorhinal cortex, medial thalamus, and the inferior region of the frontal lobes. The identification of NNs typically involves the use of ictal EEG in addition to PET and fMRI [38]. Based on this premise, the identification of any perturbation within the network can be used to predict a seizure before it is clinically and electrographically manifested. Further, the use of NNs can be used to tailor treatment strategies to the particular network involved. For example, the resection of a component within the network but distant from eloquent cortex could theoretically help diminish seizure frequency without significant morbidity to the patient [37]. The primary focus of this review paper will be based on the epileptogenic and related zones and the various diagnostic modalities that can be used to identify them.

**2.3.2. History and Physical Examination.** The presurgical workup requires a detailed history and physical exam.

Specific components of the history include a detailed account of seizure semiology, past medical history, family history, and attempted AED. Having a family member or friend who has witnessed the episodes can provide useful information, as the individual may not have any recollection of the events. A complete neurological examination can have localization value and, together with the history, can help identify the functional deficit zone.

**2.3.3. Ambulatory and Sleep Deprived Electroencephalogram.** Scalp EEG is an essential component of the initial patient evaluation. This test is often performed on an outpatient basis both for convenience and its noninvasive nature. For outpatient analysis, a 30-minute awake/sleep-deprived analysis may suffice if there is a typical clinical history and obvious imaging findings, especially if ictal recording with video-EEG telemetry in a monitoring unit is not possible [39]. However, there are situations where this may not be sufficient, for example, bilateral TLE with unilateral hippocampal sclerosis (HS). Repeated EEG, especially if performed within 48 hours of a seizure, increases the sensitivity of detecting an abnormality [40]. Sleep deprivation or cessation of AEDs can also be used to induce seizures [41]. Most patients with mTLE have unilateral anterior temporal inter-ictal spikes on surface EEG. However, some patients with unilateral mTLE may have bilateral independent spikes in the anterior

temporal lobes [20]. Some authors report that unilateral temporal rhythmic theta activity less than 30 seconds after electrical seizure onset is associated with ipsilateral mTLE [42]. Scalp EEG analysis is an invariable test performed at all comprehensive epilepsy centers. By detecting ictal and inter-ictal epileptic discharges, it enables the approximate delineation of the ictal onset and the irritative zones. At most centers, however, surgery is only undertaken after documentation of seizure onsets after long-term video monitoring in an epilepsy monitoring unit (EMU) [43].

**2.3.4. Video Electroencephalography.** Admission to the EMU for continuous scalp EEG and video monitoring is the final common pathway and is usually considered a necessary step in determining surgical candidacy. This provides localizing value for both inter-ictal and ictal onset zones, allowing for correlation of the clinical manifestation of the epileptic event to ictal and inter-ictal EEG activity. The patient may be subjected to provocative measures such as medication reduction, sleep deprivation, hyperventilation, or photic stimulation to increase the likelihood of capturing epileptiform activity [44]. In certain situations, invasive electrodes may be necessary to provide better localization (see below).

**2.3.5. Magnetic Resonance Imaging.** Magnetic resonance imaging (MRI) scanning has significantly aided the diagnosis and management of epilepsy, and it has been established as the key imaging modality of choice [45]. If neocortical epilepsy is suspected, imaging protocol should include a whole head thin-sectioned high-resolution 3D T1- and T2-weighted images as well as a gradient echo T2 sequence to investigate the presence of blood products. Gadolinium administration is not necessary unless a mass lesion or tumour is found. If mTLE is suspected, high-resolution coronal T1, T2 and fluid-attenuated inversion recovery (FLAIR) sequences through the hippocampus should be obtained, preferably with a 3 Tesla scanner [46]. HS is identified through volume acquisition T1-weighted MR images along with FLAIR sequences [45]. T2-weighted imaging can identify increased T2 signal in the mesial temporal lobe and atrophy of the hippocampus, both key features of MTS [47, 48]. The presence of hippocampal atrophy on preoperative MRI has been associated with good seizure outcomes following temporal lobectomy (TLY) [20]. Thus, MR imaging allows for the identification of the postulated epileptogenic lesion, which can be used in parallel with other diagnostic modalities to help localize the epileptogenic zone.

**2.3.6. Neuropsychological Assessment.** A comprehensive neuropsychological evaluation can identify preoperative functional deficits and predict postoperative neuropsychological outcomes [49]. The most important cognitive domains to be tested in TLE are memory and language [49]. Patients with dominant lobe TLE typically display verbal memory deficits, whereas those with nondominant TLE display visuospatial memory deficits. Word-finding difficulties (a neocortical function) are also common in patients with language dominant TLE [50, 51].

Memory decline is the most common deficit following TLE surgery. The relationship between verbal memory decline following left sided surgery is more robust compared to the relationship between visuospatial memory decline following right-sided surgery [52–54]. Patients with average or above average memory and language function are at a higher risk for developing postoperative deficits [55, 56]; therefore, a comprehensive preoperative discussion is necessary with such patients before offering surgical management. Conversely those individuals with histologically proven MTS are least likely to show significant memory decline postoperatively [57].

**2.3.7. Wada Test.** The Wada test has been traditionally used to assess language and memory function of the two cerebral hemispheres independently [58, 59]. The agent most commonly used is amobarbital, but other agents such as methohexital, propofol, and etomidate have also been used [60, 61]. Recently amobarbital has become unavailable in some countries. Cerebral angiography is used to assess the vasculature and extent of cross-over flow to contralateral arteries. Baseline memory function is typically assessed a day before the actual test. Prior to injection of the intra-arterial anesthetic agent, the patient is asked to elevate both arms (to monitor the development of contralateral hemiplegia as a surrogate for adequate anesthesia) and count out loud. Language and memory are assessed while hemiplegia persists. Efforts are made to evaluate the side harboring the postulated epileptogenic zone first; the contralateral hemisphere is usually tested 30 minutes after the initial injection although some centers choose a one-day delay.

Global aphasia develops upon the injection of the dominant hemisphere. The duration of speech arrest can also be used to identify the language-dominant hemisphere. However, some suggest that if the difference in time to development of speech arrest is less than 30 seconds among the two hemispheres, the patient may have bilateral cortical language representation. Other parameters such as dysarthria and paraphasias may also be used to assess language dominance. Recent studies suggest that language lateralization is a continuum between both hemispheres, and that language unilaterality may be secondary to a lesion in the contralateral hemisphere [62].

For memory evaluation, the patient is required to correctly identify items shown during hemiparesis. An overall passing score is assigned based on the ability of the contralateral side in supporting memory upon injection of the side ipsilateral to the epileptogenic focus. Scores ranging from 50 to 67% have been deemed as a pass [63, 64]. While there is no gold standard to compare the Wada test results to, a passing score has been associated with a decreased likelihood of postoperative amnesia [2]. Based on the same premise, the Wada test can also be used to lateralize the epileptogenic zone in TLE patients. Injection of the side contralateral to the seizure focus would be expected to result in a greater loss of memory function with the correlation being stronger if profound amnesia is observed.

Despite the high accuracy of the Wada test in lateralizing language and memory function, this test is associated with

false negatives and false positives [65]. These have important clinical implications. For example, some patients may be deemed unsuitable surgical candidates when in fact they would benefit from surgery. Also, less hippocampal resection may be performed resulting in poorer seizure control postoperatively [57].

The Wada test results can be affected by a variety of factors such as drug dose, unblinding of test assessors, and patient cooperation. Furthermore, the Wada test is associated with risks such as seizures, contrast allergy, catheter site hematoma, dissection, stroke, and infection [66, 67]. The risk of arterial dissection or stroke is estimated at 1% [68]. As a result many centers selectively use the WADA test [68] for certain clinical situations only, for example, a nonconcordant neuropsychological profile (memory deficit contralateral to the site of MTS) or patients who have bilateral memory deficits. Others restrict its use to left-handed individuals or those with ictal/postictal aphasia [69].

**2.3.8. Invasive EEG Monitoring.** Scalp EEGs are unable to lateralize the epileptogenic side in up to one-third of patients with TLE [70]. Even in cases where noninvasive tests are lateralizing, up to 10% could be falsely localizing [71]. In addition, synchronous activity across a cortical region of at least 6 cm<sup>2</sup> is necessary for detection of an abnormality on scalp EEG [72]. Thus the indications for invasive recordings that stem from the limitations of scalp recordings include discordance amongst the various preoperative tests, seemingly multifocal epilepsy which includes bitemporal epilepsy, MRI-negative TLE that requires discrimination between nTLE and mTLE and as well to determine the extent of resection [73], situations where scalp recorded fields exceed the spatial involvement that would be expected in either lesional epilepsy or MTS, and proximity of neocortical lesions to eloquence are amongst the most common indication, but this by no means represents an exhaustive list. In patients with scalp EEG suggestive of bitemporal abnormalities, depth electrodes can be placed bilaterally within the mesial temporal lobe structures to lateralize the seizure focus. Certain TLE patients can present with dual pathology wherein it is unclear whether the hippocampus alone, the extra-hippocampal pathology, or a combination of the two is the epileptogenic lesion [31]. If the analysis shows concordant localization, then removal of both lesions results in the highest likelihood of seizure freedom postoperatively [32]. In certain situations, such as tuberous sclerosis, cortical dysplasia, or head trauma, invasive EEG may be necessary as the epileptogenic zone may extend beyond the visible lesion [74, 75]. Seizures that do not present with classic mesial temporal IEDs attributed to mTLE are likely to be of neocortical origin. If there is concern regarding proximity to eloquent cortex, subdural or depth electrodes can be used to better map the epileptogenic and functional areas, thus identifying a safe resection margin for the patient [76].

With invasive recordings, the characteristic ictal EEG pattern of mTLE includes periodic spiking activity from the hippocampus followed by episodes of high-voltage rhythms, which can last up to one minute. Subsequently, a regular 5–9 Hz rhythm is commonly observed [77]. In nTLE, ictal

rhythms show high variability but a low voltage, high frequency discharge is commonly observed. Sharp waves of low frequency are also highly specific for seizures of a neocortical origin [69]. Patients with focal cortical dysplasia may demonstrate well-localized fast rhythms or repetitive fast spikes.

Upon the completion of scalp/invasive EEG video monitoring, some patients will have epilepsy that not amenable to surgery. This can be attributed to a myriad of causes including psychogenic nonepileptic seizures (PNESs), multifocal epilepsy, patients having a generalized seizure disorder, or the inability to accurately localize the ictal focus. However, almost half of the patients that flow through an adult EMU will have a distinctively identifiable symptomatogenic zone or will warrant intracranial recordings to determine surgical candidacy.

Furthermore, as deep seated or even certain superficial epileptiform activities may be missed by scalp EEG due to the filtering effect of the skull on higher frequency signals [78], intracranial recordings and in particular depth electrodes are of utility in recording from these electrographically *occult* lesions. While “ripples” (100–200 Hz) are associated with normal hippocampal electrical activity, *fast ripples* (150–500 Hz frequency) have a high likelihood of being associated with the ictal onset zone in the epileptogenic hippocampus and parahippocampal regions in patients with MTS [79–81]. While “fast ripple” detection holds great potential for the identification of the epileptogenic zone, its testing is invasive and is therefore restricted to seizure patterns originating from the hippocampus and hence less applicable to nTLE [81].

Although in extratemporal epilepsy detection of residual interictal epileptiform activity at the margins of resection can assist in deciding whether further resection is necessary, this approach appears to have little utility in the temporal lobe [27]. Disadvantages of intraoperative electrode recordings include the additional cost of equipment and extra operating room time, the need for an experienced neurophysiologist, and the rare occurrence of ictal recordings. Furthermore, with improvements in preoperative invasive monitoring, the need for intra-operative monitoring has decreased. Even though the use of invasive recording in general has diminished over time, it is nonetheless a valuable tool in select cases. Regardless, before embarking on invasive monitoring, the clinical question must be clear and the answer derived from the test should aid in the surgical evaluation of the patient.

**2.4. Ancillary Testing.** In situations where the standard presurgical assessment does not provide definitive seizure lateralization and/or localization (e.g., when the seizure focus appears to be bilateral, temporal, and extratemporal, mTLE with a larger field of activity than would otherwise be expected from standard mTLE), or there is discrepancy between the presurgical tests, the following ancillary investigations can be performed.

**2.4.1. Positron Emission Tomography.** Positron emission tomography (PET) is an imaging modality that uses radioactive isotopes linked to metabolically active molecules (such

as glucose) to analyze functionality in various regions of the body depending on metabolic activity. The nuclei of these tracers emit positrons which generate photons upon collision with electrons in the surrounding environment. The concentration of radioactive glucose, and hence amount of photon emission, within a region depends on the relative metabolic activity. Hypometabolism is not correlated with the amount of cell loss or hippocampal atrophy. In the investigation of TLE, this test seeks to identify the region of interictal hypometabolism which is slightly larger than the ictal onset zone. Occasionally in TLE, hypometabolism can be detected in regions other than the temporal lobe. This may reflect the extratemporal connections of the seizure focus [82].

Although obtaining a truly ictal PET study is rare, it can be valuable in identifying the seizure focus, by demonstrating a marked area of hypermetabolism [45, 83]. Accordingly, EEG recording during PET acquisition is important to ensure hypometabolism detected in one hemisphere is not secondary to an active seizure on the contralateral side resulting in hypermetabolism [84].

Fluorodeoxyglucose (FDG) is the most commonly used isotope in PET. The inter-ictal FDG-PET has a high specificity for mTLE (MTS is associated with hypometabolism localized to the hippocampus, amygdala, entorhinal cortex, and temporal pole) [20, 85]. In addition, hypometabolic regions identified by FDG-PET correlate well with predicted lateralization when compared to depth electrodes [86]. The sensitivity of the test is increased when the metabolic activity of both temporal lobes is sampled to quantify hypometabolism on one side in relation to the other.

PET is generally utilized in the evaluation of symptomatic (formerly referred to as cryptogenic) cases and for identifying seizure-spread patterns, thus guiding the placement of intracranial electrodes. If PET and MRI are concordant, there is prognostic utility as better seizure outcomes are predicted following surgery. However, PET does not usually provide any additional information if MTS is demonstrated on MRI [87, 88]. Therefore, it is not commonly used at all centers for presurgical evaluation.

**2.4.2. Single Photon Emission Computed Tomography.** Cerebral blood flow is increased within regions of the brain undergoing epileptic seizures to match the increased metabolic demand. Single photon emission computed tomography (SPECT) measures local cerebral perfusion using either technetium-99m hexamethyl propylene amine oxime or technetium-99m bicisate. These can be maximally extracted into the neurons within seconds of injection and remain within the cell for several hours [89]. Therefore, injection of radiotracers immediately following a seizure can help identify the ictal onset zone. The sensitivity of this test is increased further if inter-ictal SPECT studies are used for comparison to determine the relative change in cerebral perfusion during seizures. SPECT can be used as an important adjunct for localization of seizure onset, particularly in MRI-normal cases or when EEG is non-localizing [90]. While the spatial and temporal resolutions

of SPECT are not as high as PET, it is less costly and more widely available.

When independent seizure foci reside in the temporal lobes bilaterally, ictal SPECT studies must be interpreted with caution. Furthermore, SPECT may provide falsely lateralizing information if the epileptiform activity has terminated in the temporal lobe of origin but is ongoing in the contralateral temporal lobe. In certain cases of nTLE, the regional cerebral blood flow cannot be accurately identified by inter-ictal SPECT; therefore, SPECT is overall less sensitive for nTLE. Currently, SPECT imaging can only be used to provide information that is complementary to EEG. However, modifications to the SPECT analysis (as discussed below) can increase its utility in identifying the ictal zone.

**2.4.3. Subtraction Ictal SPECT Correlated to MRI.** With a higher accuracy than SPECT, subtraction ictal SPECT correlated to MRI (SISCOM) is another imaging modality that can be used to localize the epileptogenic zone, especially for those with nonlesional MRI or extensive focal cortical dysplasia [91]. In SISCOM, normalized coregistered inter-ictal SPECT images are subtracted from ictal images, and the resultant difference in cerebral blood flow (only those with intensities greater than 2 standard deviations above zero) is matched to high-resolution corresponding MR images to identify the epileptogenic zone [89]. Spiral CT images of implanted subdural electrodes can also be coregistered with SISCOM images to correlate changes in cerebral perfusion with the ictal onset zone [92]. SISCOM can also be used to guide intracranial EEG electrode placement [92]. Concordance of SISCOM with other preoperative studies identifying the epileptogenic focus may have prognostic value in postoperative seizure outcomes [91].

To improve the diagnostic yield of SISCOM, injection of radiotracers should be performed within 45 seconds of seizure onset and ideally the seizure lasting greater than 5–10 seconds [93]. Furthermore, for accurate correlation to the epileptogenic zone, continuous EEG (cEEG) recordings are required. In addition, the cost of the radioisotopes is relatively high as well. Therefore, despite SISCOM's clinical utility, its use is limited to certain comprehensive epilepsy centers.

**2.4.4. Magnetoencephalography.** The neurophysiologic process that generates the magnetoencephalogram (MEG) signal is identical as to what produces the EEG [94]. The fluctuation of the dendritic membrane potential is observed as a current dipole perpendicular to the cortical surface [95]. A certain volume of excitable cortex is required to generate a "brain wave" which is detected by MEG or EEG. MEG spike localization does not necessarily identify the epileptogenic zone or seizure onset zone. However, it does detect inter-ictal epileptiform discharges (IEDs) generated within the neocortex [96, 97].

The current indication for MEG in TLE is unknown, and its potential advantage must be weighed against the high cost and limited availability. In a retrospective study, it was found that MEG utilized in the presurgical evaluation did not provide any additional information in over half of the

patients [98]. Its utility in mTLE is suspect given its inability to detect deep sources and in particular hippocampally generated IEDs [99, 100]. Its benefit is likely larger in neocortical epilepsy or in those with equivocal findings following other testing modalities [98, 101]. Its greatest utility is perhaps in non-lesional TLE cases where a strong correlation has been established between MEG spike patterns and the seizure onset zone [102]. MEG may at the very least provide more support for the recommended treatment strategy, whether for or against surgery. The main advantage of MEG over scalp EEG is its improved accuracy in spike source localization. Although it must be borne in mind that MEG provides complimentary information to EEG, the sources that generate MEG signals are thought to arise from the sulci, whereas those generating the EEG signals arise from the crowns of the gyri [100]. As well, it can also be superimposed on other functional imaging modalities and guide surgical resections as part of the neuronavigational system [103, 104].

**2.4.5. Magnetic Resonance Spectroscopy.** N-Acetylaspartate (NAA) is primarily found in neurons, and its decrease is often indicative of neuronal loss or dysfunction. In contrast, creatinine (Cr) and choline (Cho) are present at higher concentrations within glial cells. By studying the levels of NAA, Cr, and Cho,  $^1\text{H}$  magnetic resonance spectroscopy (MRS) can also be helpful in localizing the epileptogenic zone. A decrease in the ratio of NAA to Cr + Cho has been suggested to be correlated with HS with correct seizure lateralization in greater than 90% of cases [105]. A proportion of patients may demonstrate bilateral metabolic abnormalities with  $^1\text{H}$  MRS; this may correlate with a higher likelihood of surgical failure [73].  $^1\text{H}$  MRS can aid in the placement of intracranial grid and strip electrodes as well [73]. However, due to its technical challenges and lack of widespread availability, this tool has yet to be established in the presurgical evaluation of epilepsy although it may have an expanded utility in the future [106].

**2.4.6. Functional MRI.** Functional MRI (fMRI) studies neural activity by measurement of alteration in the MRI signal due to changes in oxygenation levels (an increase in T2 signal is observed during epileptiform activity) [107]. The main indications for this imaging modality are for the identification of eloquent cortical regions such as motor and language areas. In addition, when coupled with EEG analysis, it can also be used to help identify the irritative zone and potentially the ictal onset zone [108]. Significant improvements in EEG-fMRI analysis (e.g., MRI-compatible EEG electrodes, higher strength magnets, and offline signal processing using mathematical tools) [109] have increased the application of this imaging modality in the evaluation of patients with epilepsy. Amongst its many advantages, fMRI has a spatial resolution of a few millimeters and it is a noninvasive alternative for the Wada test for language lateralization and localization of cortical speech regions [110]. Increased signal activation on fMRI during memory and language tasks on the side ipsilateral to the ictal focus has been suggested to be associated with greater deficits

post resection [111, 112]. This correlation may be an even stronger predictor than neuropsychological testing [112]. While fMRI is a sensitive tool for the evaluation of the irritative zone, its sensitivity to patient motion, including changes in patients' cardiac and respiratory parameters, makes it difficult to fully evaluate the ictal onset zone. However, the development of specific algorithms to adjust for these artifacts may allow fMRI to become a standard component of the presurgical evaluation.

### 3. Surgical Strategy

**3.1. Extent of Lateral Resection.** The extent of lateral resection is variable and commonly dependent on strategies to avoid postoperative language deficits and whether or not the patient has mTLE or nTLE.

**3.1.1. mTLE.** One approach to mTLE is to resect a predetermined amount of neocortex according to language dominance: 4.5 cm and 5 cm along the Sylvian fissure in the dominant and nondominant sides, respectively [113, 114]. Resections beyond this length may be associated with postoperative aphasia in the dominant hemisphere. In the dominant hemisphere, others spare a greater amount of superior temporal gyrus (STG) with a minimal resection combined with a 4.5 cm resection of the middle temporal gyrus (MTG) [115]. An even more conservative approach is to spare the entire STG and only resect 3.5 cm of the MTG [116]. Alternatively, the lateral resection can be tailored based on stimulation mapping of the essential language sites and avoiding resections within 2 cm of these sites [117].

The most conservative approach to the resection of the mesial structures can be accomplished by various *selective* approaches through a transcortical-transventricular [118] or a transsylvian approach [119]. The selective approach was based on a concept from Hughlings Jackson's description of an uncus lesion causing psychomotor seizures and the role of the mesial temporal lobe in epilepsy [58]. Subsequent experiments provided evidence that these structures play an important role in mTLE [120, 121]. This generated surgical interest in attempting to achieve the best results for seizure outcomes while sparing resection of brain tissue that is not believed to be involved in the generation of seizures. In theory, this approach is thought by some authors to have neuropsychological advantages compared to a more aggressive neocortical resection [122].

**3.1.2. nTLE.** The amount of neocortex to be resected in nTLE should include the epileptogenic zone as determined by preoperative testing and possibly intra-operative ECOG which seeks to identify the irritative zone through recording pre-resection IEDs. In the dominant hemisphere, the extent of posterior resection is limited by language areas. Complete removal of a radiographically identified lesion usually results in cessation of seizures when lesions are well circumscribed (e.g., benign tumors or cavernous hemangiomas) [123, 124]. However, in lesions with ill-defined borders such as cortical dysplasia and posttraumatic gliosis, the likelihood of operative success is lower as microscopic damage surrounding the visible boundaries of the lesion may be present [125].

**3.2. Extent of Mesial Resection.** Since the introduction of the en bloc ATL and the subsequent advent of selective procedures, there is much debate regarding the identity of the critical structures that should be removed to achieve seizure freedom in a temporal resection.

**3.2.1. Hippocampal Resection.** The general consensus is that the hippocampus should be included in resective procedures for TLE; however, the degree of hippocampal resection is controversial. Wyler et al.'s randomized trial demonstrated that patients that underwent a total hippocampectomy (extending to the superior colliculus) were more likely to be seizure free at 1-year followup compared to patients that underwent a partial hippocampectomy (extending to the lateral edge of the cerebral peduncle) [57]. Undergoing a partial hippocampectomy is controversial especially if the epileptogenic zone has been localized to the hippocampus. In addition, a partial resection of the hippocampus will result in its deafferentation from the entorhinal cortex and thus render it ineffective for memory storage and recall. Therefore, a partial resection is not an effective strategy.

**3.2.2. Parahippocampal Resection.** The parahippocampal gyrus (PHG) is generally removed along with the hippocampus. There is evidence from depth electrode studies to suggest that epileptiform activity originating from the PHG and amygdala is more likely to manifest clinically than activity from the hippocampus [126]. Furthermore, a retrospective study by YaSargil et al. had demonstrated that the volume of PHG resected had a greater impact on seizure outcome than the volume of any other mesial temporal lobe structure [119].

**3.2.3. Amygdalar Resection.** The amygdala has intricate connections with both limbic and neocortical structures and a great propensity to generate seizures as demonstrated following kindling experiments [127]. The combination of focal epileptic discharges from the periamygdaloid region and stimulation mapping able to reproduce automatisms and amnesia in this region indicated the importance of including the amygdala in TLE resections [128, 129]. Interestingly, some studies suggest that amygdalar sclerosis may in fact occur in isolation from the hippocampus [130].

**3.3. Risks Associated with Surgery for TLE.** Despite the potential to achieve excellent seizure control, TLE surgery is associated with several risks specific to the procedure: motor, visual field, cranial nerve, language, memory, cognitive, and psychiatric deficits. The cumulative morbidity for TLE surgery, not considering adverse psychiatric outcomes, is approximately 11% with permanent deficits in approximately 3% [24, 131].

**3.3.1. Motor Deficits.** Contralateral hemiplegia is a well-described complication of TLE surgery. It is thought to result due to manipulation of the anterior choroidal artery with subsequent infarction of the posterior limb of the internal capsule. This is estimated to occur in 2% of the cases with

the majority of patients improving over the course of several months to a year [132, 133].

**3.3.2. Cranial Nerve Deficit.** Cranial nerve morbidity is mainly associated with the oculomotor (CNIII) and the trochlear (CNIV) nerves. The oculomotor nerve traverses the ambient cistern bordering the medial aspect of the temporal lobe on route to the cavernous sinus. The trochlear nerve travels lateral to the cerebral peduncles and between the posterior cerebral and superior cerebellar arteries lateral to the oculomotor nerve prior to entering the cavernous sinus. Cranial nerve injury occurs most commonly due to traction, is estimated at 1.5–3%, and is usually transient [132, 134].

**3.3.3. Visual Field Deficits.** The most common visual field deficit following TLE is a superior quadrantanopsia, resulting from damage to the optic radiations comprising the most lateral aspect of Meyer's loops as they course inferomedially. However, visual deficits can range from small triangular defects to a complete homonymous hemianopsia. A more extensive hemianopsia has been attributed to a greater amount of resection as well as individual variance on the course of the optic radiations. A randomized trial of temporal lobe epilepsy surgery found quadrantic visual field defects in 55% of the patients [35]. However, in the vast majority of cases, this is diagnosed on formal visual field testing and the patient is unaware of this deficit [35]. A selective surgical approach does not appear to offer an advantage [135]. Damage to the optic radiations in these cases has been attributed to suction devices and retractors being driven through the optic radiations en route to the mesial temporal lobe structures.

**3.3.4. Language Deficit.** Dominant TLE surgery is associated with a language risk due to the close proximity of Broca's and Wernicke's area localized to the inferior frontal gyrus and the posterior STG, respectively. However, the most common language deficit is a transient anomia [136, 137]. Some surgeons routinely perform a tailored resection by conducting intra-operative language mapping and/or avoid resection of the STG, while others argue that this does not provide a benefit [136]. In a large multicenter study comparing a tailored resection utilizing intra-operative mapping, tailored resection without intra-operative mapping, a standard approach sparing the STG, and a standard approach not sparing the STG, a similar decline in visual confrontational naming as assessed by the Boston Naming Test (BNT) was observed in all groups with no differences between groups [138]. Although there is variability between centers, most do not perform tailored resections according to language mapping, and they routinely spare the STG except the first centimeter or so [116]. A multicenter trial demonstrated that early age of seizure onset was a protective factor for postoperative anomia, perhaps due to the early collateralization of language [139].

**3.3.5. Memory Deficit.** While the Wada test is an important adjunct that assesses the ability of the contralateral hemisphere in supporting memory function, carefully selected

patients may still suffer significant memory deficits following TLE surgery. The lateral neocortical temporal lobe is associated with naming and short-term working memory while the mesial temporal lobe is implicated in long-term consolidation of memory and retrieval [140]. In individuals with typical language dominance, visuospatial and verbal memory is commonly associated with the right and left hippocampi, respectively [141]. High ipsilateral memory function and lack of radiographic features of MTS on preoperative MRI are associated with a greater degree of postoperative memory decline. Patients with contralateral hippocampal dysfunction are generally not candidates for an ipsilateral mesial temporal lobe resection as bilateral hippocampal lesions can result in a severe anterograde amnesia [140, 142].

**3.3.6. Psychiatric Risks.** TLE has been associated with a high risk (almost 50%) of depression [143]. In particular, a preoperative history of depression is a strong predictor of postoperative depression [143]. In addition, suicide rates are 5 times greater than the general population. While most patients improve following surgery as a result of greater seizure control and increased independence, others are at risk of developing further psychiatric illnesses. In a cohort of 28 patients undergoing ATL, impairments of facial recognition of expression of fear, anger, disgust, and sadness were identified [144]. Although rare, some patients may develop a psychotic-type illness similar to schizophrenia [145]. Therefore, there must be a low threshold to refer a patient for psychiatric assessment.

## 4. Case Examples

**4.1. Typical MTS.** Ms. A is a 34-year-old, right-hand-dominant female who presented with her first convulsive seizure at the age of 27 years although a detailed past history suggested that she may have been suffering from brief partial seizures without loss of awareness for many years prior to that. These seizures were confirmed on EEG. Initial drug therapy, with 400 mg per day of carbamazepine, maintained her seizure free for 7 years until she presented again with a generalized tonic-clonic seizure (GTCS) during sleep. Subsequently her dose was increased to 800 mg per day, but this did not fully prevent the GTCSs. Also, she had been suffering from simple partial seizures as well as up to 7 CPSs per month. She described auras of nausea and a “funny feeling” up her spine. She also felt that she tried to remember something that had not happened. This would then tend to be followed by a blank stare and lip smacking. From a neuropsychological point of view, she complained of blunted emotions and poor memory.

Ms. A was admitted to the EMU where 7 seizures from the right temporal lobe, all with maximal onset over the anterior/mid and basolateral structures were detected. One of the seizures secondarily generalized towards the end of this event ictal discharges was recorded over the left posterior temporal structures. MRI demonstrated sclerosis of the right mesial temporal lobe (Figure 1). Neuropsychological testing demonstrated deficits in non-verbal memory. Given that all

testing was concordant with a right mTLE, a right selective amygdalohippocampectomy was recommended. The procedure was carried out without complications. At 6-month postoperative followup, Ms. A was free of seizures including auras. She had been maintained on her preoperative medications. She noted significant improvement of memory and concentration.

**4.2. MRI Normal nTLE.** Mr. B is a 28-year-old, right-hand dominant who was first seen at the age of 22 for evaluation of a long-standing seizure disorder. He had been suffering from complex partial seizures from the age of 10, which were described as periods of disorientation, twitching, lip smacking, picking at his shirt, and difficulties with speech lasting 1-2 minutes. He also described auras of epigastric discomfort and fear. He had not experienced any GTCSs seizures or secondary generalization of his seizures. Carbamazepine, valproic acid, and phenytoin had been attempted without significant benefit. Previous MRI with supplementary detailed views of the temporal lobes was normal (Figure 2). Mr. B was subsequently admitted to the EMU, with scalp EEG monitoring.

Abnormalities, concentrated in the left anterior quadrant of the head, consisted of continuous dysrhythmia with spread to the frontal regions in the form of long-lasting 4-5 Hz, monorhythmic trains of activity with abrupt onset and offset without clinical accompaniment. He demonstrated interictal slow wave activity localizing to the left mesial temporal as well as left temporal region. Furthermore, distinctive phase reversals were identified in electrodes approximating Wernicke’s area and inferior. Ictal activity always began on the left side starting anteriorly and then proceeding posteriorly. Main source imaging spikes all localized to the mesial temporal region. No inter-ictal activity was noted in the posterior temporal region.

Neuropsychological evaluation demonstrated diminished verbal functioning with a pattern most consistent with left-sided neocortical dysfunction rather than mesial temporal (verbal learning and retention were excellent). fMRI revealed left hemispheric language dominance. As a result of these investigations, the benefit of a surgical resection was unknown. He was discharged on 100 mg per day of topiramate, which also failed to decrease his seizures. Therefore, to better delineate the site of seizure onset and for functional mapping, intracranial monitoring was recommended.

A large square grid was placed at the end of the distal sylvian fissure and overlying the inferior and superior parietal lobules. Three subtemporal strip electrodes (labeled as frontal, middle, and posterior temporal) were also placed. Subsequent monitoring in the EMU demonstrated the middle temporal subdural strip electrode to be most epileptogenic. MRI correlated these leads to the left inferior temporal and fusiform gyri.

Surgical resection, guided by ECOG and language mapping, was performed. The mesial temporal structures were spared to avoid memory deficits. Pathological examination revealed mild cortical and subcortical gliosis. Postoperatively, he experienced a few very brief auras (similar to ones

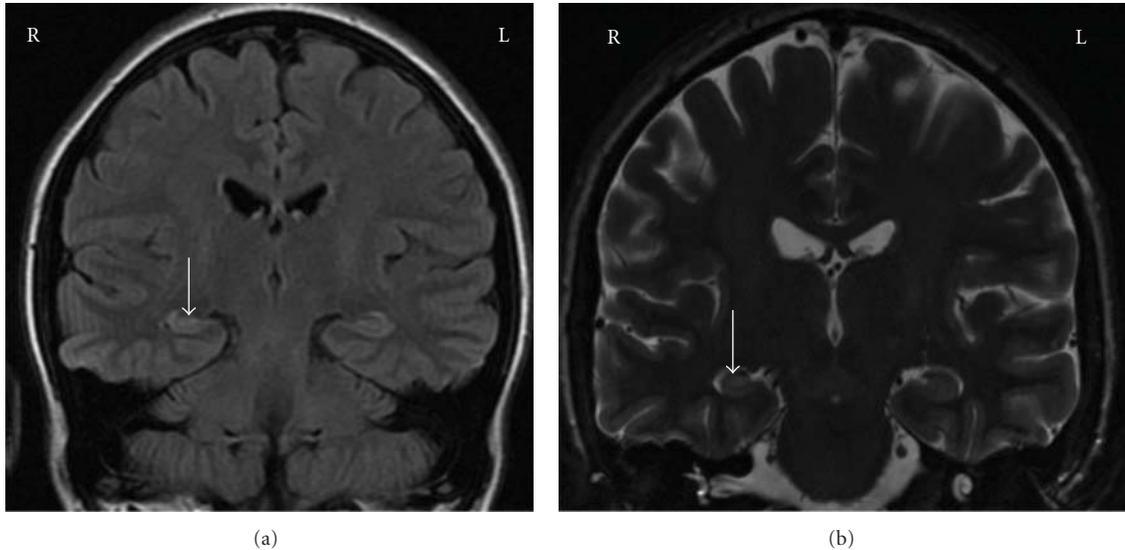


FIGURE 1: Ms. A—FLAIR and T2-weighted MR demonstrating right MTS as can be identified based on the loss of architecture and high signal of flair images.

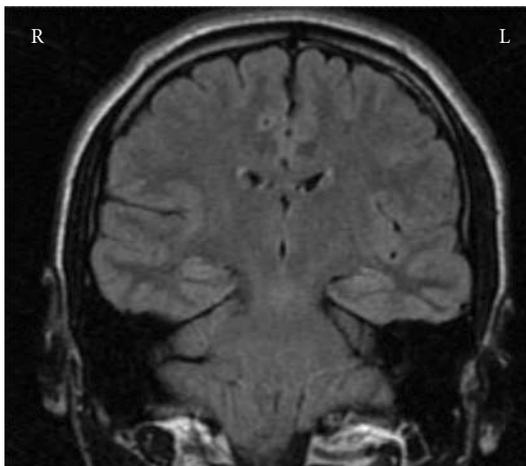


FIGURE 2: Mr. B—normal MR.

experienced in the past) but no progression to CPSs. He also complained of poor memory and reading ability, but spoken language was intact. He was maintained on 400 mg per day of topiramate. At 2 years postoperative followup, Mr. B was seizure free although he did complain of intermittent sensations of his typical aura. He also complained of mild word finding difficulties which did not interfere with daily life. He maintained a full-time job without any difficulties.

**4.3. Dual Pathology.** Mr. C is a 34-year-old, left-hand-dominant man who started having seizures at 25 years of age. His family described his episodes as starting with a few minutes of increased rate and volume of speech followed by fatigue, slowed speech, and occasional automatisms. Postictally, he would fall asleep and rarely remember these episodes. Seizures occurred approximately twice a week. He presented to the hospital following his first episode of a GTCS.

EMU studies at a peripheral hospital had been able to record eight seizures of similar clinical semiology. Two were electrographically of left temporal origin while the remaining six were poorly lateralized, appearing bi-hemispheric and perhaps even right hemispheric predominancy at onset followed by rhythmic activity localized to the left temporal head regions within 3-4 seconds. An ictal SPECT scan during one of these episodes demonstrated left temporal activation. MRI at that point had been interpreted as normal. Conservative medical management with trials of phenytoin, topiramate, and pregabalin was attempted without success.

For further clarification, he was monitored in the EMU at our institution where bilateral inter-ictal abnormalities from both the left anterior temporal regions as well as the right midlateral or midposterior temporal regions were demonstrated. On certain days, seizures, of a 3:1 ratio, favoring the right hemisphere was observed. He also had multiple electrographic seizures that were either poorly lateralized or not lateralized at onset. Subsequent MRI demonstrated left HS in addition to signal abnormalities in the inferior right temporal region as well, likely representing cortical dysplasia (Figure 3). Neuropsychological testing suggested a full-scale IQ of 119 with only a slight relative weakness in verbal memory; otherwise, the tests were nonlateralizing. At this point, he had worsening depression, loss of motivation, and problems with short-term memory and concentration, all contributing to him quitting his graduate degree. To better delineate the epileptogenic focus/foci, anterior and posterior temporal strip electrodes, subtemporal strip electrodes, along with hippocampal depth electrodes, were placed bilaterally for EMU monitoring.

During this stay, many CPSs, all stereotypically involving the right temporal mesial and neocortical structures before spreading to involve the left temporal mesial and neocortical structures, were noted. The exact localization within the right temporal lobe was not clear given that the first electrographic changes were subtle and comprising

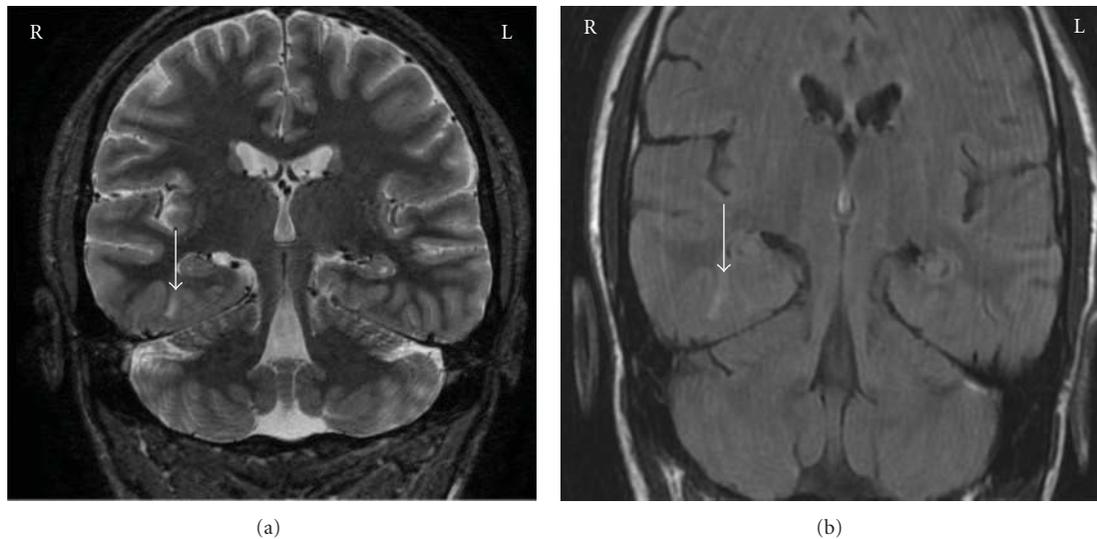


FIGURE 3: Mr. C—T2-weighted and FSTIR sequence MR demonstrating a right inferior temporal lobe lesion in addition to left MTS.

of an attenuation of background activity over the right hippocampal depth and RMT electrode contacts. Occasional low-amplitude 20 Hz rhythms at right hippocampal depth electrode 2 prior to subsequent spread were also detected. Left temporal spiking, occurring more frequently than right temporal spiking, raised the concern regarding the role of the left temporal lobe being involved; however, brief ictal rhythmic discharges appeared solely from the right temporal lobe structures which correlated well with the patient's clinically relevant seizures. Given that the seizures were primarily right-sided but that he also demonstrated left-sided HS, a WADA test was performed which showed left-sided memory dominance. He has been scheduled for a right TLY.

## 5. Conclusion

Once a patient has been deemed medically refractory, the main requirement to determine surgical candidacy is the ability to accurately localize the epileptogenic zone [146]. There are tools in the armamentarium of the epilepsy team to help localize the epileptogenic zone and ensure that resection can be done in a safe manner to minimize any neurologic deficit. All ancillary testing is not employed simultaneously; rather they are tailored to the anatomical, electrical, and clinical features of each patient [147]. The best patients for surgical resection are those with concordance in localization of their seizures electrographically, radiographically, and semiologically.

TLE is the most common epilepsy syndrome that is responsive to surgical treatment. Although various pathologies can give rise to TLE including cortical dysplasia, tumours, and vascular malformations, HS remains the most common entity. Surgical patient selection is made after a thorough discussion of each case in a multidisciplinary conference including epileptologists, epilepsy surgeons, neuro-radiologists, neuropsychologists, clinical psychologists, EEG

technologists, and nurses. In the appropriately selected patients, seizure freedom can be achieved with no or manageable neurological deficits following surgery.

## Authors' Contribution

A. Mansouri and A. Fallah should be considered co-first authors as they equally contributed to preparing the first draft of the paper. A. Fallah was responsible for several revisions of the paper. T. A. Valiante was responsible for the final editing of the paper.

## Disclosure

There are no sources of support for this paper. It has not been published or presented in any form.

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## Review Article

# Genetics of Temporal Lobe Epilepsy: A Review

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Received 27 June 2011; Revised 6 November 2011; Accepted 7 December 2011

Academic Editor: Seyed M. Mirsattari

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Temporal lobe epilepsy (TLE) is usually regarded as a polygenic and complex disorder. To understand its genetic component, numerous linkage analyses of familial forms and association studies of cases versus controls have been conducted since the middle of the nineties. The present paper lists genetic findings for TLE from the initial segregation analysis to the most recent results published in May 2011. To date, no genes have been clearly related to TLE despite many efforts to do so. However, it is vital to continue replication studies and collaborative attempts to find significant results and thus determine which gene variant combination plays a definitive role in the aetiology of TLE.

## 1. Introduction

Temporal lobe of epilepsy (TLE) is known to be the most common form of partial epilepsy and accounts for 60% of seizures [1]. Depending on the seizure origin, TLE should be subdivided into mesial, lateral, and neocortical. Partial epilepsies are often associated with antecedent of brain injury, such as head trauma, stroke, or infection, and are therefore classified as “symptomatic” [1]. The term “cryptogenic” is related to syndromes where there is insufficient evidence to assign a specific aetiology, whereas “idiopathic” partial epilepsy is associated with a putative genetic origin [1]. Family studies have shown that relatives of patients with epilepsy are at higher risk of suffering from seizures compared to relatives of controls [2, 3]. Moreover, relatives of patients with focal temporal EEG abnormalities have generally been found to have higher risks of EEG abnormalities which seem to be caused by an autosomal dominant gene [4]. Therefore, various susceptibility genes and environmental factors are believed to be involved in the aetiology of TLE, which is considered to be a heterogeneous, polygenic, and complex disorder. However, few families with a monogenic type of TLE [5] have been reported. To date, only a few chromosomal localisations and genes have been involved in TLE.

## 2. Methods

In the present paper, PubMed (<http://www.ncbi.nlm.nih.gov/sites/entrez>) was used as a search engine with no language restrictions from its creation to May 15, 2011. Searching strategy was for linkage analysis (“epilepsy, temporal lobe” [MeSH Terms] OR (“epilepsy” [All Fields] AND “temporal” [All Fields] AND “lobe” [All Fields]) OR “temporal lobe epilepsy” [All Fields] OR (“temporal” [All Fields] AND “lobe” [All Fields] AND “epilepsy” [All Fields])) AND (“genetic linkage” [MeSH Terms] OR (“genetic” [All Fields] AND “linkage” [All Fields]) OR “genetic linkage” [All Fields]) and for association studies (“epilepsy, temporal lobe” [MeSH Terms] OR (“epilepsy” [All Fields] AND “temporal” [All Fields] AND “lobe” [All Fields]) OR “temporal lobe epilepsy” [All Fields] OR (“temporal” [All Fields] AND “lobe” [All Fields] AND “epilepsy” [All Fields])) AND (“association” [MeSH Terms] OR “association” [All Fields]) AND (“clinical trials as topic” [MeSH Terms] OR (“clinical” [All Fields] AND “trials” [All Fields] AND “topic” [All Fields]) OR “clinical trials as topic” [All Fields] OR “study” [All Fields] OR “biomedical research” [MeSH Terms] OR (“biomedical” [All Fields] AND “research” [All Fields]) OR “biomedical research” [All Fields]). All the references cited in this paper were reviewed to identify additional works not

indexed by the database selected. Suitable studies had to be independent studies using original data which had been published in a peer-review journal.

### 3. Familial Monogenic Temporal Lobe Epilepsy

**3.1. Autosomal Dominant Lateral Temporal Epilepsy (ADLTE).** The first localisation of ADLTE or autosomal dominant partial epilepsy with auditory features (ADPEAF) was established on chromosome 10q by linkage analysis in a three-generation family with 11 affected individuals. This family showed an autosomal dominant segregation of the phenotype with reduced penetrance [6]. Subsequent families with similar clinical descriptions were linked to the same chromosomal region [7, 8]. This locus was also linked to ADPEAF in 5 other families [9, 10]. This well-established chromosome 10q24 locus contains leucine-rich, glioma-inactivated 1 (*LGII*) gene, which has a putative role in development [11]. Kalachikov and colleagues were the first to describe 5 *LGII* mutations in five ADLTE families with auditory features (Table 1) [11]. After these initial results, numerous different *LGII* mutations have been linked to ADLTE (Table 1). Interestingly, 50% of ADLTE families did not show any *LGII* mutations [12]. Moreover, *de novo* *LGII* mutations in unrelated sporadic TLE cases with auditory features, also called idiopathic partial epilepsy with auditory features (IPEAF) [13], account for about 2% of cases only [14]. A recent study, evaluating *LGII* promoter, *prodynorphin* (*PDYN*), and *GABA (B) receptor 1* (*GABBR1*) genes in 104 sporadic IPEAF, did not show any statistically significant differences between patients and controls [15].

**3.2. Pure Familial Mesial Temporal Lobe Epilepsy (FMTLE).** FMTLE is a benign syndrome, which is not associated with hippocampal sclerosis (HS) or febrile seizure (FS). The main symptoms are aura with prominent psychic and autonomic features and *déjà vu* and *jamais vu* [33]. This disorder shows an autosomal dominant mode of inheritance with incomplete penetrance in a three-generation Italian family with 8 affected people [34]. A few large pedigrees have been published and only one linkage has been found on chromosome 4q13.2–21.3 in a four-generation family with 12 patients [35]. To date, no mutated gene has been linked to FMTLE.

**3.3. Febrile Seizures, Hippocampal Sclerosis, and Familial Temporal Lobe Epilepsy.** Many studies have shown that FS, HS and familial TLE are closely interconnected [36–39]. MRI studies of TLE families have shown not only that hippocampal abnormalities are the consequence of repeated seizures but also that genetic mechanisms could play a significant role in their development of hippocampal damage [40]. Therefore, genetic predisposition seems to be a key causal factor for HS and for specific subsyndromes displaying FS [41–43]. The familial syndrome called genetic epilepsy with febrile seizure plus (GEFS<sup>+</sup>) [44] exemplifies these links. A large study of 9 GEFS<sup>+</sup> families showed that two of them included TLE patients [45]. Furthermore, another GEFS<sup>+</sup>

family with TLE showed a mutation in the *SCN1A* gene (Table 1) [31], initially linked to GEFS<sup>+</sup> pedigree without partial epilepsy [46]. More recently, Scheffer and colleagues reported three TLE and GEFS<sup>+</sup> families with specific mutations in the *SCN1B* gene (Table 1) [32], which was initially linked to a pure GEFS<sup>+</sup> pedigree [47]. Linkage analysis of two FS families with TLE showed evidence for digenic inheritance on chromosomes 18qter and 1q25–31 [48] and on chromosomes 3p23–24.2 and 18p [49]. A particular gypsy family from an isolated founder population was linked to chromosome 5q31.3–32. The affected individuals suffered from TLE associated with FS with mild intellectual deficit [50]. Recently, a FS family with two patients with possible benign TLE showed a putative new linkage to chromosome 17q12–14 [51]. Even though the literature reported some chromosomal localisation and gene mutations, some TLE families with FS and HS were not linked to any loci or genes [28, 52, 53]. These findings indicate that familial TLE is genetically heterogeneous.

### 4. Sporadic TLE Cases

As suggested by segregation and linkage studies, TLE could be considered to be a complex disorder. Therefore, association study has been proposed as the method of choice in understanding the genetic background of TLE in sporadic cases [54]. However, this proposal remains controversial [55] because replication studies of the first-positive association often revealed conflicting results. To date, no genes have been clearly associated with sporadic cases of TLE as presented in this paper. All association studies cited in the text below are shown in Table 2 that contains genetic variation counts and ethnicity of samples. The term of “replication study” was used only if the following study was conducted in the same group or subgroup of patients with the same ethnicity as the original one. Every study cited below assessed DNA extracted from peripheral blood.

**4.1.  $\gamma$ -Aminobutyric Acid B Receptor 1 (*GABBR1*).** *GABBR1* gene encodes one subunit of the GABA (B) receptor, and higher levels of *GABBR1* mRNA have been found in hippocampal resection of TLE patients with HS as compared to postmortem controls [88]. On this basis, Gambardella and colleagues assessed a missense mutation in exon 7 of *GABBR1*, c.1465G>A (p.Gly489Ser) in sporadic cases of TLE in Caucasians. They found a significant association, which displayed an increased level of heterozygosity in patients compared to the controls [56]. Subsequent studies did not find this initial positive result [5, 57–60], even in Chinese populations [61, 62]. Only one study yielded similar results to those obtained by Gambardella and colleagues in an Argentinean population. The authors proposed that this significant replication was given by the migration of Italian people in Argentina [63].

**4.2.  $\gamma$ -Aminobutyric Acid B Receptor 2 (*GABBR2*).** *GABBR2* gene encodes another subunit of the GABA (B) receptor. A positive association was found in the Chinese population

TABLE 1: Genomic variations linked to familial TLE.

Gene	Genomic variation	Protein alteration	Accession number	Type of TLE	Reference
<i>LGII</i>	c.1639insA	Frameshift, protein truncation	CI020606	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
<i>LGII</i>	c.611delC (835delC)	Frameshift, protein truncation	CD020573	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
<i>LGII</i>	c.136-3C>A (359-3C>A)	Intron retention, protein truncation	CM022035	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
<i>LGII</i>	c.1050-1051delCA	Frameshift, protein truncation	CD020574	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
<i>LGII</i>	c.1148A>C	p.Glu383Ala	rs28937874	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
<i>LGII</i>	c.758delC	Frameshift, protein truncation	CD021020	ADLTE/ADPEAF	Morante-Redolat et al. 2002 [16]
<i>LGII</i>	c.1420C>T	Premature stop codon, protein truncation	CM020950	ADLTE/ADPEAF	Morante-Redolat et al. 2002 [16] Bisulli et al. 2004 [13]
<i>LGII</i>	c.136T>C	p.Cys46Arg	rs104894166	ADLTE/ADPEAF	Gu et al. 2002 [17]
<i>LGII</i>	c.953T>G	p.Phe318Cys	rs28939075	ADLTE/ADPEAF	Fertig et al. 2003 [18]
<i>LGII</i>	c.598T>C	p.Cys200Arg	CM034239	ADLTE/ADPEAF	Michelucci et al. 2003 [19]
<i>LGII</i>	c.1295T>A	p.Val432Glu	CM034240	ADLTE/ADPEAF	Michelucci et al. 2003 [19]
<i>LGII</i>	Unknown	p.Leu26Arg	Unknown	ADLTE/ADPEAF	Pizzuti et al. 2003 [20]
<i>LGII</i>	c.839-2A>C	Intron retention, protein truncation	Unknown	ADLTE/ADPEAF	Kobayashi et al. 2003 [21]
<i>LGII</i>	c.124T>G	p.Cys42Gly	CM041029	ADLTE/ADPEAF	Berkovic et al. 2004 [22]
<i>LGII</i>	c.1418C>T	p.Ser473Leu	CM041033	ADLTE/ADPEAF	Berkovic et al. 2004 [22] Kawamata et al. 2010 [23]
<i>LGII</i>	c.124T>C (348T>C)	p.Cys42Arg	CM041030	ADLTE/ADPEAF	Ottman et al. 2004 [24]
<i>LGII</i>	c.893T>C	p.Ile298Thr	CM041032	ADLTE/ADPEAF	Ottman et al. 2004 [24]
<i>LGII</i>	c.329C>A	p.Ala110Asp	CD044789	ADLTE/ADPEAF	Ottman et al. 2004 [24]
<i>LGII</i>	c.329delC	Frameshift, protein truncation	CD044789	ADLTE/ADPEAF	Hedera et al. 2004 [25]
<i>LGII</i>	c.435C>G	p.Ser145Arg	CM044660	ADLTE/ADPEAF	Hedera et al. 2004 [25]
<i>LGII</i>	c.461T>C	p.Leu154Pro	CM055408	ADLTE/ADPEAF	Pisano et al. 2005 [26]
<i>LGII</i>	c.406C>T	p.Arg136Trp	rs119488099	ADLTE/ADPEAF	Michelucci et al. 2007 [14]
<i>LGII</i>	c.431+1G>A	Deletion, protein truncation	Unknown	ADLTE/ADPEAF	Chabrol et al. 2007 [27]
<i>LGII</i>	c.695T>C	p.Leu232Pro	rs104894167	ADLTE/ADPEAF	Chabrol et al. 2007 [27]
<i>LGII</i>	c.365T>A	p.Ile122Lys	rs119488100	ADLTE/ADPEAF	Striano et al. 2008 [28]
<i>LGII</i>	c.367G>A	p.Glu123Lys	Unknown	ADLTE/ADPEAF	Bonaventura et al. 2009 [29]

TABLE 1: Continued.

Gene	Genomic variation	Protein alteration	Accession number	Type of TLE	Reference
<i>LGII</i>	c.1421G>A	p.Arg474Glu	CM020950	ADLTE/ADPEAF	Kawamata et al. 2010 [23]
<i>LGII</i>	c.1219C>T	p.Arg407Cys	Unknown	ADLTE/ADPEAF	Striano et al. 2011 [30]
<i>SCN1A</i>	c.3809A>C	p.Lys1270Thr	rs121918626	TLE + GEFS <sup>+</sup>	Abou-Khalil et al. 2001 [31]
<i>SCN1B</i>	c.363C>G	p.Cys121Trp	rs104894718	TLE + GEFS <sup>+</sup>	Scheffer et al. 2007 [32]
<i>SCN1B</i>	Unknown	p.Arg85Cys	CM071081	TLE + GEFS <sup>+</sup>	Scheffer et al. 2007 [32]
<i>SCN1B</i>	Unknown	p.Arg85His	CM071082	TLE + GEFS <sup>+</sup>	Scheffer et al. 2007 [32]

for the rs967932 A-allele of *GABBR2*, which increased the risk of TLE in patients [62]. Moreover, a particular haplotype of *GABBR2* (G-C-A-C, rs3780428-rs1999501-rs967932-rs944688, resp.) occurred more frequently in cases than in controls (12.26% and 6.51%, resp.,  $P = 0.0004$ ) [62]. In addition, TLE patients with this haplotype showed an earlier onset of the disease. So far, these results have not been confirmed in other independent groups of sporadic TLE.

**4.3. Prodynorphin (*PDYN*).** *PDYN*, the precursor of the dynorphin opioid peptides, is widely expressed in the central nervous system (CNS). Its promoter showed a 68-bp tandem repeat containing one binding site per repeat for the transcription factor AP-1 [89]. Three or four repeats, named H-allele, are associated with a significant increase in gene expression, whereas one or two repeat(s), named the L-allele, cannot be stimulated over basal conditions [89]. A first association study showed that the L-allele of the variable number of tandem repeats (VNTR) of *PDYN* promoter is a risk factor for TLE in patients with a family history of seizures [64]. This result was not replicated in 4 independent studies of the Caucasian population with TLE [5, 65–68].

**4.4. Apolipoprotein E (*ApoE*).** *ApoE* is a constitutive protein of the triglyceride-rich lipoproteins, very-low-density lipoprotein, and chylomicrons and plays a role in lipoprotein metabolism [90]. *ApoE* gene encodes 3 protein isoforms:  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$ . In a first association study, the  $\epsilon 4$  isoform was not associated with an early age of onset of TLE [69], but the association was found to be statistically significant in a second study [70]. Subsequently, five other replication studies were conducted [5, 67, 71–73] and only one of them found the same association in the same direction [67]. Other subtypes of TLE were considered to be associated with the *ApoE*  $\epsilon 4$  isoform. A study evaluating the memory in cases of mild, well-controlled nonlesional TLE found that  $\epsilon 4$  carriers showed a verbal learning deficit compared to noncarriers (50% and 19%, resp.,  $P = 0.004$ ) [71]. A subsequent very similar study demonstrated that patients with medically intractable TLE and a long history of epilepsy had the poorest

memory performance if they carried the  $\epsilon 4$  allele ( $P < 0.01$ ) [91]. Two additional studies evaluated the relationship between the *ApoE*  $\epsilon 4$  allele and postictal confusion in medically intractable TLE. Results were inconsistent. Chapin and colleagues found an association (68% of  $\epsilon 4^+$  and 43% of  $\epsilon 4^-$ ,  $P = 0.04$ ) [92], whereas Kauffman and coworkers did not (30.4% of  $\epsilon 4^+$  and 46.3% of  $\epsilon 4^-$ ,  $P = 0.2$ ) [93]. A final study investigated if *ApoE*  $\epsilon 4$  allele is associated with increased risk of late onset posttraumatic seizures, early onset, refractory complex partial seizures (CPSs), and postictal confusion in a Chinese population with TLE. They found a significant association between prior trauma and  $\epsilon 4$  allele in their TLE patients only (20.7% of  $\epsilon 4^+$  and 12.1% of  $\epsilon 4^-$ ,  $P = 0.023$ ) [94].

**4.5. Interleukin 1 $\alpha$  (*IL-1 $\alpha$* ).** *IL-1 $\alpha$*  is a major proinflammatory cytokine, which is synthesized during infection and inflammatory processes [90]. A single nucleotide polymorphism (SNP) on *IL-1 $\alpha$*  5'UTR (*IL-1 $\alpha$* -889) was genotyped in some subgroups of TLE: with or without HS (TLE-HS<sup>+/−</sup>) [74] and with or without FS (TLE-FS<sup>+/−</sup>) [75]. No associations were found. A third team found three statistically positive associations. Genotype 1-1 was more frequently displayed in the TLE group and in subgroups of TLE-HS<sup>+</sup> and TLE-FS<sup>−</sup> [67].

**4.6. Interleukin 1RA (*IL-1RA*).** *IL-1RA* is an antagonist that competes for the same IL-1 receptor as for *IL-1 $\alpha$*  [74]. A VNTR on *IL-1RA* intron 2 (*IL-1RA*-int2) was associated with TLE-HS<sup>−</sup>. Allele 1 and genotype 1-1 showed lower frequencies, while allele 2 and genotypes 1-2 and 2-2 showed higher frequencies in TLE-HS<sup>−</sup> patients than in controls [67]. The primary study failed to show any association [74].

**4.7. Interleukin 1 $\beta$  (*IL-1 $\beta$* ).** *IL-1 $\beta$*  is another major proinflammatory cytokine and acts on the same IL-1 receptor as *IL-1 $\alpha$*  [74]. Two SNPs (*IL-1 $\beta$* -511 and *IL-1 $\beta$* +3953) were studied by Kanemoto and colleagues in TLE-HS<sup>+/−</sup> patients. For *IL-1 $\beta$* -511, they found a high frequency of genotype 2-2 in TLE-HS<sup>+</sup> compared to the controls [74] and confirmed their result in a larger sample [76]. This association was

TABLE 2: Genomic variations associated with sporadic TLE cases.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, n (%)	Genomic variation counts	Controls, n (%)	P value
GABBR1	c.1465G>A → p.Gly489Ser (CM031183)	Gambardella et al. 2003 [56]	Nonlesional TLE	Caucasian	n = 141	A/A = 0 (0.0) A/G = 24 (17.0) G/G = 117 (83.0)	n = 372	<0.0001
		Initial study				A/A = 0 (0.0) A/G = 2 (0.5) G/G = 370 (99.5)		
		Cavalleri et al. 2005 [5]	Nonlesional TLE	Caucasian	n = 245	A/A = 0 (0.0) A/G = 2 (1.0) G/G = 218 (99.0)	n = 1089	NS
		Replication study				A/A = 0 (0.0) A/G = 8 (1.0) G/G = 1062 (99.0)		
		Ma et al. 2005 [57]	TLE-FS <sup>+</sup>	Caucasian	n = 120	A/A = 0 (0.0) A/G = 1 (0.84) G/G = 119 (99.16)	n = 118	NS
		Replication study				A/A = 1 (0.85) A/G = 0 (0.0) G/G = 117 (99.15)		
		Salzmann et al. 2005 [58]	Nonlesional TLE	Caucasian	n = 110	A/A = (0.0) A/G = 2 (1.82) G/G = 108 (98.18)	n = 145	NS
		Replication study				A/A = (0.0) A/G = (0.0) G/G = 145 (100)		
		Tan et al. 2005 [59]	Nonlesional TLE	Caucasian	n = 234	A/A = (0.0) A/G = 1 (0.4) G/G = 233 (99.6)	n = 164	NS
		Replication study				A/A = (0.0) A/G = 1 (0.6) G/G = 163 (99.4)		
Stögmänn et al. 2006 [60]	TLE	TLE	Caucasian	n = 188	A/A = 0 (0.0) A/G = 2 (1.1) G/G = 186 (98.9)	n = 259	A/A = 0 (0.0) A/G = 0 (0.0) G/G = 259 (100)	NS
Wang et al. 2008 [62]	TLE	TLE	Chinese	n = 315	A/A = 0 (0.0) A/G = 0 (0.0) G/G = 315 (100)	n = 318	A/A = 0 (0.0) A/G = 0 (0.0) G/G = 318 (100)	NS

TABLE 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, n (%)	Genomic variation counts	Controls, n (%)	P value
<i>GABBR2</i>	G>A → intron 1 (rs967932)	Wang et al. 2008 [62] Initial study	TLE	Chinese	n = 315 A/A = 72 (22.64) A/G = 164 (51.57) G/G = 82 (25.79)	n = 318 A/A = 63 (20.0) A/G = 136 (43.17) G/G = 116 (36.83)		0.003
<i>PDYN</i>	68 bp tandem repeat → promoter H-allele = 3 or 4 repeats L-allele = 1 or 2 repeats (rs71193945)	Stögmänn et al. 2002 [64] Initial study  Gambardella et al. 2003 [65] Replication study  Tilgen et al. 2003 [66] Replication study  Cavalleri et al. 2005 [5] Replication study  Salzmann et al. 2008 [67] Replication study  Kauffman et al. 2008 [68]	Nonlesional TLE, familial risk  Nonlesional TLE, familial risk  Nonlesional TLE, familial risk  Nonlesional TLE, familial risk  Nonlesional TLE, familial risk	Caucasian  Caucasian  Caucasian  Caucasian  Argentinean	n = 43 L/L = 10 (23.3) L/H = 23 (53.5) H/H = 10 (23.3)  n = 115 L/L = 9 (7.8) L/H = 40 (34.8) H/H = 66 (57.4)  n = 46 L/L = 3 (7.0) L/H = 21 (45.0) H/H = 22 (48.0)  n = 50 L/L = 8 (17.0) L/H = 22 (47.0) H/H = 17 (36.0)  n = 21 L/L = 2 (9.5) L/H = 11 (52.4) H/H = 8 (38.1)  n = 18 L/L = 1 (5.5) L/H = 8 (44.5) H/H = 9 (50.0)	n = 202 L/L = 18 (8.9) L/H = 88 (43.6) H/H = 96 (47.5)  n = 259 L/L = 16 (6.2) L/H = 105 (40.5) H/H = 138 (53.3)  n = 205 L/L = 22 (11.0) L/H = 84 (41.0) H/H = 99 (48.0)  n = 384 L/L = 30 (8.0) L/H = 160 (44.0) H/H = 175 (48.0)  n = 206 L/L = 14 (6.8) L/H = 78 (37.9) H/H = 114 (55.3)  n = 86 L/L = 8 (9.3) L/H = 37 (43.0) H/H = 41 (47.7)		0.005  NS  NS  NS  NS  NS
<i>ApoE</i>	Isoform ε4 (CI056481)	Gambardella et al. 1999 [69] Initial study	Nonlesional TLE	Caucasian	n = 63 ε4 <sup>+</sup> = 5; years not indicated ε4 <sup>-</sup> = 58; years not indicated			NS

TABLE 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, n (%)	Genomic variation counts	P value
<i>IL-1<math>\alpha</math></i>	c.-889C>T $\rightarrow$ promoter Allele 1 = C Allele 2 = T (unknown)	Briellmann et al. 2000 [70] Replication study	Early onset of TLE associated with $\epsilon 4$	Caucasian	n = 43 $\epsilon 4^+$ = 10; 5 $\pm$ 5 years $\epsilon 4^-$ = 33; 10 $\pm$ 15 years	Controls, n (%)	0.004
		Cavalleri et al. 2005 [5] Replication study	Early onset of TLE associated with $\epsilon 4$	Caucasian	n = 181 $\epsilon 4^+$ = 30; 13.7 $\pm$ 10 years $\epsilon 4^-$ = 151; 16.7 $\pm$ 11 years		NS
		Gambardella et al. 2005 [71] Replication study	Early onset of TLE associated with $\epsilon 4$	Caucasian	n = 13 $\epsilon 4^+$ = 24; 26.2 $\pm$ 20.1 years $\epsilon 4^-$ = 114; 33.9 $\pm$ 20.7 years		NS
		Yeni et al. 2005 [72]	Early onset of TLE-HS <sup>+</sup> associated with $\epsilon 4$	Turkish	n = 47 $\epsilon 4^+$ = 8; 7.44 $\pm$ 6.13 years $\epsilon 4^-$ = 39; 8.75 $\pm$ 7.61 years		NS
		Salzmann et al. 2008 [67] Replication study	Early onset of TLE associated with $\epsilon 4$	Caucasian	n = 106 $\epsilon 4^+$ = 26; 10.54 $\pm$ 6.36 years $\epsilon 4^-$ = 80; 16.51 $\pm$ 9.90 years		0.003
		Kauffman et al. 2010 [73]	Early onset of TLE-HS <sup>+</sup> associated with $\epsilon 4$	Argentinean	n = 78 $\epsilon 4^+$ = 23; 14.3 $\pm$ 12.13 years $\epsilon 4^-$ = 55; 16.5 $\pm$ 12.54 years		NS
		Kanemoto et al. 2000 [74] Initial study	TLE-HS <sup>+/−</sup>	Japanese	TLE-HS <sup>+</sup> n = 50 1/1 = 38 (76.0) 1/2 = 10 (20.0) 2/2 = 2 (4.0)	n = 112 1/1 = 87 (77.7) 1/2 = 25 (22.3) 2/2 = 0 (0.0)	TLE-HS <sup>+</sup> versus controls = NS

TABLE 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, <i>n</i> (%)	Genomic variation counts	<i>P</i> value
					TLE-HS <sup>-</sup>	Controls, <i>n</i> (%)	TLE-HS <sup>-</sup> versus controls = NS
					<i>n</i> = 53		
					1/1 = 44 (83.0)		
					1/2 = 8 (15.1)		
					2/2 = 1 (1.9)		
					<i>n</i> = 47	<i>n</i> = 99	NS
		Ozkara et al. 2006 [75]	TLE-HS <sup>+</sup>	Turkish	1/1 = 23 (48.9)	1/1 = 37 (37.3)	
					1/2 = 23 (48.9)	1/2 = 52 (52.5)	
					2/2 = 1 (2.1)	2/2 = 10 (10.1)	
					TLE-FS <sup>+</sup>		TLE-FS <sup>+</sup> versus controls = NS
					<i>n</i> = 28		TLE-FS <sup>-</sup> = NS
					1/1 = 16 (57.1)		
					1/2 = 12 (42.8)		
					2/2 = 0 (0.0)		
					TLE-FS <sup>-</sup>		
					<i>n</i> = 19		
					1/1 = 9 (47.3)		
					1/2 = 10 (52.6)		
					2/2 = 0 (0.0)		
					TLE-HS <sup>+</sup>	<i>n</i> = 235	TLE-HS <sup>+</sup> versus controls = 0.027
					<i>n</i> = 86	1/1 = 99 (42.1)	
					1/1 = 50 (58.1)	1/2 = 118 (50.2)	
					1/2 = 29 (33.7)	2/2 = 8 (7.7)	
					2/2 = 7 (8.1)		
					TLE-HS <sup>-</sup>		TLE-HS <sup>-</sup> versus controls = NS
					<i>n</i> = 23		
					1/1 = 15 (65.2)		
					1/2 = 7 (30.4)		
					2/2 = 1 (4.4)		
					TLE-FS <sup>-</sup>		TLE-FS <sup>+</sup> versus controls = 0.0078
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		
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					1/1 = 33 (61.1)		
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					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
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					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		
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					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
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					TLE-FS <sup>-</sup>		
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					1/1 = 33 (61.1)		
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					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
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					TLE-FS <sup>-</sup>		
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					1/1 = 33 (61.1)		
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					TLE-FS <sup>-</sup>		
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					1/1 = 33 (61.1)		
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					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		
					<i>n</i> = 54		
					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		
					TLE-FS <sup>-</sup>		

TABLE 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, n (%)	Genomic variation counts	P value
<i>IL-1RA</i>	86 bp tandem repeat → intron 2 Allele 4 = 5 repeats Allele 1 = 4 repeats Allele 2 = 2 repeats Allele 3 = 3 repeats Allele 5 = 6 repeats (rs2234663)	Kanemoto et al. 2000 [74] Initial study	TLE-HS <sup>+/-</sup>	Japanese	TLE-HS <sup>+</sup>	n = 112	TLE-HS <sup>+</sup> versus controls = NS
					n = 50	1/1 = 102 (91.9)	
					1/1 = 46 (92.0)	1/2 = 6 (5.4)	
					1/2 = 3 (6.0)	1/3 = 1 (0.9)	
					1/3 = 1 (2.0)	1/4 = 2 (1.8)	
					1/4 = 0 (0.0)		
					TLE-HS <sup>-</sup>	n = 53	TLE-HS <sup>-</sup> versus controls = NS
					n = 52 (98.1)		
					1/2 = 1 (1.9)		
					1/3 = 0 (0.0)		
1/4 = 0 (0.0)							
<i>IL-1β</i>	c.-511C>T → promoter Allele 1 = C Allele 2 = T (rs1799916)	Kanemoto et al. 2000 [74] Initial study	TLE-HS <sup>+/-</sup>	Japanese	TLE-HS <sup>+</sup>	n = 242	TLE-HS <sup>+</sup> versus controls = NS
					n = 86	1/1 = 128 (52.9)	
					1/1 = 43 (50.0)	1/2 = 90 (37.2)	
					1/2 = 36 (41.9)	1/4 = 5 (2.1)	
					1/4 = 1 (1.2)	1/5 = 0 (0.0)	
					1/5 = 0 (0.0)	2/2 = 16 (6.6)	
					2/2 = 6 (7.0)	2/4 = 3 (1.2)	
					2/4 = 0 (0.0)		
					TLE-HS <sup>-</sup>	n = 23	TLE-HS <sup>-</sup> versus controls = 0.001
					n = 5 (21.7)		
1/1 = 5 (21.7)							
1/2 = 13 (56.5)							
1/4 = 0 (0.0)							
1/5 = 1 (4.3)							
2/2 = 4 (17.4)							
2/4 = 0 (0.0)							
<i>IL-1β</i>	c.-511C>T → promoter Allele 1 = C Allele 2 = T (rs1799916)	Kanemoto et al. 2000 [74] Initial study	TLE-HS <sup>+/-</sup>	Japanese	TLE-HS <sup>+</sup>	n = 112	TLE-HS <sup>+</sup> versus controls = 0.0085
					n = 50	1/1 = 31 (27.7)	
					1/1 = 9 (18.0)	1/2 = 58 (51.8)	
					1/2 = 19 (38.0)	2/2 = 23 (20.5)	
					2/2 = 22 (44.0)		
					TLE-HS <sup>-</sup>	n = 53	TLE-HS <sup>-</sup> versus controls = NS
					n = 13 (24.5)		
					1/1 = 13 (24.5)		
					1/2 = 30 (56.6)		
					2/2 = 10 (18.9)		

TABLE 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, n (%)	Genomic variation counts	Controls, n (%)	P value
		Kanemoto et al. 2003 [76] 16 TLE-HS <sup>+</sup> and 11 TLE-HS <sup>-</sup> were added to initial study [74]	TLE-HS <sup>+/-</sup>	Japanese	TLE-HS <sup>+</sup> n = 66 1/1 = 12 (18.2) 1/2 = 24 (36.4) 2/2 = 30 (45.5) TLE-HS <sup>-</sup> n = 64 1/1 = 16 (25.0) 1/2 = 36 (56.3) 2/2 = 12 (18.7)	n = 163 1/1 = 44 (27.0) 1/2 = 82 (50.3) 2/2 = 37 (22.7)	TLE-HS <sup>+</sup> versus controls = 0.0028  TLE-HS <sup>-</sup> versus controls = NS	
		Heils et al. 2000 [77]	TLE-HS <sup>+</sup>	Caucasian	n = 86 1/1 = 33 (38.0) 1/2 = 42 (49.0) 2/2 = 11 (13.0)	n = 133 1/1 = 57 (42.0) 1/2 = 60 (45.0) 2/2 = 16 (12.0)	NS	
		Buono et al. 2001 [78]	TLE-HS <sup>+</sup>	Caucasian	n = 61 1/1 = 31 (50.8) 1/2 = 24 (39.3) 2/2 = 6 (9.8)	n = 119 1/1 = 44 (37.0) 1/2 = 68 (57.1) 2/2 = 7 (5.9)	NS	
		Jin et al. 2003 [79]	TLE-HS <sup>+/-</sup>	Chinese	TLE-HS <sup>+</sup> n = 67 1/1 = 16 (24.0) 1/2 = 32 (48.0) 2/2 = 19 (28.0) TLE-HS <sup>-</sup> n = 45 1/1 = 12 (27.0) 1/2 = 24 (53.0) 2/2 = 9 (20.0)	n = 115 1/1 = 26 (23.0) 1/2 = 62 (54.0) 2/2 = 27 (23.0)	TLE-HS <sup>+</sup> versus controls = NS  TLE-HS <sup>-</sup> versus controls = NS	
		Cavalleri et al. 2005 [5]	TLE-HS <sup>+</sup>	Caucasian	n = 141 1/1 = 59 (45.0) 1/2 = 57 (44.0) 2/2 = 15 (11.0)	n = 384 1/1 = 161 (44.0) 1/2 = 162 (45.0) 2/2 = 41 (11.0)	NS	
		Ozkara et al. 2006 [75]	TLE-HS <sup>+</sup>	Turkish	n = 47 1/1 = 16 (34.0) 1/2 = 21 (44.6) 2/2 = 10 (21.2)	n = 99 1/1 = 41 (41.4) 1/2 = 41 (41.4) 2/2 = 17 (17.1)	NS	
		Ozkara et al. 2006 [75] Initial study	TLE-FS <sup>+/-</sup>	Turkish	TLE-FS <sup>+</sup> n = 28 1/1 = 9 (32.1) 1/2 = 13 (46.4) 2/2 = 6 (21.4) TLE-FS <sup>-</sup> n = 19 1/1 = 5 (26.3) 1/2 = 9 (47.3) 2/2 = 5 (26.3)	TLE-FS <sup>+</sup> versus TLE-FS <sup>-</sup> = NS		

TABLE 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, n (%)	Genomic variation counts	P value
		Salzmann et al. 2008 [67]	TLE-HS <sup>+/−</sup>	Caucasian	TLE-HS <sup>+</sup> n = 86 1/1 = 35 (40.7) 1/2 = 45 (52.3) 2/2 = 6 (7.0) TLE-HS <sup>−</sup> n = 23 1/1 = 12 (52.2) 1/2 = 9 (39.1) 2/2 = 2 (8.7)	Controls, n (%) n = 227 1/1 = 99 (43.6) 1/2 = 108 (47.6) 2/2 = 20 (8.8)	TLE-HS <sup>+</sup> versus controls = NS  TLE-HS <sup>−</sup> versus controls = NS
<i>IL-1β</i>	IL-1β + 3953 → exon 5	Kanemoto et al. 2000 [74]	TLE-HS <sup>+/−</sup>	Japanese	TLE-HS <sup>+</sup> n = 50 1/1 = 45 (90.0) 1/2 = 5 (10.0) 2/2 = 0 (0.0) TLE-HS <sup>−</sup> n = 53 1/1 = 49 (92.5) 1/2 = 3 (5.7) 2/2 = 1 (1.9)	n = 112 1/1 = 105 (93.8) 1/2 = 7 (6.3) 2/2 = 0 (0.0)	TLE-HS <sup>+</sup> versus controls = NS  TLE-HS <sup>−</sup> versus controls = NS
	Allele 1 and allele 2 (CM040228)	Initial study					
		Ozkara et al. 2006 [75]	TLE-HS <sup>+</sup>	Turkish	n = 47 1/1 = 28 (59.5) 1/2 = 18 (38.2) 2/2 = 1 (2.1)	n = 99 1/1 = 63 (63.6) 1/2 = 30 (30.3) 2/2 = 17 (17.1)	NS
		Ozkara et al. 2006 [75]	TLE-FS <sup>+/−</sup>	Turkish	TLE-FS <sup>+</sup> n = 28 1/1 = 19 (67.8) 1/2 = 9 (32.1) 2/2 = 0 (0.0) TLE-FS <sup>−</sup> n = 19 1/1 = 12 (63.1) 1/2 = 7 (36.8) 2/2 = 0 (0.0)		TLE-FS <sup>+</sup> versus TLE-FS <sup>−</sup> = NS
		Initial study					

TABLE 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, n (%)	Genomic variation counts	P value
		Salzmann et al. 2008 [67]	TLE-HS <sup>+/−</sup>	Caucasian	TLE-HS <sup>+</sup> n = 86 1/1 = 45 (52.3) 1/2 = 34 (39.5) 2/2 = 7 (8.2) TLE-HS <sup>−</sup> n = 23 1/1 = 14 (60.9) 1/2 = 8 (34.8) 2/2 = 1 (4.3)	Controls, n (%) n = 234 1/1 = 118 (50.4) 1/2 = 101 (43.2) 2/2 = 15 (6.4)	TLE-HS <sup>+</sup> versus controls = NS  TLE-HS <sup>−</sup> versus controls = NS
PRNP	p.Asn171Ser (CM971239)	Walz et al. 2003 [80] Initial study	Refractory TLE-HS <sup>+</sup>	Brazilian	Seizure-free n = 85 Asn/Asn = 70 (82.4) Asn/Ser = 15 (17.6) Seizure n = 13 Asn/Asn = 6 (46.2) Asn/Ser = 7 (53.8)	n = 384 Asn/Asn = 360 (99.8) Asn/Ser = 1 (0.2) Ser/Ser = 0 (0.0)	Seizure-free versus Seizure = 0.005
		Cavalleri et al. 2005 [5]	Refractory TLE-HS <sup>+</sup>	Caucasian	n = 121 Asn/Asn = 109 (100) Asn/Ser = 0 (0.0) Ser/Ser = 0 (0.0)	n = 141 Met/Met = 77 (54.6) Met/Val = 54 (38.3) Val/Val = 10 (7.1) n = 312 Met/Met = 302 (96.79) Met/Val = 10 (3.31) Val/Val = 0 (0.0)	NS
PRNP	p.Met129Val (CM890104)	Labate et al. 2007 [81] Initial study	Women, nonlesional TLE	Caucasian	n = 162 Met/Met = 64 (39.5) Met/Val = 77 (47.5) Val/Val = 21 (13.0)	n = 150 Met/Met = 146 (97.33) Met/Val = 4 (2.67) Val/Val = 0 (0.0)	0.021
		Wang et al. 2008 [82]	Women, nonlesional TLE	Chinese	n = 150	n = 302	NS
5-HTT	5-HTTLPR ins/del → 5'UTR S-allele = short variant L-allele = long variant (rs12720056)	Manna et al. 2007 [83] Initial study	Nonlesional TLE	Caucasian	n = 276 L/L = 77 (21.1) L/S = 146 (60.6) S/S = 53 (18.3)	n = 309 L/L = 90 (29.1) L/S = 142 (46.0) S/S = 77 (24.9)	NS

TABLE 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, n (%)	Genomic variation counts	Controls, n (%)	P value
5-HTT	17 bp tandem repeat → intron 2 9, 10 and 12 repeats (rs71360731)	Stefulj et al. 2010 [84]	TLE	Caucasian	n = 101	n = 170	NS	
					L/L = 42 (41.6)	L/L = 60 (35.3)		
					L/S = 45 (44.6)	L/S = 93 (54.7)		
Schenkel et al. 2011 [85]	TLE	Brazilian	n = 175	n = 155	NS			
			L/L = 48 (27.4)	L/L = 54 (34.8)				
			L/S = 91 (52.0)	L/S = 64 (41.3)				
Manna et al. 2007 [83]	Nonlesional TLE	Caucasian	n = 276	n = 309	0.0145			
			12/12 = 126 (48.6)	12/12 = 115 (37.2)				
			12/10 = 112 (46.2)	12/10 = 136 (44.0)				
Kauffman et al. 2009 [86]	Response to treatment	Argentinean	Nonresponsive	10/10 = 58 (18.8)	Nonresponsive versus responsive = 0.006			
			n = 74					
			12/12 = 40 (54.0)					
Stefulj et al. 2010 [84]	TLE	Caucasian	Responsive	n = 170	NS			
			n = 31					
			12/12 = 7 (22.6)	12/12 = 64 (39.5)				
Schenkel et al. 2011 [85]	TLE	Brazilian	12/10 = 21 (67.7)	12/10 = 74 (45.7)	NS			
			10/10 = 3 (9.7)	10/10 = 24 (14.8)				
			12/9 = 0 (0.0)	n = 155				
Stefulj et al. 2010 [84]	TLE	Caucasian	n = 101	n = 170	NS			
			12/12 = 30 (30.9)	12/12 = 67 (43.2)				
			12/10 = 46 (47.4)	12/10 = 67 (43.2)				
Schenkel et al. 2011 [85]	TLE	Brazilian	10/10 = 21 (21.6)	10/10 = 21 (13.5)	NS			
			n = 175	n = 155				
			12/12 = 62 (35.4)	12/12 = 67 (43.2)				
5-HTT	c.861C>G → synonymous (rs6296)	Stefulj et al. 2010 [84]	TLE	Caucasian	n = 101	n = 170	0.0642	
					C/C = 2 (2.0)	C/C = 14 (8.2)		
					G/C = 35 (34.7)	G/C = 65 (38.2)		
CALHM1	A>G → 3'UTR (rs11191692)	Lv et al. 2011 [87]	TLE	Chinese	n = 551	n = 399	0.004	
					A/A = 50 (9.1)	A/A = 30 (7.5)		
					A/G = 257 (46.6)	A/G = 149 (37.3)		
Lv et al. 2011 [87]	Replication study	Chinese	G/G = 244 (44.3)	G/G = 220 (55.1)	0.006			
			n = 360	n = 300				
			A/A = 34 (9.4)	A/A = 20 (6.8)				
Lv et al. 2011 [87]	Replication study	Chinese	A/G = 168 (46.7)	A/G = 111 (37.0)	0.006			
			G/G = 158 (43.9)	G/G = 169 (56.2)				

n: number of individuals; TLE: temporal lobe epilepsy; NS: nonsignificant; TLE-FS<sup>+/−</sup>: temporal lobe epilepsy with/without personal history of febrile seizures; TLE-HS<sup>+/−</sup>: temporal lobe epilepsy with/without hippocampal sclerosis; e4<sup>+/−</sup>: e4 present or not; significant P-values are in italic.

not observed in six other ethnically different populations [5, 67, 75, 77–79]. No association was found for *IL-1 $\beta$* +3953 [67, 75, 76].

**4.8. Prion Protein (PRNP).** Cellular PRNP is a cellmembrane glycoprotein which is highly expressed in neurons in adults [95]. Two *PRNP* variants, p.Asn171Ser and p.Met129Val, have been studied in TLE patients. A first study found that p.Asn171Ser is associated with the seizure persisting after temporal lobectomy in TLE-HS<sup>+</sup> patients [80]. A replication study did not show this association in their unrelated patients [5]. Cognitive performance associated with the two *PRNP* variants was assessed in patients with medically refractory TLE-HS<sup>+</sup>, as mentioned above [80]. These experiments showed no significant results [96]. However, recently, valine at codon 129 was shown to be highly represented in women with benign TLE as compared to the matched controls [81]. A Chinese study did not observe this difference in its TLE group [82].

**4.9. Serotonin Transporter (5-HTT).** 5-HTT is a key regulator of the level of serotonergic neurotransmission through serotonin inactivation [97]. Moreover, 5-HTT is a target for selective serotonin reuptake inhibitors which have an anticonvulsant action [98]. The effect of two well-known functional polymorphisms of *5-HTT*, 5-HTTLPR (an insertion/deletion in 5'UTR) and 5-HTTVNTR (a VNTR in intron 2) was estimated in different TLE cohorts. Ten repeats at 5-HTTVNTR showed significantly lower frequencies in TLE than in controls, but no differences were displayed for 5-HTTLPR [83]. Subsequent studies showed that TLE-HS<sup>+</sup> patients carrying homozygous 5-HTTVNTR 12 repeats had an increased risk of not responding to medical treatment [86]. A particular genotype combination of 5-HTTLPR and 5-HTTVNTR (L/L-12/12) was associated with a worse response to optimal drug therapy in TLE patients [99]. Interestingly, this particular combination was significantly less frequently observed in another group of TLE patients than in the matched controls [85]. A recent study, which investigated several 5-HTT-related genes in Croatian TLE patients, did not show any association with the two functional polymorphisms of *5-HTT* but exhibited a significant allelic difference for *5-HT-1B* G861C. G-allele was slightly overrepresented in the TLE group [84].

**4.10. Complement (C3).** Complement factor C3 is a major component of the immune complement system. Experimental evidences have shown that this system plays a role in epileptic processes [100]. Moreover, increased expression of C3 gene and protein has been found in brain tissues from patients with mesial TLE (mTLE) [101, 102]. A dinucleotide repeat polymorphism (GF100472) located in the C3 promoter and included in four particular haplotypes of 3 markers made by a combination of 5 SNPs (rs339392, rs2230199, rs428453, rs344550, rs379527) showed significant association even after the Bonferroni correction in TLE-FS<sup>+</sup>. Replication in a second similar independent group confirmed one of the four haplotypes to be protective against

TLE with a personal history of FS. This most significant protective haplotype in the initial and the replicative groups of TLE-FS<sup>+</sup> was (CA8)-G-T (GF100472- rs344550- rs379527) with a frequency of 0.025 and 0.022 in the control groups and 0.0 in the two patient groups ( $P = 0.0003$  and  $P = 0.00008$ , resp.). Moreover, reporter gene assays confirmed that GF100472 significantly influenced C3 promoter activity [103]. Up to now, no replicated association study has been assessed in another independent sample of TLE patients.

**4.11. Calcium Homeostasis Modulator 1 (CALHM1).** CALHM1 influences calcium (Ca<sup>2+</sup>) homeostasis, which plays an important role in the development and maintenance of epilepsy [104]. Five SNPs (rs11191692, rs729211, rs2986016, rs2986018 and rs2986017) of *CALHM1* were genotyped in a Chinese population with TLE. Only one positive association was found between rs11191692, located in 3'UTR of the gene, and TLE patients [87]. As for the last one association study, no replication has yet been performed.

**4.12. Lack of Association Results.** Some studies found different genes to be of interest in TLE patients. A four-base insertion 12 bp before exon 2 in *sodium/potassium-transporting ATPase alpha 2 subunit (ATP1A2)* did not show any association between DNA from TLE anterior lobectomy tissue samples (15 TLE patients with 4bp insertion among 56 patients) and DNA from control blood samples (16 controls with 4bp insertion among 56 controls) [105]. Two SNPs (C271T and Val66Met), often associated with neurological conditions, in *brain-derived neurotrophic factor (BDNF)* were not associated with TLE in a European sample ( $n = 151$ ) as compared to the matched controls ( $n = 189$ ) [106]. A last negative result was obtained for *matrix metalloproteinase 9 gene (MMP-9)* and TLE. In this experiment, 17 SNPs along *MMP-9* were tested and neither single SNP analysis nor haplotype analysis detected the *MMP-9* implication in 218 Norwegian TLE patients [107]. Today, association studies have been enlarged to genomewide association study (GWAS) in large cohort of patients. This strategy appears to be a method of choice for discovering SNPs or loci associated to numerous complex diseases [108]. The first GWAS in epilepsy field was recently achieved in 3445 patients showing partial epilepsy compared to 6935 matched controls [109]. This study did not find genomewide significant association. This was probably due to the important heterogeneity of the case sample. Unfortunately, the authors did not consider analysis in more homogeneous subsamples, such as TLE subgroup, that accounted for 919 patients with HS. They also did not make any effort to obtain a more homogenous sample of patients [109].

## 5. Conclusion

The main conclusion of the present paper is that the involvement of *LGII* gene in familial ADLTE is the only replicated result in the field of the genetics of TLE. Several reasons could explain this lack of replication. First, this may be due to the small sample size of the TLE patients and/or

to the clinical heterogeneity in nearly all of the studies. Another reason is that gene-environment interaction has never been taken into account in the published studies, while this is likely to be an important etiological factor in such complex diseases. In connection with that is the absence of epigenetic studies in TLE (see below). Finally, TLE may also be caused by multiple rare mutations. This hypothesis is supported by the very recent mutations we identified in the *Carboxypeptidase A6* gene in a family as well as in sporadic TLE patients [110].

**5.1. Future Directions.** GWAS will require large and homogeneous samples of TLE that will certainly be possible through international collaborations. Despite the complexity of such studies GWAS must be emphasized since the common—variant—common—disease has not yet been definitively rejected in TLE. In addition, high-throughput sequencing (HTS) of the whole genome or of the exome, the coding part of the genome, is the new way to consider this problem [111, 112]. To date, such HTS has not still been done in TLE. This was partially performed in a recent exome sequencing of ion channel genes in patients with idiopathic and symptomatic (formerly known as cryptogenic) epilepsy [113]. The study suggests that the phenotypic variation could occur because of many different channel alleles at a single locus or a collection of novel alleles in related or distant subunit genes [113]. Another type of rare polymorphisms to consider is structural variants such as copy number variations (CNVs) [114]. A recent genomewide CNVs study in various idiopathic, nonlesional epilepsies reported several rare CNVs in patients exhibiting generalized and focal epilepsies [115]. Although numerous efforts have been made to find a large number of causal genetic variations in complex diseases, there has been a growing interest for epigenetic variations, such as DNA methylation in complex human disease [116]. After a careful literature search, we only found one DNA methylation study on hippocampal subregions from mesial temporal sclerosis in patients with TLE. Results showed a greater level of reelin promoter methylation in TLE hippocampal dissections than in the controls [117]. Transcript levels of reelin, which is an extracellular matrix protein playing a role in the hippocampus cortical lamination, have been found downregulated in TLE specimens [117]. Epigenetic studies in the field of epilepsy are just at the starting point. Therefore, there are many avenues to understand how nongenetic components can act on the development of TLE. By combining these different approaches, we will be able to better understand the etiology of TLE. By doing so, we hope to provide personalized treatment to patients with complex disease, such as TLE.

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## Review Article

# The “Natural” History of Medically Treated Temporal Lobe Epilepsy: What Can an Evidence-Based Approach Tell Us?

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Received 14 September 2011; Accepted 5 December 2011

Academic Editor: Seyed M. Mirsattari

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We systematically reviewed the literature to describe the “natural” history of medically treated temporal lobe epilepsy (TLE). No population-based studies recruiting incident cases of TLE irrespective of age exist. Prospective, population-based studies were limited to those recruiting only childhood-onset TLE or those reporting TLE as a subgroup of cohorts of focal epilepsies. Few studies have been performed in the “MRI era” limiting information on natural history secondary to specific pathologies. Available data suggests that TLE is highly variable, with unpredictable transient remissions and low rates of seizure freedom (30 to 50%). Etiology and failure of first and second drug seem to be the most important predictors for treatment prognosis. The role of initial precipitating injuries remains speculative, as imaging information of related events is either missing or conflicting. Prospective cohorts of new-onset TLE with long-term followup using advanced MRI techniques, timely EEG recordings, and assessments of psychiatric comorbidities are needed.

## 1. Introduction

Temporal lobe epilepsy (TLE) is the most frequent medically refractory epilepsy syndrome seen in epilepsy outpatient clinics. It has received considerable attention in recent years owing to the remarkable rates of remission that can be achieved through surgical intervention [1]. Mesial temporal lobe epilepsy (mTLE) associated with hippocampal sclerosis (mTLE-HS), a condition that can be detected by modern magnetic resonance imaging (MRI) techniques with a high sensitivity and specificity, is now the most common indication for epilepsy surgery.

To date, therapeutic advances in TLE have far outpaced our understanding of the natural history of the disorder. According to a recent International League Against Epilepsy (ILAE) commission report [2], the natural history of mTLE-HS is characterized by key features such as a history of an initial precipitating injury and a presence of a latent and/or silent period. Prior publications have attempted to assess the course and prognosis of TLE, mTLE, and mTLE-HS using sophisticated electroencephalography (EEG), MRI,

and histological techniques trying to identify the “natural” history of all types of TLE. Almost all these studies are limited by the fact that their perspective comes from tertiary care centers and surgical series [3].

The ideal natural history study requires a large prospective cohort of patients with new-onset TLE undergoing extensive structural and functional testing with a followup of >10 years. We conducted a systematic review of the literature to identify prospective, population-based natural history studies of TLE and reviewed appropriate longitudinal and retrospective case series. We extracted critical information on initial precipitating injury, seizure outcome, silent periods, and long-term remission to describe the natural history of this condition. Natural history in its strictest sense means the course of a disorder from onset without intervention until the disorder resolves or death ensues [4]. However, data from drug-naïve TLE patients are only anecdotal. Therefore, for the purposes of this study, we defined the “natural history” of TLE as the course of the disorder under medical treatment without surgical intervention.

## 2. Methods

We performed a comprehensive literature search of Medline and Embase using validated search terms (See the Appendix) on August 10th, 2011. We searched the bibliography of relevant reviews and articles to identify additional studies that may not have been retrieved by our search strategy. One of the authors (CBJ) independently applied the following study inclusion criteria: (i) unselected cohorts of epilepsy patients drawn from the general population; (ii) a minimal study population of  $\geq 20$  participants; (iii) quantitative report of patient demographics, initial precipitating injuries, the results of EEG and MRI, and seizure outcomes. Titles were screened and abstracts or full articles were reviewed when there was doubt concerning the article's potential relevance. Questions concerning eligibility were resolved through consensus discussion between the two authors. All relevant articles were retrieved for full review. We abstracted data from the most recent publication if there were multiple articles identified from the same study population. Full-length English articles were selected without restriction on place or date of publication.

We accepted the authors' diagnosis of TLE. One of the authors (CBJ) abstracted all data and priority was given to prospective, population-based cohorts of incident diagnoses of TLE. The primary outcome was seizure freedom at the end of followup. Age at onset, the frequency of risk factors such as a family history or initial precipitating injuries, frequency of abnormalities found on electrophysiological and neuroimaging studies, the existence of an intervening "silent" period between diagnosis and later seizure relapse, and the longest duration of remission were considered secondary outcomes of interest. Additional measures such as psychosocial and cognitive outcomes were not analyzed due to the limited scope of the paper.

## 3. Results

We identified 1774 articles and reviewed titles and abstracts to retrieve 39 (2%) that were potentially relevant to the review. We performed a full review of all 39 articles and 5 (13%) were ultimately included in our analysis (Figure 1). No population-based studies recruiting all incident cases of TLE irrespective of age exist. Prospective, population-based studies were limited to those recruiting only childhood-onset TLE or those reporting on TLE as a subgroup of population-based cohorts of focal epilepsies (Table 1). Few studies have been performed in the "MRI era" thus limiting information on the natural history and prognosis of TLE secondary to specific underlying pathologies.

**3.1. Seizure Outcome.** Only one population-based study dedicated solely to TLE was identified by our search. It enrolled incident and prevalent cases of TLE in the state of Victoria, Australia, (interval from seizure onset to enrollment was 1 week to 3.9 years) and found that 31% of individuals were able to achieve a minimum of two-year seizure freedom off antiepileptic drugs (AEDs) over a median follow-up

period of 13.7 years. All other individuals in the cohort either continued to have seizures despite AED status or had progressed to surgery. Interestingly, all patients still taking AEDs at the end of followup had failed to achieve seizure remission. However, only two children who went greater than one-year seizure free had a recurrence of seizures before their terminal remission. The only predictor of seizure freedom according to a univariable analysis was the absence of a lesion on MRI [5].

Additional prospective, population-based studies of focal epilepsies have been informative. The National General Practice Study of Epilepsy (NGPSE) captured incident diagnoses of epileptic seizures across the United Kingdom over a three-year period from 1984–1987 [6]. They stratified patients into anatomical groups whereby 27% of the total population were classified as having seizures of a temporal lobe origin mainly based on clinical and EEG information. Patients were followed for 4 to 7 years and, of those with temporal lobe seizures, 49% achieved two-year seizure freedom while 33% had less than four seizures per year. It is unclear whether any of the patients included in the follow-up analysis underwent surgical resection. A study of 1448 people with epileptic and febrile seizures from Rochester, MN, USA, found that 41% of individuals with temporal lobe epilepsy had achieved two-year seizure freedom at the point of last followup [7]. Likewise, a prospective population-based evaluation of 144 incident cases of childhood-onset generalized and focal epilepsy from Turku, Finland found that 53% of individuals with TLE were able to achieve seizure-freedom for five or more years at the end of a median of 40 years of followup (range 11 to 42). A further 19% entered a five-year period of seizure remission at some point during the follow-up period [8].

There is little prospective information available for the prognosis of individual subtypes of TLE. A prospective study of incident and prevalent cases of familial mesial temporal lobe sclerosis suggested that its prognosis may not differ significantly from sporadic TLE. Patients were classified according to their degree of seizure freedom at the beginning of follow-up (seizure-free for two or more years, less than six complex partial seizures per year and no more than two secondarily generalized seizures per year, or six or greater complex partial seizures per year despite adequate AED therapy). At the end of a mean of 7.8 years followup (standard deviation of  $\pm 1.3$  years), 50% of participants had achieved seizure freedom for two or more years. However, none of the patients who started the study with medically refractory epilepsy achieved seizure remission by the end of followup [9]. As expected, symptomatic family members appeared more likely to develop epilepsy (11%) than those from the general population.

Retrospective studies from tertiary care centres reported far more variable rates of seizure remission. Rates of seizure freedom of one year or more by last followup ranged from 11–63% in populations of patients with TLE [10–16] or in cohort or subgroup analyses of those with mesial temporal lobe sclerosis [10, 17]. When evaluated according to number of seizures per month, 37–61% had improved

TABLE 1: Prospective population-based studies of sporadic and familial temporal lobe epilepsies.

Study	Country	Setting	Sample size	Follow-up duration	Age at onset	Silent period	History of IPI	Family history	EEG	Imaging	Rate of seizure freedom	Longest remission
Hauser and Kurland 1975 [7]	USA	Childhood and adult onset	?	?	?	?	?	?	?	?	41% 2-year seizure freedom	?
Manford et al. 1992 [6]	UK	Childhood and adult onset	43	3 to 7 years	Mean 40 years-old (standard deviation 20 years)	?	6 (14%)	?	38/43 (89%); abnormality 4/38 (11%)	CT (30/43; 70%); abnormality (3/30; 10%)	49% 2-year seizure freedom	?
Sillanpää and Schmidt 2006 [8]	Finland	Childhood onset	43	Median 40 years	?	8/43 (19%)	?	?	?	?	53% 5-year seizure freedom	?
Spooner et al. 2006 [5]	Australia	Childhood onset	62	Median 13.7 years	Median 6.4 years old	16/62 (26%)	17 (27%)	13 (21%)	vEEG temporal lobe seizure (31/62 (50%))	MRI 58/62 (94%); abnormality 28/58 (48%)	31% 2-year seizure freedom	Median seizure-free duration 10 years (range 5–15 years)
Morita et al. 2008 [9]	Brazil	Familial mesial temporal sclerosis	64	Mean 7.8 years	?	?	?	100%	?	?	50% 2-year seizure freedom	?

CT = computed tomography; EEG = electroencephalography; IPI = initial precipitating injury; MRI = magnetic resonance imaging; vEEG = video electroencephalography.

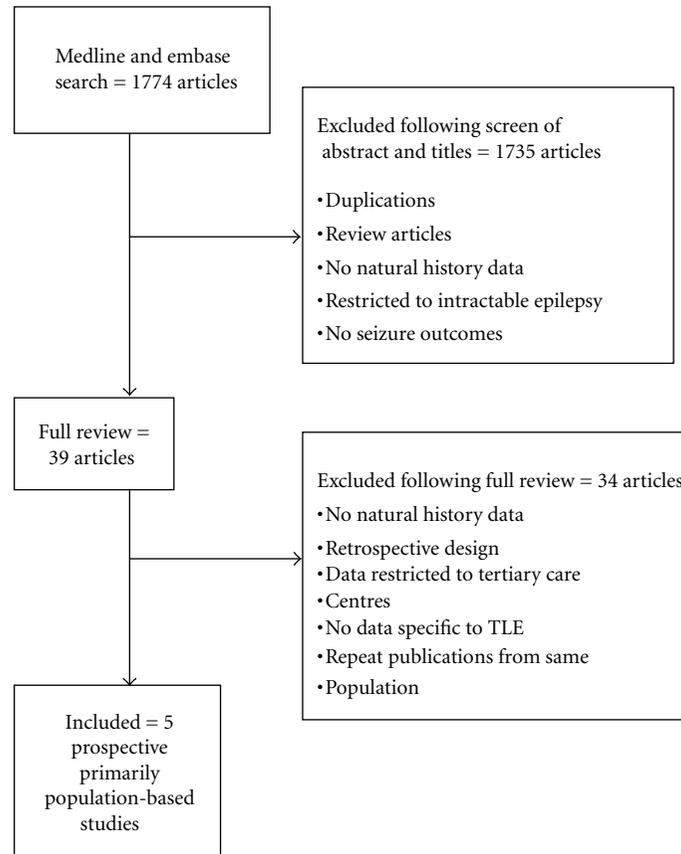


FIGURE 1: Search strategy and evidence base.

seizure control or <1 seizure per month after mean follow-ups of up to 6.6 years. Those with idiopathic (normal neurological status and intelligence with no risk factors for epilepsy other than a family history of seizures) TLE showed an improved prognosis (79% seizure free at last followup [minimum follow-up of two years] versus 52% in patients without idiopathic TLE) [13], as may those who respond successfully to their first AED (odds ratio for refractory TLE 93.8 [95% confidence interval, 95% CI, 20.1 to 437.8]) [16].

**3.2. Initial Precipitating Injuries.** Two studies reported on rates of potential precipitating injuries that may have contributed to the development of temporal lobe epilepsy. Common antecedent events considered risk factors for epilepsy included complicated febrile convulsions, prolonged afebrile seizures, infantile spasms, meningitis or encephalitis, hypertensive encephalopathy, apnea and respiratory arrest, tumours, congenital malformations, remote trauma, and vascular events including intracranial hemorrhage [5, 6]. The reported frequency of events between cohorts differed considerably with an earlier study reporting an identified risk factor in 14% of the population [6] compared to a later study in the MRI era that reported an identified risk factor in 27% of the cohort [5].

**3.3. Abnormalities on Functional and Structural Tests.** Two studies reported proportions of patients undergoing electrophysiological and neuroimaging studies. Electroencephalography (EEG) was performed in 89% of patients with temporal lobe epilepsy in one study and revealed evidence of a focal abnormality in 11% of those tested [6]. A second study reported evidence of seizures of temporal lobe origin on video-EEG telemetry in 50% of the study cohort [5]. The percentage of patients undergoing neuroimaging varied between these two studies. Seventy percent of one cohort from the pre-MRI era underwent a CT scan of the head [6] while 94% of participants in a later study [5] underwent an MRI scan. A focal lesion was detected in 10% of those investigated with a CT scan of the brain (in which two of the three identified focal abnormalities, all of which were primary tumours, were located in an extratemporal area) [6] and in 48% of those undergoing MRI [5]. Temporal lobe lesions detected by MRI included hippocampal sclerosis in 10 children, tumour in 8, cortical dysplasia in 7, and temporal lobe atrophy, gliosis, or cystic change in 3.

**3.4. “Silent Periods”.** No studies reported the delay from the first seizure to the diagnosis of epilepsy. However, in one study of epilepsy in Rochester, MN, there were more cases of temporal lobe epilepsy in an undiagnosed subgroup whose

epilepsy had developed but had not yet been localized to the temporal lobe on the dates from which cases were drawn to determine incidence and prevalence. A disproportionate number of these patients were eventually diagnosed with TLE suggesting a longer interval between initial seizure onset and ultimate epilepsy classification when compared to other types of epilepsy [7].

Few studies reported on periods of seizure remission followed by symptomatic relapse. One study of childhood-onset temporal lobe epilepsy, which included individual patient data, reported that 16 of 62 cases (26%) had periods of at least one year of seizure freedom before relapsing; some of which occurred between five to ten years after the onset of epilepsy [5]. A similar finding was reported in a subgroup analysis of patients with temporal lobe epilepsy from another prospective, population-based study of new onset epilepsy. In this subgroup, 19% of patients with temporal lobe epilepsy failed to achieve complete seizure control following a period of at least 5 years of seizure freedom [8].

*3.5. Longest Remission Period.* Only one study reported on the duration of seizure freedom. Spooner et al. [5], in their study of childhood onset temporal lobe epilepsy from Victoria, Australia, reported a median duration of seizure freedom of 10 years in those who achieved complete remission. The range of seizure freedom extended from 5 to 15 years.

#### 4. Discussion

This systematic review of the literature highlights the relative dearth of information available on the natural course of medically treated TLE. It supports the notion that our knowledge of the “natural” history of medically treated TLE is very poor. Clinical impression of the benign or malign nature of TLE typically derives from what is often a highly selected surgical series with potentially nonrepresentative patient populations. Patient groups in these studies mainly consist of medically refractory cases of TLE and are often restricted to the subpopulation of mTLE. This is further complicated by the fact that within the mTLE group, the focus has primarily been on mTLE-HS, which is only one well-described disorder in what is otherwise a wide range of heterogeneous conditions that cause mTLE [2]. A recent review of the natural history of mTLE [3] emphasized the importance of the age of onset (childhood versus adult form) and the relative complexity of its course. It may appear relatively benign at first, with high variable times of remission and seizure freedom, but then later develop into an absolutely medically refractory seizure disorder. The review describes a typical surgical TLE patient using a “3-rule” pattern: the average patient is in his or her 3rd decade when diagnosed with drug resistance and identified as a surgical candidate, 1/3rd of all patients have a history of febrile seizures and two-thirds show hippocampal sclerosis on MRI [3].

Not surprisingly, our systematic review of the literature revealed many deficiencies in our knowledge and raised

several questions. We did not identify any population-based studies recruiting all incident cases of temporal lobe epilepsy over the whole life span. Our extracted information was limited to few studies, including a prospective, population-based study on childhood-onset temporal lobe epilepsy [5] or those where TLE was a subgroup of population-based cohorts of focal epilepsies [6–9]. Information on imaging protocols was poor and MRI data were often lacking.

Prognosis in general, measured by seizure freedom, was worst in the most rigorous prospective study of childhood onset-TLE. Only 31% of individuals were able to achieve a minimum of two-year seizure freedom off AEDs over a median follow-up period of 13.7 years [5], compared to 49% of TLE patients in a prospective, population-based study of focal epilepsies [6] and 41% of a subgroup of TLE patients in 1448 cases of epileptic and febrile seizures in the Rochester Study [7]. Familial “benign” mTLE had only a slighter better prognosis with 50% of participants achieving seizure freedom for >2 years [9]. All patients who failed initial AED therapy remained refractory to medical therapy throughout [9]. This finding is in keeping with a retrospective study in childhood temporal lobe epilepsy, in which failure of the first AED was the strongest predictor for outcome [16]. Both studies emphasize the predictive role of initial drug failure for long-term prognosis. Significant variations of rates of seizure freedom and very high rates of seizure freedom (in up to 63%) were only found in the retrospective series [10–16] underlining the importance of prospective studies. The high rate of seizure freedom in 79% of individuals with “idiopathic” TLE [13] has to be interpreted with caution due to the small retrospective nature of the series which could have led to selection bias.

Initial precipitating injuries, including complicated febrile convulsions and nonspecific brain insults (meningitis or encephalitis), were found in 14% in the NGPSE study [6] and in almost double (27%) the participants in the prospective childhood TLE study by Spooner et al. Most of these patients had complicated febrile convulsions, followed by meningitis and a diverse array of other conditions.

Sophisticated imaging is crucial to assess the potential causal role of associated temporal lobe pathology. While CT scans in the pre MRI-era NGPSE study only detected abnormalities in 10% (mainly extratemporal tumours), almost half of all patients (48%) in the Australian study [5] had subtle lesions on MRI with an equal distribution of hippocampal sclerosis, cortical dysplasia, and tumours. The presence of a temporal lesion was the only significant predictor for long-term refractoriness to medical therapy. While spontaneous remission in this childhood cohort occurred in one-third of all patients over a median follow-up of 13.7 years, the remaining two-thirds with intractable seizures all had a lesion on MRI at seizure onset. The issue of hippocampal pathology on MRI (signal increase and atrophy) in newly diagnosed epilepsy and new-onset epilepsy remains controversial as it may precede seizure occurrence [18], it may be entirely missed or absent at onset [19–21], or hippocampal atrophy and volume loss can develop over the next three to four years [19, 22]. Furthermore, nearly 40% of cases of “benign” mTLE (in which patients remain

seizure free for at least 24 months with or without AEDs) displays evidence of hippocampal sclerosis on MRI [23]. These conflicting data reflect the ongoing debate of whether mesial temporal lobe atrophy in patients with TLE is a cause or consequence of repeated seizures [24]. Our search only retrieved two studies that documented EEG results [5, 6], and these surprisingly added only limited information to the natural course of TLE. The NGPSE study found focal abnormalities in one of every ten TLE patients and did not comment on their prognostic value. In the Australian study, focal EEG abnormalities were associated with poor seizure outcome ( $P < 0.05$ ), but these results were strongly interrelated with corresponding MRI findings that were highly predictive of seizure intractability ( $P < 0.001$ ).

Based on this systematic review of the literature, we currently cannot predict whether the course of new-onset TLE will be straightforward with rapid long-term seizure control, rapidly progress to drug resistance, or go into short- or long-term remission. Stuttering, relapsing, and silent periods may be a characteristic features of TLE. Over one-quarter (26%) of the prospective childhood-onset temporal lobe epilepsy had periods of at least one year of seizure freedom before relapsing [5]. Almost every fifth patient in a prospective, population-based study with a seizure-free period of 5 years turned out to be refractory over the long term [8]. This is in keeping with another prospective study of children with focal seizures (not TLE only) where 76% of those patients who became finally refractory to medical therapy had a preceding remission of at least one year. Interestingly, however, failing two or more AEDs did not preclude remission times of greater 1 year [25]. Current data do not offer much useful information on whether the duration of seizure freedom can be used to predict overall long-term seizure remission. Only one study has directly addressed this issue reporting on childhood onset TLE from Victoria, Australia, where seizure freedom ranged from 5 to 15 years for those who finally became seizure free [5].

*4.1. Where Does This Information Take Us?* Our systematic review confirmed that the course TLE could be highly variable with unpredictable phases of transient remissions and low rates of seizure freedom that range between 30 and 50% in prospective studies. Based on the limited available data, etiology and failure of first and second AED are the most important predictors for prognosis. The role of initial precipitating injuries remains speculative, as imaging information of related events is either missing or conflicting. Our understanding of the basic mechanisms of epileptogenesis remains limited.

Prospective, population based studies of new-onset epilepsies suggestive of TLE are needed to adequately address these questions in the context of a reliable, evidence-based framework. For instance, a rigorous approach to determining epilepsy syndromes upon evaluating the first seizure (including new-onset epilepsy) was adopted by King et al. (1998) [26] using MRI in up to 90% of their patients and early EEG (within 24 hours of the seizure) plus sleep-deprived EEG, if routine EEG was normal. The authors were

able to classify localization-related or generalized syndromes in only 47% of the cases with clinical information versus 77% of those with the addition of EEG findings and 81% of those with the addition of MRI. Their findings emphasize the clinical usefulness of EEG, which was found to be superior to MRI in classifying epilepsy syndromes, although the low yield may have been improved by the use of modern MRI techniques that were not available during the study period of 1994–1996. Our systematic review highlights the paucity of evidence-based longitudinal data on the use of EEG over the course of TLE. This is an important observation since EEG findings are the most relevant predictor for seizure recurrence besides etiology and first-seizure presentation [27].

There is now considerable interest in the role of advanced neuroimaging technology in early stages of epilepsy [28, 29]. The First Halifax International Epilepsy Conference in September, 2010, which focused on the role of advanced neuroimaging in new-onset epilepsy, reached an expert consensus that first seizures and new-onset epilepsy most likely reflect a change in the complex biochemical and neurobiologic environment of the brain in which seizures themselves only represent one key symptomatic feature [29]. It therefore seems logical to apply the same sophisticated structural and functional investigations that have been developed for study of chronic stages of epilepsy to the first seizure and newly diagnosed epilepsy. A careful evaluation of preceding psychiatric comorbidities, such as anxiety and depression, is also required as they often reflect temporal pathology as part of a bidirectional relationship between epilepsy and psychiatric findings patients with TLE [29, 30]. It is likely that advanced MRI techniques including diffusion tensor imaging and MR spectroscopy, in addition to timely EEG recordings, will provide new insights into the early course of TLE and help to identify predictors for pharmacoresistance and further define the potential dynamic course of TLE [28]. Extensive ongoing followup of these prospective cohorts of new-onset epilepsy or newly diagnosed TLE is needed as highly variable, and unpredictable phases of intermittent remission can occur over the long-term “natural” course of medically treated TLE.

## Appendix

### Medline and Embase Search Strategy

- (1) exp epilepsy, temporal lobe/
- (2) ((epilepsy adj3 temporal) or TLE).tw.
- (3) exp incidence/
- (4) exp mortality/
- (5) exp prognosis/
- (6) exp quality of life/
- (7) exp survival analysis/
- (8) (incidence or mortality or prognos\* or predict\* or course or outcome or “quality of life” or memory or “survival analysis”).tw.

- (9) exp cohort study/
- (10) exp case-control study/
- (11) exp Randomized Controlled Trial/
- (12) (“randomi\* control\* trial” or cohort or risk or case-control).tw.
- (13) exp followup studies/
- (14) (1 or 2) and (3 or 4 or 5 or 6 or 7 or 8) and (9 or 10 or 11 or 12 or 13)
- (15) limit 14 to humans.

## Disclosures

Dr. C. Josephson reports no disclosure. Dr. B. Pohlmann-Eden reports no disclosure.

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## Research Article

# Establishment of a Comprehensive Epilepsy Center in Pakistan: Initial Experiences, Results, and Reflections

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Received 16 May 2011; Revised 22 October 2011; Accepted 20 November 2011

Academic Editor: Seyed M. Mirsattari

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**Background.** Developing countries, home to 80% of epilepsy patients, do not have comprehensive epilepsy surgery programs. Considering these needs we set up first epilepsy surgery center in Pakistan. **Methods.** Seventeen teleconferences focused on setting up an epilepsy center at the Aga Khan University (AKU), Karachi, Pakistan were arranged with experts from the University of Alberta Hospital, Alberta, Canada and the University of West Virginia, USA over a two-year period. Subsequently, the experts visited the proposed center to provide hands on training. During this period several interactive teaching sessions, a nationwide workshop, and various public awareness events were organized. **Results.** Sixteen patients underwent surgery, functional hemispherectomy (HS) was done in six, anterior temporal lobectomy (ATL) in six, and neuronavigation-guided selective amygdalohippocampectomy (SAH) using keyhole technique in four patients. Minimal morbidity was observed in ATL and, SAH groups. All patients in SAH group (100%) had Grade 1 control, while only 5 patients (83%) in ATL group, and 4 patients (66%) in HS group had Grade 1 control according to Engel's classification, in average followups of 12 months, 24 months and 48 months for SAH, ATL, and HS, respectively. **Conclusion.** As we share our experience we hope to set a practical example for economically constrained countries that successful epilepsy surgery centers can be managed with limited resources.

## 1. Introduction

A patient with epilepsy, whose seizures cannot be controlled after at least two years having tried and failed two major antiepileptic drugs (AEDs) with demonstrated therapeutic levels, is regarded as medically refractory [1–3]. Approximately 35% of patients with epilepsy are refractory to medical therapy [4]. In such cases where medical management has failed, surgery is generally considered as the next step in the management of their ailment. Surgery is indicated in lesion-related symptomatic epilepsy syndromes such as temporal lobe epilepsy (TLE) with mesial temporal sclerosis (MTS), intracranial tumors, and cortical dysplasias. The number of medically refractory patients as well as lesion-related epilepsy patients is higher in the developing countries due

to the higher incidence of infections and perinatal asphyxia leading to greater cortical pathologies. Regrettably, many of the developing countries do not have comprehensive epilepsy centers, leaving patients to suffer with incapacitating seizures and other lifelong comorbidities.

In 1997 the World Health Organization, the International League Against Epilepsy, and the International Bureau for Epilepsy launched a Global Campaign against Epilepsy “Out of the Shadows,” from Geneva as well as Dublin, during the 22nd International Congress of Epilepsy. The campaign aimed to increase public and professional awareness of epilepsy as a universal and treatable brain disorder, promote public and professional education about epilepsy, identify the needs of people with epilepsy at the national and regional levels, and encourage governments and departments of health

to address the needs of people with epilepsy including awareness, education, diagnosis, treatment, care, services, and prevention.

However, the position in developing countries did not change significantly. There is a limited literature available on epilepsy surgery and its application in the developing countries, and proposals to possibly set up comprehensive epilepsy center in low income countries have been put forward [1, 5, 6], and few pragmatic applications have ensued from these proposals. A pilot project to develop a comprehensive epilepsy center in Uganda demonstrated a framework for such a program to function in a very low resource setting [7].

Here we would like to share our experience right from the initial stages of planning, recruitment, arrangement of transnational teleconferences and identification of potential patients to carrying out successful surgeries and training of future human resources. In doing so we hope to set a practical example for economically constrained countries and to make a difference in the quality of life of patients with medically refractory epilepsy.

## 2. Importance of International Collaboration in the Developing World

Of the 50 million people suffering from epilepsy all over the world, 80% reside in the developing countries, where the estimated incidence is as high as 190 per 100,000 [8, 9]. Approximately 90% of these patients are deprived of proper treatment due to a lack of resources and proper medical facilities, leading to social stigma, isolation and discrimination [10, 11]. Further they are subjected to unemployment, inadequate access to education, and psychiatric comorbidities [12–16]. All these put together result in severe depression; a study conducted in a hospital setting with focused clinic psychiatric evaluation found that nearly 60% of patients with epilepsy suffered from depression at the time of interview [17].

International collaboration between a developed and developing countries in the treatment of patients with epilepsy is mutually beneficial [18]. Both collaborating partners develop joint strategies to medically and surgically treat patients within restricted resources. If the center in the developed country has experience in a certain area such as epilepsy surgery, that experience will also help to gain the confidence of the patients in the developing countries. The Canadian Neurological Sciences Federation (CNSF) and Canadian Society of Clinical Neurophysiologists (CSCN) are developing means to improve communications between the Canadian physicians and those in the developing countries (Personal communication with Seyed M. Mirsattari, president CSCN).

We need not look far in the developing world to see such examples, South Africa, a country of 38 million people, has only 8000 registered medical practitioners out of which only 18 are neurologists, [5] and there is just one state hospital carrying out epilepsy surgery [19]. In 1997 there were no trained neurologists in Namibia, with a complete lack of investigational tools [14]. Nepal, a country of 21 million people, has a workforce of 7 neurologists equipped with 3

magnetic resonance imaging (MRI) scanners, 4 electroencephalograms (EEG) machines, and just 10 computed tomography (CT) scanners [20]. The condition in other developing countries is similar. Few countries like Pakistan, India, and Iran that have trained neurologists and neurosurgeons lack technical resources [5].

Keeping the described scenario in mind, International collaborations among developed and developing countries for setting up comprehensive epilepsy surgery programs are very important. It may not be possible to provide the most sophisticated or costly of investigative technologies in developing countries. However, a model for a comprehensive epilepsy program in the developing world has been developed for treatment of pharmaco-resistant TLE using technology and expertise reasonably available in the developing world [7]. This model relies on partnering with epilepsy experts so that expertise and available knowledge can be shared with the developing countries. In developing countries that have capable neurologists and neurosurgeons, this interaction greatly expands the capacity in developing countries to embark on more expertise driven medical approaches such as the evaluation of pharmaco-resistant epilepsy and treatment with surgery for epilepsy.

## 3. Epidemiology of Epilepsy in Pakistan

The most recent data on the prevalence of epilepsy in Pakistan comes from a population-based survey conducted in 1994. The authors found an overall prevalence rate of 999 in 100,000, with an increased prevalence in rural areas (1480 in 100,000) as compared to urban areas (740 in 100,000). The authors noted that treatment status was deplorable in rural areas, with only 2% of patients receiving AEDs in rural settings compared to an equally poor 27% patients in urban populations [21]. Based on this study, an estimated 1.38 million people suffer from epilepsy in Pakistan. In 1994, the population of Pakistan was estimated to be 126 million, making it the ninth most populous country in the world. The number of these patients eligible for epilepsy surgery remains unclear; however, figures extrapolated from available data suggest that around 34,000–45,000 potential surgical candidates are present in the Pakistani population indicating a dire need for a comprehensive epilepsy center [1].

## 4. Steps in Setting up an Epilepsy Surgery Center

*4.1. Choice of Location.* The resources required in setting up a comprehensive epilepsy center are substantial; the choice of location is thus of utmost importance. The location must be central and accessible to most parts of the country and nestled close to tertiary medical and diagnostic facilities vital to its operation. Of equal importance is the access via road, rail, and air. Preferably, the comprehensive epilepsy center should be a part of a tertiary medical center in order to better manage presurgical patients and their postoperative care.

In our setting for Pakistan, Karachi appears as an ideal choice. The city ranks as a beta world city, for its significant impact on the global economy. It is home to 18 million

approximately 11% of Pakistan's population. Augmenting this resident population is the constant influx of seasonal migrants and traders, providing a wide mix of ethnic and cultural backgrounds. As the major center of trade, commerce, and industry, it has access to all parts of the country via strategic sea, road, rail, and air links.

On the biomedical front Karachi has been a major center for research in the country and the region. It is home to nearly 30 public, 80 registered private hospitals and specialized health units, and 12 recognized medical colleges. Additionally a vast number of health care services are available across the city, owing to which it is a major destination for medical tourism with visitors from across the country and its neighbors.

The Aga Khan University Hospital, which is a private university hospital, pioneering this project, is among the leading hospitals in South Asia, chartered in 1983 and accredited by the Joint Commission International Accreditation (JCIA) in 2006. It is associated with the Aga Khan University, a private, autonomous, and international university that promotes human welfare through research, teaching, and community service.

*4.2. Collaborations and Telemedicine.* Telemedicine has opened new frontiers for world-wide healthcare and global collaborations. Its applications and implementations as a medical tool have expanded by leaps and bounds over the last decade, providing ease of communication between collaborating centers.

Between June 2006 and July 2008, 17 teleconferences were successfully arranged between the Aga Khan University (AKU), Karachi, Pakistan, and University of Alberta Hospital (UAH), Alberta, Canada [18]. The teleconferences were focused on discussing challenging cases in epilepsy, and brainstorming the setting up of an epilepsy surgery center at AKU under guidance of the previously established center in UAH. In January 2008 the program was extended to include University of West Virginia (UWV) in the collaborations. Dr. Warren W. Boling from UWV visited our center and performed SAH on selected patients along with local neurosurgeons.

File transfer protocols (FTPs) were also successfully established enabling the participants to share power-point presentations, patient details, scans, and video-EEG files effectively. Facets requiring special attention when initially setting up international telemedicine collaboration included the difference of time zones, compatible high-speed connections, audio backup, hardware and software compatibility, and connection security. These important technical and practical aspects need to be kept under consideration along with the possibility of technical incompatibility and failure. Details of our personal experience in successfully establishing telemedicine conferences have been discussed previously in order to aid other developing countries planning to embrace this technology and setup similar collaborations [18].

*4.3. Gaining Patient Confidence.* Among other factors, lack of knowledge, social stigma, cultural myths, and minimum

resources create an impediment for the treatment of epilepsy patients in developing countries. Furthermore if they do manage to cross this barrier, the lack of facilities and trained personnel adds to the shaky confidence these patients have in the surgical management of these problems.

An integral part of establishing a comprehensive epilepsy surgery program is gaining patient confidence in the procedure. After identifying potential candidates for surgery, patients and their families were initially included in the teleconferences to discuss the potential risks and benefits of epilepsy surgery with our collaborators. Multiple interactive sessions were held between the families and the collaborators to remove any doubts before the candidates for surgery were finalized. Interaction with these foreign teams played a central role in gaining confidence in the patients for surgery.

When our collaborators came to the center, numerous public education programs were held for patients and their families.

*4.4. Procedures Performed.* Patients were carefully selected by our team of epileptologists. For the initial stages in the development of comprehensive epilepsy center, we considered patients who were suffering from medically refractory seizures secondary to MTS or evident brain pathology. After detailed selection and preoperative assessment, 16 patients were operated; of the 16 patients 4 underwent selective amygdalohippocampectomy (SAH) under international collaboration.

The use of cerebral hemispherectomy for seizure control was carried out in patients in whom the seizure focus was lateralized, though diffusely localized to one hemisphere. Major indications for HS included progressive chronic encephalitis (Rasmussen's), extensive Sturge-Weber syndrome, and infantile spasms. Patients who were suffering from TLE secondary to MTS were selected for ATL. Later on there was a change in surgical philosophy by switching to SAH in patients with classic MTS with international collaboration. This transition was smooth as basic requirements like Video EEG and MRI scanner, and frameless neuronavigation guidance system was already available.

For SAH candidates, the surgery was carried out with the assistance of an intraoperative neuronavigation system (Medtronic Stealth System). The patients were positioned supine with their heads fixed in a Mayfield clamp and turned to the contralateral side. A minimally invasive approach was performed with a linear preauricular incision, followed by the dissection of the temporalis muscle. A 3 × 3 centimeter craniotomy was performed. The dura was incised using a cruciate incision, followed by a standard middle temporal gyrus dissection developed by Niemeier and popularized by Olivier [22]. The amygdala and hippocampus were observed under microscope and confirmed by neuronavigation. An attempt was made to perform enbloc resection of these structures. Specimens were then sent for histopathological examination.

Postoperatively the patients were kept in high-dependency units for 24 hours, after which they were shifted to regular care units. The average day of discharge was postoperative

TABLE 1: Dominant seizure types based on clinical assessment for all the 469 patients included in the study.

Simple partial	Complex partial	Primary GTC	Secondary GTC	Others, for example, JME, BRE	Unclassified
7%	16%	43%	19%	3%	12%

day 3. After discharge each patient was regularly followed by a neurosurgeon and an epileptologist. Postoperative AED management was under the discretion of the epileptologist.

## 5. Results

Six hundred and nineteen patients either visited or were referred to the epilepsy clinic, out of which 573 records were accessible for review. One hundred and four patient records were excluded from the study as the diagnosis of epilepsy was not established. Four hundred and sixty-nine patients were diagnosed as true cases of epilepsy, confirmed by either of the two epileptologists (Table 1). The visiting patients included 252 (53.6%) males and 217 (46.3%) females. Eight of the patients had history of seizures since birth, and 278 patients (60%) had their first seizure before the age of 12 years.

Three hundred and six patients underwent EEG evaluation of which eighty-eight patients' (28.8% of 316) EEG reports demonstrated focal abnormalities and 66 (22% of 316) had more specific findings supporting TLE (temporal spikes, sharp waves, or dysfunction). EEGs were not performed in the remaining patients due to the patient's financial situation or the fact that the neurologists were able to clinically classify and manage the patients based on their clinical manifestations and history. The neurologists diagnosed 84 patients with TLE. The average cost of EEG in Pakistan is US\$ 50 (Figure 1).

Seventy four of the 84 patients diagnosed as TLE (88%) had undergone EEG testing, and 66 had temporal spikes, sharp waves, slow waves, or temporal dysfunction. The other 8 patients had normal EEG findings. MRI was done, and a radiologist's report was available for 52 (62%) of the 84 TLE patients. All MRI images of selected patients were reviewed by epileptologist and neurosurgeon as well. Video EEG was not conducted in most of these patients secondary to a lack of resources and financial constraints.

Twenty-four patients with TLE were refractory to drug therapy, while the remaining was either well controlled with medication or undergoing drug trials. Around 10% of the patients with TLE had mental retardation or delayed milestones, while 7% of those with TLE had moderate-to-severe psychosocial problems like depression, severe anxiety, or outbursts.

Out of all patients who were candidates for epilepsy surgery, sixteen patients consented for surgery. We retrospectively reviewed these sixteen cases of epilepsy surgery and assessed their outcome on the basis of Engel's classification for seizure control.

Of the sixteen patients who underwent surgery for medically intractable epilepsy, ten were male. Average age was 22 years. Functional hemispherectomy (HS) was done in six patients who had TLE plus anterior temporal lobectomy



FIGURE 1: One of the epileptologists performing an EEG evaluation on a patient.

(ATL) in six and neuronavigation-guided SAH using keyhole technique in four patients (Figure 2). These four cases of SAH are those which were carried out after international collaboration. The average operative time for SAH was two and half hours as compared to three hours in case of ATL. Similarly the average blood loss was 200 cc in SAH as compared to 350 cc in ATL. HS had maximum average blood loss among all the three procedures, which was around 600 cc. Because of less invasive technique involved in SAH, patients in this group showed early recovery and shorter hospital stay as compared to other groups. There was minimal morbidity and no mortality in ATL and SAH groups. Poor outcome was encountered in only two patients; both patients had undergone functional HS. One developed hemiplegia and the other died of postoperative acute cerebral edema. The average duration of follow-up was 12 months, 24 months, and 48 months for SAH, ATL, and HS, respectively. Seizure control was assessed using modified Engel's classification. All patients in SAH group (100%) had Grade 1 control, while 5 patients (83%) in ATL group and 4 patients (66%) in HS group had Grade 1 control (Table 2).

**5.1. Cost.** Of the four patients undergoing SAH, two opted for regular inpatient care, while two opted for private care. The average direct cost for the patients undergoing regular inpatient was Rs. 148,000 (US\$ 1644) whereas the direct cost with private care rose significantly to an average of Rs. 274,000 (US\$ 3044). Of interest to note here was that the patients under private care had a longer mean hospital stay (3 days more than those under regular care) due to reluctance of the patient's family to leave early. This cost, however, was the direct cost associated with the procedure and primary admission. It does not include the cost of



FIGURE 2: One of our pilot patients undergoing SAH with international collaborators.

TABLE 2: Summary of the procedures performed.

	SAH <i>n</i> = 4	ATL <i>n</i> = 6	HS <i>n</i> = 6
Blood loss	200 cc	350 cc	600 cc
Surgery duration	2 : 30 hours	3 hours	4 hours
Hospital stay	4 days	8 days	10 days
Followup	12 months	24 months	48 months

preoperative evaluation including neurology consultations, MRIs, EEGs, and so forth.

This cost is significantly lower than the cost in other developing countries. In the year 2000, a study came from Chile reporting a total cost of US\$ 5,020 including preoperative evaluation and surgery for an anterior temporal lobectomy (ATL) [23]. Similar paper came from neighboring country India in which the total direct cost of US\$ 5000 was reported for an ATL. Keeping inflation in mind, these costs would be much higher today.

Compared to other centers in the region and other developing countries, our surgical center appears to provide cost-effective treatment and in the long run may cater to patients from nearby regions.

**5.2. Sustainability of the Program.** Even with the collaboration of the international epilepsy surgery team, sustainability of the established program was an important aspect. The whole inpatient and outpatient management was done by residents of the in house neurosurgical program under the supervision of their attending surgeons and the international collaborators. This enabled our team to be actively involved in all aspects of patient care and become acquainted with all stages from preoperative assessment of patients to microsurgical techniques and postoperative care required to carry on epilepsy surgery.

In addition, didactic teaching sessions were conducted, which included seminars and case discussions. Neurosurgeons and residents from across the country were invited to participate in these sessions in order to increase their knowledge in epileptology. Special attention was given to senior

residents in order to develop their interest in surgical treatment of epilepsy. Apart from the interactive sessions, numerous formal and informal discussions were arranged with neurologists, neurosurgeons, fellows, technologists, nurses, and medical students interested in epilepsy surgery. A nationwide three-day epilepsy workshop was organized on similar lines as that of the Physician's Assistant Program through Bowman Gray [24].

## 6. Conclusion

As we share our experience in setting up a comprehensive epilepsy center in a developing nation, with international collaboration, we hope to set a practical example for economically constrained countries that comprehensive epilepsy centers can be managed with limited resources.

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## Review Article

# Language Mapping in Temporal Lobe Epilepsy in Children: Special Considerations

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Received 29 July 2011; Accepted 6 November 2011

Academic Editor: Seyed M. Mirsattari

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Temporal lobe epilepsy (TLE) in children is a slightly different entity than TLE in adults not only because of its semiology and pathology but also because of the different approach to surgical treatment. Presurgical investigations for eloquent cortex, especially language, must take these differences into account. Most diagnostic tests were created for adults, and many of the assessment tools need to be adapted for children because they are not just small adults. This paper will highlight the specific challenges and solutions in mapping language in a pediatric population with TLE.

## 1. Introduction

In refractory temporal lobe epilepsy (TLE), it is important to be able to determine which hemisphere is dominant and hosts the majority of the language areas. When a patient is evaluated as a potential candidate for resective surgery, language mapping should be able to indicate which hemisphere is dominant and precisely identify where the language areas are situated within the brain.

While the general principle of mapping language for TLE in children might be the same as for adults, many challenges are encountered in the mapping process because children are not small adults but differ from adults in many aspects.

To understand some of the differences between children and adults in TLE features, a brief overview of TLE is provided, focusing on surgical candidates and preoperative investigations. Then, a brief summary of language development and lateralization differences between normal children and children with epilepsy is provided. Finally, various techniques for language assessment are described.

## 2. Temporal Lobe Epilepsy in Children

The semiology of temporal lobe originating seizures is not as well characterized in children compared to adults and is dependent on age. For example, infants have a predominance of behavioral arrests, they also tend to have more prominent convulsive activity than adults, and their seizures appear clinically generalized. In younger patients, the automatisms are first discrete and mostly orofacial, but the complexity of hand automatisms increases with age. After the age of 3 years, tonic or myoclonic spasms decrease, as do other motor phenomena, which might have been reminiscent of frontal lobe seizures, and the overall semiology becomes closer to that observed in adults [1, 2].

The etiology of the seizure in children is also different. Mesial temporal sclerosis (MTS) is the most common adult etiology, while in children it is relatively rare. In the pediatric population, when MTS is present, it is often accompanied by a neocortical pathology (dual pathology) [3–6], and curative surgery therefore necessitates a temporal lobectomy instead of a selective amygdalohippocampectomy to maximize the chances of being seizure-free [7]. Other pathologies, such

as focal malformation of cortical development, tumors (such as gangliogliomas and dysembryoplastic neuroepithelial tumors), are frequent and also necessitate a neocortical resection. Because language is not only affected by interindividual differences but also variably modified by epilepsy, exact language mapping is required before any neocortical resection to minimize postoperative neurological deficit.

Epilepsy surgery has been shown to lead to better cognitive development [8, 9] if the epileptogenic zone can be completely resected, but it also carries a higher risk of some language deficit (up to 50% in a series) [10].

### 3. Language and TLE

Language is progressively acquired over the years, and its development might be affected by seizures themselves, age at the onset of seizures, seizure severity, and the underlying pathology. Surgery also has a different impact depending on the age at which it is performed.

The general population, independent of handedness, has a 10–18% chance of having a right or bilateral dominant hemisphere (5% in a right-handed population and 22% in a left-handed population [11–14]) the majority of them are left handed. By contrast, among the epilepsy population, 77% have an atypical pattern for language (right or bilateral) as determined by the Wada test or functional MRI (fMRI) [15–17]. Language might be displaced to the contralateral hemisphere or be reorganized within the same hemisphere, either a different location in that hemisphere, or compensated with additional areas recruited [14, 15, 18–25].

It has also been shown that more children with epilepsy have an atypical language network than adults with epilepsy; whether these findings are correlated with the age of onset of the seizures is a matter of debate. Some studies have shown a difference in language pattern with early-onset seizures [17, 19, 26], while other studies have not been able to show that correlation [16, 27–30]. In addition, the percentage of atypical language seems even higher when the epilepsy is probably symptomatic (formerly known as cryptogenic, i.e.,: no lesion detected on the MRI) [21]. However, even if language could be influenced by seizures and might be shifted to the contralateral side in some patients, it could also remain in the “normal” anatomical location on the left even when the seizures are arising from that area [31], which is important to remember when considering surgery to treat epilepsy.

While it was initially thought that language lateralization was acquired later in life, recent functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) studies have shown signs of lateralization in infants, with the left frontal region being implicated in the discrimination of speech sounds, for example, [32–35]. However, there seems to be an increase in lateralization with age as shown by fMRI and MEG studies in normal children [36, 37], which could explain the better potential outcome in language reorganization following surgery before the age of 5–6 years [38–40]. Most studies have demonstrated a difference in

lateralization depending on the task. For example, verb-generation and story-processing tasks demonstrate more changes in lateralization over time than word-picture matching tasks [36, 41–43].

### 4. Tools to Map Language

All of the tools to assess language were developed in adults and then adapted for pediatric populations. While new technologies allow us to move away from invasive techniques, these technologies still carry challenges when applied to children. When considering all these methods, there are general constraints based on the age of the patient, which will be the same for all.

Currently, language assessment is not performed in infants and toddlers, except in specific research settings; therefore, the following will focus on children who have developed enough language skills to communicate and be tested by visual and/or oral questions.

Because all of the techniques require cooperation of the subject, it is important to keep age-specific abilities in mind when developing the tests. The attention span increases with age and is relatively short in younger children. In addition, antiepileptic drugs as well as cognitive delay resulting from epilepsy might affect attention span.

Cognitive psychologists have made us quite aware of the timeline of language development, which should be considered when developing tests of language function. Development of phonological, semantic, grammatical, and pragmatic components of language during childhood influences the design of the studies. To obtain satisfactory results and map the language accurately, it is essential to use tasks that are appropriate for the age of the patient.

In addition, processes occurring during brain development (such as the formation of synaptic contacts and myelination) also affect most of the imaging and mapping techniques and may thus influence the results. Their influence on each technique will be analyzed individually below. The last point to consider when interpreting the results of a patient compared to a study is that many imaging studies have a relatively small number of subjects, and the subject population is heterogeneous. For the same type of study, a pediatric study should have a larger number of subjects than an adult study because there is significantly more variability among children due to development, yielding an even more heterogeneous population.

The various mapping techniques are described below, beginning with neuropsychological assessment, moving to more invasive tests, such as cortical stimulation, sodium amobarbital (Wada) test, and nuclear medicine (Single-Photon Emission Computed Tomography—SPECT—and Positron Emission Tomography—PET), then to contemporary tools, which are being used increasingly more in the clinic (fMRI and MEG), and finally to newer tools that are currently being assessed, such as functional Near-infrared spectroscopy (fNIRS) and diffusion tensor imaging (DTI).

**4.1. Neuropsychological Evaluation.** In the context of epilepsy, clinical language assessment begins with a neuropsychological assessment that helps to determine lateralization and guides the decision as to whether more in-depth assessment is needed (i.e., if language is thought to be on the left and the surgery is a right temporal lobectomy, it is not generally necessary to investigate further). The neuropsychological assessment includes a battery of standardized, age-appropriate tests for language and memory, among other cognitive domains, such as attention, visual-spatial skills, motor skills, and executive functions, interpreted in the context of developmental milestones, academic skills, psychosocial functioning, and so forth [44]. This global assessment helps determine assets and deficits and detect whether the pattern is consistent with dysfunction in a specific region of the brain or with a known neurological syndrome.

As part of the neuropsychological test battery, fused dichotic word listening tests (FDWLTs) have proven to be cost-effective, noninvasive methods for identifying language dominance as left, right, or bilateral in adults, children, and adolescents [45–47]. During this behavioral test, different words are presented to both ears simultaneously, and the subject reports which one they heard. The number of correct answers for each ear is counted, and the value indicates a right or left ear advantage. The rationale behind this test is that contralateral projections from the ear to the brain are stronger than ipsilateral projections [48].

It is well known that ongoing seizures in refractory epilepsy can affect development therefore by reducing the number of seizures, surgery does help in ameliorating learning and general development deficits. However, studies show that temporal lobectomy of the dominant hemisphere, even in children, leads to some degree of postoperative deficit in language. A study of 24 children with complex partial seizures, aged 5.8–15.7 years, showed a preoperative left-language dominance in 65% of subjects, with an estimated language delay of 1.7–3.5 years. Postoperatively, these same children had an increase in language delay in all areas except for receptive syntax [49]. This increased language delay postoperatively might be less of a problem in younger children [50].

While language lateralization is important, it is not the only factor when considering surgery. The traditional notion of two areas well demarcated anatomically within the frontal and temporal lobes—Broca and Wernicke—has been replaced by the knowledge of a language network that has some interindividual variability [51]. When further information beyond laterality alone is required, imaging or further investigations with more language specificity are undertaken.

**4.2. Sodium Amobarbital or Wada Test.** The Wada test consists of an injection of intracarotid sodium amobarbital to freeze half of the brain to lateralize function. The procedure consists of a dose of 40–125 mg (depending on the body weight) of sodium amobarbital into the internal carotid through a femoral catheter. The catheter is usually inserted

under general anesthesia. Once the patient has returned to a normal baseline after anesthesia, the side where the seizure focus is present is tested first followed by the opposite side. The contralateral injection is typically performed 30–45 minutes after the first using the same procedure as for the first. Hemiplegia is first examined, and then language is tested either by a pediatric epileptologist or neuropsychologist. This is subject to variation from one centre to the next and is sometimes even performed on different days.

The sodium amobarbital test requires full cooperation of the child, who has been subjected to a stressful situation because the injection also causes transient hemiplegia. While the situation can be explained and tolerated by older children (teenagers) [52, 53] or adults, it is extremely difficult in younger children. Nonetheless, successful sodium amobarbital testing has been reported in children as young as 2 years old [53, 54]. In a study that tested 22 patients between the ages of 5 and 12 years (median 10), language lateralization was clearly identified in 50% of patients; ten children had left hemispheric language while one had a right hemispheric dominance. Furthermore, the percentage of successful sodium amobarbital procedures was higher among children with higher IQs (100% over IQ 70, 57% of IQ < 70) [53]. A later study from the same group reported a 62.5% success rate in 42 children; 7.5% failed because of inconclusive results from the test (intact language after both injections, or a mix of intact language after one injection and then noncooperation), and 30% failed because of inadequate cooperation [55]. Similarly, Schevon reported a successful sodium amobarbital test in 57% of patients younger than 10 years but as high as 93% in patients older than 10 years of age [54].

However, the information obtained during the sodium amobarbital test is whether language is impaired after injecting sodium amobarbital into a particular side and therefore determines the dominant side. It might help to detect some bilateral patterns and predict language deficit after a proposed surgery; however, a cortical map of the language network cannot be created based on this procedure. Another useful function of the sodium amobarbital test, which will not be discussed here, is to assess memory, which can be performed in the same setting.

**4.3. SPECT and PET.** Nuclear imaging, such as Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET), has been used in the past to map eloquent cortex, including language areas. However, even though studies have shown good correlation between nuclear imaging and intraoperative language mapping [56] or sodium amobarbital tests [57], such imaging exposes children to radiation. Furthermore, these imaging methods are limited by the lack of spatial and temporal resolution [57–59]. SPECT (especially SISCOM techniques—the subtraction of the ictal and interictal SPECT then registering to the MRI) and PET are still used to find the epileptogenic zone, but, currently, they are not as commonly used to map language [60, 61].

**4.4. Cortical Stimulation/Mapping.** Cortical stimulation to map eloquent cortex was described by Penfield in the early 1950s [62]. However, because the procedure required a cooperative patient in the operating room, until the advent of implanted subdural or depth electrodes, it was only amenable to older children or adults.

Leaving subdural electrodes in place allows the use of cortical stimulation in the perioperative period. It also allows distribution of the language tests and mapping on different days, which is more suitable to children's shorter attention spans. However, because it is invasive and carries some surgical risks, subdural electrodes, grids, or depth electrodes would not only be implanted for language mapping, but might also be used when invasive recording is otherwise necessary to determine the epileptogenic zone. Of note, only a restrictive part of the brain is exposed and, therefore, available for testing. Another drawback of this method is the fact that, especially with strips and grids, only the gyri are recorded and the activity in the depth of the sulci is not.

The main difference between cortical stimulation mapping (and the sodium amobarbital test) and the other mapping techniques is the fact that stimulation directly interferes with the language task under examination. Therefore, cortical stimulation identifies areas that are critical to language instead of highlighting active areas that are part of the language network for a given task but might not be essential (such as seen with nuclear medicine or fMRI).

Even though perioperative testing made stimulation more amenable to children and can now be performed by the bedside without restricting the child's movements significantly, it has again proved to be more difficult in children than in adults [54, 63–65]. Standard stimulation protocols used in adults had to be modified to obtain some response from the stimulation in children. Most studies use variations of the Jayakar et al. protocol [63] using rectangular biphasic pulses of current on two adjacent contacts, starting the stimulation at 1 mA with a 0.3 ms pulse of alternating polarity and a train duration of 3–5 seconds. The stimulation intensity is then increased by steps of 1 mA and pulse duration by steps of 0.1–0.2 ms until after-discharges are seen, a seizure occurs, or there is a physiological response (speech arrest, motor, or sensory response) [63]. The various protocols use frequencies in the 20–50 Hz range, an intensity between 1 and 20 mA, a pulse train 3–25 seconds in duration, and a pulse width between 0.14 and 0.2 ms [54, 66–68]. While intensities as low as 2–4 mA in adults generally evoke a response, in children, those intensities might have to be as high as 16–17 mA to be effective [67, 69–71].

The possible reasons for the difficulties encountered include incomplete myelination and the greater proportion of small fibers. The chronaxie, which is the pulse duration needed for stimulation to evoke a response, is directly affected by the myelin deposition, and increasing myelination leads to a decrease in time of chronaxie [63].

Schevon et al. found that 10.2 years was a cut-off age for successfully mapping cortex. He studied children with both the sodium amobarbital test and cortical stimulations and found that, before the age of 10, 19% of children had positive cortical stimulation versus 87% for children older than 10

[54]. While a positive response is in general synonymous with critical language areas, having no response does not rule out critical language involvement in that area. The tasks administered during the stimulation are important, and, for example, expressive tasks show a better correlation with the sodium amobarbital test than receptive tasks [72]. However, within the expressive tasks, the generation of sentences might generate a larger perisylvian network of expressive and receptive language [73, 74] than a verb-generation task.

Various studies have used cortical stimulation to study intrahemispheric reorganization of language in epileptic patients. For example, Kadis et al. [75] demonstrated anterior reorganization of language in expressive language in the left frontal lobe.

**4.5. fMRI.** The basics of fMRI will not be discussed here because they are explained in another chapter of this issue (Wang et al.—Functional Magnetic Resonance Imaging for Language Mapping in TLE).

Once again, pediatric fMRI studies are more challenging than most adult fMRI studies. First, the cognitive level of the child is dependent on his age; therefore, the battery of tests should be age dependent. In addition, it is more difficult for a child than an adult to stay perfectly still in an MRI during acquisition of the task. Yuan showed a difference in age and gender in the motion of the head during acquisition; younger (5- to 9-year-old) male children moved the most. All groups moved less when engaged visually instead of just with an auditory stimuli (picture-word matching versus syntactic prosody, story processing, and verb generation) [16]. Another study showed a similar trend and demonstrated better results in children with normal developmental milestones as well as older children [76].

In addition, because children have smaller heads, the head coil should be adjusted for younger age groups. This modification is especially important for younger patients who, in addition to a small head have a shorter neck, would have their head in the lower quadrant of the coil if using an adult coil. In addition, the thickness of the skull changes with age, which influences the quality of the image. To adjust for all ages would require an institution to have different head size coils and to avoid surface coils that increase heterogeneity due to the thinner skull (signal is enhanced in thinner skulls of younger compared to older people) [77, 78]. Thinner skulls also produce increased physiological noise due to the increased heart and breathing frequency in children.

The entire MRI environment should be adapted to children. First, the addition of videos for viewing at the beginning of the acquisition, during the anatomical MRI as well as in between runs, would likely reduce motion artifact. Second, the buttons subjects push to answer questions should be adapted to smaller children's hands. Third, the child should be brought into the room and the magnet before the task without being rushed to acclimatize to the environment [77]; he/she should be fully prepared for the task and the environment before beginning the session [79].

Despite the above-mentioned problems, fMRI is starting to replace sodium amobarbital tests and cortical stimulation

as a clinical tool for language mapping in some comprehensive epilepsy centres because it is less invasive, has a good spatial resolution (1–3 mm), and shows a good correlation with more invasive techniques [15, 72, 80–82].

fMRI can be used to investigate lateralization of language (laterality indexes are calculated based on the number of voxels activated on each side [82]) as well as to show a more precise localization of language areas. The areas with activated voxels are specific to the task being tested. As previously stated, there are various types of tasks that can be used, some active (verb generation, semantic decision, sentence completion, etc.) and some involving passive listening. The activations can be analyzed by contrasting any of these tasks with a resting state, during which the patient is instructed to do nothing, or between any of the conditions. The language map (pattern and lateralization) resulting from the analysis should differ depending on which tasks have been studied and contrasted [83].

Language protocols have to be developed especially for children and according to their age groups. In addition, delay in language development is common among epileptic children, which should be taken into account and tested before putting the child in the scanner.

fMRI shows the entire network of areas involved in the specific task (Figures 1 and 2). Because it is important to be as sensitive as possible to decrease the risk of postoperative deficit, paradigms capturing a wider network are usually preferred in pediatric populations (i.e., verb generation). While some studies have shown the possibility of performing 3–4 language tasks during image acquisition, so many tasks might be difficult in a clinical setting where the available time to train the child on the task and to remove him/her from the magnet in between tasks is less. However, one must be aware that only one language task might not be enough [84]. The authors illustrated with two case reports that hemispheric dissociation in language function is possible, which can only be detected when administering different types of language tasks (i.e., vowel identification tasks and “beep” story) [84].

The design of the study must be carefully developed to adequately capture the language network. Verb-generation tasks, in which the subject is asked to generate a maximum number of verbs related to a noun that is being presented (i.e., horse: jump, ride, etc.), seem to have a good reliability in determining hemispheric dominance [41, 82, 85].

Story-processing tasks, in which the subject listens to a story with the instructions of listening carefully enough to be able to answer questions on each story after the MRI, seem to produce wider bilateral activation and show some asymmetries in pathological subjects [86, 87].

Another task commonly used in settings is a picture-word matching, in which the subject sees one or a couple of images and must decide whether it matches the name that is presented orally [42].

In younger children, a passive language (listening) task can also be used for patients between the ages of 2 and 4 years. However, it is difficult to control whether the subject is actually listening to the story as opposed to dreaming or sleeping [88].

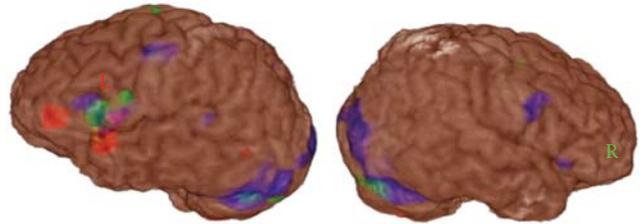


FIGURE 1: Example of fMRI with the superposition of different language tasks. While most of the tasks produce a left dominant hemispheric language activation, naming has a bilateral activation in the Broca area. Red: Verb generation, Green: sentence completion, Blue: naming.

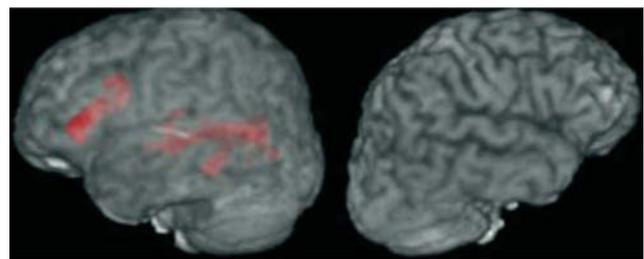


FIGURE 2: Another example of fMRI language activation map. This time the language map is solely left hemispheric in this sentence completion task.

In each task, different designs for each age group must be developed to provide an appropriate level of difficulty for the patient.

All tasks should include resting states or control tasks, such as button press, sensory test, or a finger-tapping task, to compare the task data to.

Additional unknowns remain when performing pediatric fMRI. The fMRI signal uses the hemodynamic response and the changes in oxyhemoglobin and deoxyhemoglobin to determine which areas of the brain are activated. Because cerebral blood flow varies across ages, should it be corrected for age when doing a group study? Does the immaturity of the brain affect the BOLD signal [88]? The grey/white matter ratio also varies greatly until the age of 7 years then continues to change over time [89]. The major fiber pathways are in place by the age of 3, but the average density of neurons and synapses changes until the age of 16, when it stabilizes until the late 60s. At the age of 7, the average synaptic density of the frontal lobe is approximately 1.4-fold greater than that of an adult [77, 90]. Do these developmental variations provide a stable enough environment to use the same methods of analysis when investigating a pediatric population? While most pediatric studies that have analyzed correlations with other modalities have found a good correlation, which indicates that fMRI seems to yield valid data even in children, those questions have to be considered.

The last caveat when using fMRI is analysis of data. The pediatric brain differs from an adult one, so group studies should not be normalized to an adult atlas, such as the Talairach atlas [88, 91, 92]. Recently, a pediatric atlas was

developed and should be used instead [93]. This problem does not occur in a clinical setting in which the images of the patient are directly coregistered to his/her own anatomical MRI.

Careful analysis of the data is of paramount importance, keeping in mind that misused statistics can show anything. One should be sure of how the analysis has been performed and of the statistical value of the results before interpreting the data.

Similar to other functional imaging modalities, fMRI can be used to assess verbal and non-verbal memory. While in adults, memory mapping by fMRI is sometimes used as a clinical tool, it is usually part of a research protocol in the pediatric population. Because the hippocampus represents only a small area, the motion artifact and the difficulty of the tasks (without real-time feedback to know if the child is actually doing the task), it is difficult to have a valid study in a child.

While it is not as evident as using MEG, some studies have attempted to use fMRI to detect interictal spikes (spike-triggered fMRI) [94, 95].

## 5. Emerging Techniques

**5.1. MEG.** The creation of superconducting quantum interference devices (SQUIDs) in the late 1960s/early 1970s allowed a different method of recording of brain electrical activity [96]. MEG captures neuronal activity by recording the net current of the flow of ions, leading to an intracellular electrical current generating a magnetic flux. Repetitive events generate event-related potentials leading to evoked magnetic fields, which can then be recorded by the 248 channels positioned around the head. Because magnetic fields are less deformed than electrical fields on the scalp, the spatial resolution of the MEG (2–4 mm) is better than the EEG, and the images can be coregistered with an anatomical MRI to visualize them. In addition, because MEG measures neuronal activity, its temporal resolution is excellent ( $10^{-3}$  sec) [97].

In epileptic patients, MEG allows the recording of interictal spikes, sometimes seizures, and eloquent cortex.

Breier et al. demonstrated a good correlation between an MEG study and sodium amobarbital test in the pediatric population [98] such results have been reproduced in adults too [99]; Papanicolaou et al. [100] showed no differences in language pattern with age, but other studies on normal subjects comparing MEG to fMRI for receptive language mapping showed significant differences in language patterns between the two methods [101], and another study showed good concordance between MEG and fMRI lateralization in normal teenagers for picture verb-generation, but only 75% concordance for the word verb generation task, and even lower when looking at precise localization (voxel overlap 50%) [102]. In patients requiring surgery near language-related eloquent brain areas (mostly for tumors), a German group combined MEG and fMRI and showed a good congruence between the two modalities (96%); however for some patient language activation was only seen in one

of the modality [103]. MEG is still in its infancy when considering language mapping in epileptic patients, and more studies are required to see how it can be used in presurgical planning. The National Institute of Neurological Disorders and Stroke is currently recruiting patients for a large trial (NCT00706160).

**5.2. fNIRS.** Near-infrared spectroscopy is a noninvasive technique used to measure hemodynamic changes using the different light absorption spectra of oxyhemoglobin (HbO) and deoxyhemoglobin (HbR). It necessitates a light-emitting source (at two different wavelengths, usually between 680 and 1000 nm), a detector, and a dispersive element. This method is also called optical tomography because it uses an exogenous optical tracer to extrapolate the blood flow, blood volume, or oxygenation of a specific region of the brain. For example, it can be used in conjunction with a bolus injection of indocyanine green to measure cerebral blood flow. It is also used to detect changes produced by neuronal activity (similarly to fMRI). When there is regional activation during a task, there is an “initial dip” with a reduction of HbO and an increase of HbR, then a large increase of HbO and a decrease of HbR (focal arterial blood flow). Because of the shallow penetration of photons (3–5 cm below the scalp), the activity of the cortex can be monitored but not activity of deeper structures [104].

The advantage of fNIRS is that it does not restrict the child to a small space such as an MRI scanner does, and because the device is directly on the head of the child, motion artifacts are not a problem. The other advantage of fNIRS is that the child can actually speak during the task; therefore, his understanding and involvement in the task are actively monitored.

fNIRS seems to be more sensitive to bilateral speech pattern, which is sometimes more difficult to analyze with fMRI, as shown by Benke et al. [105], when there is a dissociation between frontal and temporal activations [104, 106, 107]. However, fNIRS is currently only used in research and in some specific centers.

**5.3. DTI.** Diffusion tensor imaging is a technique that enables tracing of neuronal tracts in the brain. Because of the tubular nature of neurons, water can move freely in the direction of the axis but is restricted transversally by the membrane. When applying various field gradients to the brain in the MR scanner, the difference between the diffusivity in the two axes can be represented by a tensor and subsequently mapped to the brain by coregistering it with an anatomical image to obtain mean diffusivity and fractional anisotropy maps. These maps can aid in the understanding of functional connectivity of the brain by displaying fibers connecting two regions [108, 109].

There are currently no pediatric studies investigating the use of DTI and fMRI together for language mapping. However, in adults, a few groups have tried to predict language lateralization by studying the arcuate fasciculus, inferior longitudinal fasciculus, or uncinate fasciculus and their asymmetry reflected by the anisotropy value [110], the

association between anisotropic or mean diffusivity values and language deficits in patients with TLE [111], or finally with DTI and cortical mapping to assess colocalization of language areas in the anterior and posterior part of the arcuate fasciculus. A number of studies have shown that increased mean diffusivity and decreased fractional anisotropy, interpreted as structural compromise of the white matter tracts, are associated with language deficits in patients with epilepsy [111–114].

**5.4. TMS.** Transcranial magnetic stimulation (TMS) is a noninvasive technique, which uses focal magnetic field generated by a rapidly changing current within a conducting coil. The coil can be applied to the scalp, so the magnetic field has a direct effect on the brain by depolarizing or hyperpolarizing neurons. Experiments have shown that TMS can induce a transient change in behavior by interfering in a manner similar to cortical stimulation. There are several methods for delivering the magnetic field, including single-pulse, paired pulse, and repetitive pulses.

A first study on language and TMS was performed in adults by Pascual-Leone et al. [115], who was able to induce speech arrest when stimulating the perisylvian cortex with 10-s trains of repetitive TMS (rTMS) applied at rates of 8–25 Hz. Variations in the frequency of the stimulation were tried, and speech was also disrupted at 4 Hz in another study [116]. The same group showed a good correlation between sodium amobarbital test and TMS in 12/16 epilepsy patients [117], while other studies showed better even better correlations [115, 118].

While some studies have been performed in children and one review article described the safety of TMS in children (including a potential for increased risk of seizures in children younger than 5 years [119]), there are no language studies in this group of patients. Some motor studies have shown that it is feasible [120]; however, recommendations state that TMS should be avoided in young children [119].

## 6. Conclusion

Language mapping in children requires a specialized multidisciplinary team with specific protocols designed from a developmental perspective. However, an increasing number of noninvasive techniques have been shown to be reliable and are being implemented clinically in preoperative investigation for epileptic children.

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## Review Article

# Neuropsychology in Temporal Lobe Epilepsy: Influences from Cognitive Neuroscience and Functional Neuroimaging

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Received 4 July 2011; Accepted 9 October 2011

Academic Editor: Seyed M. Mirsattari

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Neuropsychologists assist in diagnosis (i.e., localization of dysfunction) and in prediction (i.e., how cognition may change following surgery) in individuals being considered for temporal lobe surgery. The current practice includes behavioural testing as well as mapping function via stimulation, inactivation, and (more recently) functional imaging. These methods have been providing valuable information in surgical planning for 60 years. Here, we discuss current assessment strategies and highlight how they are evolving, particularly with respect to integrating recent advances in cognitive neuroscience.

## 1. Introduction

Neuropsychologists have been core members of epilepsy surgery teams since the 1950s. In his excellent historical review, Loring [1] notes that this began contemporaneously at centres at the University of Illinois, the University of London, and the Montreal Neurological Institute/McGill University; at each institution, there was a close collaboration amongst surgeons, neurologists, and neuropsychologists. As these surgeries were performed in many instances “blind” to any structural abnormality underlying the seizure focus, the initial task of the neuropsychologist was to provide converging evidence for localization, together with EEG (and later CT/MRI), by characterizing the focal functional deficit. Another key objective was to use the assessment to predict how function might change following surgery in an attempt to avoid catastrophic cognitive losses; this was a task for which neuropsychology was uniquely qualified. Prediction of more subtle changes also required a substantial investment in systematic postsurgical assessments that would provide the evidentiary basis for those predictions, and this is an important legacy of Brenda Milner at the MNI, whose contributions to the field are widely appreciated.

The goals of localization/diagnosis and prediction of change remain at the forefront of neuropsychology practice

in epilepsy surgery programs, which relies primarily on the use of standardized neuropsychological tests with proven sensitivity and specificity in this population. However, there is a growing appreciation that additional information from tools such as structural MRI (e.g., presence/absence of mesial temporal sclerosis) need to be incorporated into our models to improve accuracy. Furthermore, neuropsychologists recognize that characterizing both the functional integrity of the tissue to-be resected as well as the functional reserve of the rest of the brain to a high level of accuracy for the individual patient requires that we continue to develop more sophisticated conceptualizations and analytic tools. In particular, as we come to understand how cognitive operations such as memory are supported by somewhat flexible and overlapping brain networks, new modes of analysis are required. Finally, recent data clearly show both that there is a fair degree of reorganization of these networks in patients with temporal lobe epilepsy (TLE) and that even when seizures are exclusively in mesial temporal regions, there is more widespread anatomic and functional disturbance [2]. In our view, this means that the neuropsychology of epilepsy is at, perhaps, another “landmark” period in its development. In this paper, we share some of our thoughts regarding the state of the art and the ways forward in that trajectory.

## 2. Neuropsychological Assessment of Memory

In general terms, the neuropsychological evaluation of individuals with epilepsy involves the administration of an extensive battery of standardized behavioural tests tapping multiple cognitive domains (intellectual abilities, attention, visuospatial skills, language, executive function, and memory) with an emphasis on laterality [3]. In temporal lobe epilepsy, while determining language lateralization is a priority, extensive memory testing has been at the core of this assessment, initially motivated by the report of severe postoperative memory decline in two individuals who underwent unilateral resection, PB and FC [4]. Their devastating memory outcome was attributed to dysfunction of their remaining right temporal lobes given that their memory decline was of similar magnitude to that noted in HM who underwent bilateral temporal resections [5]. These findings highlighted the importance to test for functional reserve of the contralateral mesial temporal lobe, in addition to test the functional adequacy of the to-be-resected temporal lobe. Some of the typical standardized tests of memory and language used in presurgical assessments are described in Table 1; more complete descriptions, specific test citations, commentaries, and norms can be found in a comprehensive compendium of neuropsychological tests [6].

## 3. Material Specificity

A key concept in assessing the function of each temporal lobe “independently” is the material-specificity principle which proposes that verbal memory is a function of the left temporal lobe and visual or spatial memory is a function of the right temporal lobe [7]. In practice, the neuropsychologist compares an individual’s verbal memory and visual memory to normative data as well as to each other. The presence of an asymmetry provides information on lateralization of dysfunction (e.g., left for poor verbal), and performance on the nonepileptic temporal lobe provides information on reserve. Impaired performance on the latter would raise concerns of significant risk to memory postoperatively and additional investigations (e.g., the intracarotid amobarbital procedure or IAP) would be indicated. The level of functional integrity of the to-be-resected temporal lobe also helps predict postoperative outcome as patients with intact preoperative function have “more to lose” following surgery relative to those who show a memory asymmetry concordant with EEG and/or MRI findings.

While the material specificity principle generally holds true, especially with respect to verbal memory [8, 9], its reliability in identifying laterality of dysfunction is not perfect. Saling [10] identified two main issues. First, sensitivity of verbal memory tests to left mesial temporal damage is variable across instruments, suggesting that verbal memory is not a unitary construct. For instance, people with left TLE (but not right TLE) show impaired memory for word pairs but have intact memory for prose passages [11]. Second, many visual memory tests lack both specificity and sensitivity to right TLE. Some studies do show a relationship between right TLE and visual memory [12–14], but others do not

or show impairments of similar magnitude in both left and right TLE [15].

Additional concepts from contemporary neuroscience may supplement the material specificity principle and improve our ability to characterize functional adequacy and reserve. Some of these can be applied currently in test selection and interpretation (at least with respect to localization), as well as in the development of new standardized clinical tests, although much of this translational work remains to be done. Several models propose that the temporal lobes are functionally heterogeneous; different memory systems, processes, or types of information rely on different regions of the temporal lobes. Here, we review distinctions between episodic and semantic memory, relational and nonrelational processes, as well as the hippocampus’ involvement in pattern separation and consolidation.

## 4. Semantic versus Episodic Memory

Declarative memory includes two memory systems, namely, semantic memory (i.e., conceptual knowledge about words, the world and the self) and episodic memory (i.e., memory for personally experienced events with a spatiotemporal context [16]). Based, in part, on double dissociations noted in patients with mesial temporal lobe (MTL) damage or disease and with frontotemporal dementia (e.g., [17]), it is widely accepted that the lateral temporal neocortex is critical for semantic memory and MTL regions, such as the hippocampus, support episodic memory. This division is reflected in current neuropsychological practice as typical evaluations include tasks of episodic memory (e.g., list learning) and of semantic knowledge (e.g., naming, verbal fluency), which are interpreted as reflecting function of mesial and lateral temporal regions, respectively.

However, the two memory systems have a certain degree of interdependence or collaboration that varies as a function of task characteristics and demands (for review see [18]). This overlap provides a parsimonious explanation for the variable sensitivity of verbal “episodic” memory tests to left TLE because this sensitivity is proportional to the degree to which the material is semantically rich or consists of novel relationships. For instance, test sensitivity to left TLE is greater for list learning tests containing unrelated words or arbitrary word pairs (e.g., RAVLT or *hard* pairs on Paired Associates subtest of the WMS) than for semantically related ones (CVLT or *easy* pairs on the WMS), [19, 20]. Similarly, memory for prose passages, which is highly semanticized, relates to the integrity of the lateral neocortex rather than that of the hippocampus [11] (see Table 1 for further description of tests).

In these examples, semantic memory clearly contributes to performance on episodic memory tasks, but the reverse influence is also true. In a group of MTL amnesic individuals, Greenberg et al. [21] demonstrated deficits in semantic fluency that were of greater magnitude for categories that generally elicited autobiographical retrieval strategies in healthy controls (e.g., imaging their own kitchen when asked to generate a list of kitchen utensils rapidly) relative to those that did not. Of interest, functional neuroimaging of this

TABLE 1: Neuropsychological tests in common use in epilepsy surgical centres.

Test name/domains	Description
<b>Verbal memory</b>	
California Verbal Learning Test-II (CVLT-II)	Examinees recall a list of 16 words from 4 categories (furniture, vegetables, ways of travelling, and animals) after each of 5 learning trials. Retention is assessed by free recall and cued recall of the list following the presentation of interfering material and following a 20-minute delay period, as well as by delayed yes-no recognition.
Rey Auditory Verbal Learning Test (RAVLT)	Examinees recall a list of 15 unrelated words after each of 5 presentations. Retention is assessed by free recall of the original list after a second list is presented and following a 20-minute delay period, as well as by delayed yes-no recognition trial or a recognition trial involving recognizing the studied words embedded in a prose.
Verbal Paired Associates I & II subtests—Wechsler Memory Scale (WMS), WMS-R, WMS-III, and WMS-IV	Measures relational memory of word pairs over repeated learning trials. After each presentation of the list of pairs, the first word is given and the examinee is required to provide its associate. Errors are corrected immediately. The format of the test has changed across versions in terms of number of pairs (from 8 to 14), types of pairs (both easy/related pairs and hard/unrelated pairs in most versions), number of learning trials (3 to 6), and the inclusion of a 20- to 30-minute delayed cued recall and delayed recognition trials (present since WMS-R).
Logical Memory I & II subtests—WMS, WMS-R, WMS-III and WMS-IV	Consists of immediate recall and delayed recall of two orally presented prose passages as well as yes-no delayed recognition of story elements. Some changes in test format and content have been introduced across versions.
Names subtest—Doors & People Test	Examinees read two lists of names (12 per list) and recognize these names on a four-alternative forced-choice recognition task.
Words subtest—Recognition Memory Test	Examinees rate 50 words as <i>pleasant</i> or <i>unpleasant</i> and recognize these words on a two-alternative forced-choice recognition task.
<b>Visual memory</b>	
Rey-Osterrieth Complex Figure	This task involves copying a complex figure, which provides a measure of construction skills and planning, followed by an unexpected recall and recognition tests given at various delays depending on the center's protocol.
Visual Reproduction I & II subtests—WMS, WMS-R, WMS-III, and WMS-IV	Four or five visual designs are shown for 10 seconds each and are reproduced from memory. Delayed reproduction and yes-no recognition are also done 20- to 25-minutes after learning.
Designs I & II (WMS-IV)	Measures memory for visual designs and their spatial locations. On each of four trials, 4 to 8 unfamiliar visual designs on a 4 × 4 grid are presented for 10 seconds. The examinees then reproduce the display by selecting the appropriate designs and placing them in their studied spatial location. Retention is also assessed by delayed trials given 20 to 30 minutes after learning.
Faces I & II subtests—WMS-III	Examinees study 24 colour photographs of faces that vary by age, sex, and race and then perform a yes-no recognition test for these pictures immediately following presentation and after a 25–35-minute delay period.
Faces subtest—Recognition Memory Test	Examinees rate 50 black-and-white photographs of male faces as <i>pleasant</i> or <i>unpleasant</i> and subsequently recognize these faces on a two-alternative forced-choice recognition task.
Doors subtest—Doors & People Test	Examinees study two series of photographs of doors (12 per series) and recognize these doors on a four-alternative forced-choice recognition task.
<b>Language</b>	
Boston Naming Test	Assesses visual confrontation naming using line drawings of common objects. Semantic and phonemic cues are provided for items that are not named within 20 seconds. Versions of different lengths exist (15, 30, and 60 items).
Verbal Fluency	Assesses the spontaneous production of words under particular search rules over a set period of time (usually 60 seconds per trial). Phonemic fluency and semantic fluency require examinees to generate words beginning with particular letters (e.g., F, A, and S) and belonging to particular categories (e.g., animals, fruits, and vegetables), respectively. Other rules have also been used, including proper names and actions.

task with healthy controls reveals bilateral mesial temporal activation, suggesting that both dominant and nondominant MTL regions are engaged [22]. In TLE, semantic fluency deficits are typically interpreted as dysfunction of the left lateral neocortex, but the above findings raise the possibility that hippocampal dysfunction also may contribute to certain

impairments in semantic access, including the nondominant MTL. This certainly provides a compelling explanation of findings showing impaired semantic fluency not only in left TLE, but also in right TLE individuals with hippocampal (but not neocortical) involvement [23]. Another example wherein episodic memory enhances semantic retrieval

pertains to memory for famous people. Fame judgment and speeded reading tasks of famous names were shown to be facilitated for those associated with autobiographical significance (e.g., most people recollect a personal event related to John F. Kennedy) in healthy controls and individuals with semantic dementia, but not in MTL amnesic individuals [24]. Although autobiographical significance of the material used was not investigated directly, it may have contributed to the deficit noted on a famous people memory task, which was of equal severity in left, right, pre- and postoperative TLE individuals [25].

In sum, the separation between episodic and semantic memory is less distinct than previously thought and the degree to which semantic memory contributes to a given episodic task, and vice versa, need to be considered in test selection and interpretation. Selecting tasks with various degree of respective contribution from semantic and episodic memory may help characterize the source of potential difficulties.

### 5. Relational versus Nonrelational Memory

Within episodic memory, several dissociations have been found between memory of nonrelational information (e.g., single words or objects) and memory for relational information (e.g., pairs of single elements such as word-word or word-object). According to dual process models, the hippocampus is crucial for relational memory and recollection which enable retrieval of contextually rich events, while adjacent mesial temporal regions (e.g., perirhinal cortex) can support nonrelational memory via familiarity, which is a process characterized by a decontextualized feeling of oldness or of prior exposure (for review see [26, 27]). These memory processes typically work in concert but are preferentially called upon in tasks involving particular types of material or test format. Tasks of free recall, novel pair associates, source memory, and autobiographical memory are more recollection based, while tasks of single item recognition can be supported by familiarity. Experimental procedures have also been devised to extract purer indices of each process [27].

Some studies tested relational memory/recollection in TLE using a variety of material (sounds, faces, spatial locations, words, and descriptions of personally experienced autobiographical events) and test formats, but only a few of these also assessed familiarity. As expected given hippocampal involvement, all studies showed relational memory/recollection deficits in TLE and, in most of these, the deficits were present regardless of seizure or excision laterality [28–33], although these deficits were material specific in others [20, 34]. With respect to familiarity, it was intact in one study [34] and impaired for material processed by the damaged hemisphere in others [28, 30]. This deficit is likely related to perirhinal lesions or dysfunction based on findings with NB, who, following a temporal lobe resection that spared the hippocampus, but not the surrounding regions (amygdala, entorhinal and perirhinal cortex, and lateral temporal neocortex), demonstrated impaired familiarity but intact recollection [35].

Together, these findings suggest that relational memory tasks may provide information on the functional integrity of the hippocampus, although they may not consistently provide information on laterality. Tasks that rely to a greater extent on familiarity may be more lateralized, consistent with the material specificity principle, and be indicative of dysfunction of the perirhinal cortex. These principles can be applied to selection of current tools, for instance, when contrasting performance on free recall tasks (which are more recollection based) and forced-choice recognition (which are more familiarity based).

### 6. Pattern Separation

Computational models of memory, such as the complementary-learning-systems model [36, 37], proposed that the neocortex contributes to memory by slowly extracting general information over repeated similar experiences while the hippocampus allows quick encoding of specific episodes as distinct representations. The latter is achieved via a *pattern separation* operation which minimizes the overlap between similar representations. Subregions of the hippocampus, including the dentate gyrus and its projection to CA3, are specifically involved in pattern separation. CA1 and extrahippocampal regions, such as the entorhinal cortex, support retrieval via *pattern completion*, which allows reconstruction of a memory representation when provided with a fragment of the original studied item or events [38]. Pattern separation enables one to discriminate between highly similar items or experienced events at retrieval and to distinguish them from similar lures. While this model is most studied in animal models, a case study with an individual with damage restricted to the hippocampus [39] and a high-resolution fMRI study in healthy participants confirmed this functional division using a recognition task in which lures are highly similar to targets [40].

To our knowledge, pattern separation has not been systematically investigated in TLE, but some results in two studies with postoperative TLE may be interpreted as evidence of significant deficits with this operation. In one study, we used an associative recognition task in which participants had to discriminate studied word pairs from lures composed of studied words rearranged in a novel way [28]. Interestingly, TLE patients had significantly greater difficulties rejecting these overlapping lures than endorsing studied pairs, which requires a recall-to-reject strategy (i.e., retrieving the original pairings in order to reject the current rearranged one) thought to depend on pattern separation. In another study, [41] left and right postoperative TLE were impaired on verbal and visual standardized recognition tasks, respectively (Doors & People Test), in which lures and distractors are very similar to one another. Interestingly, the effect size for the visual subtest was markedly greater than that of the verbal subtest (Cohen's  $d$  of 2.05 for doors versus 0.54 for names) and those typically reported with visual memory tasks [42].

Further studies, especially with preoperative patients, may ultimately inform us about dysfunction in specific

subregions of the hippocampus. Until then, findings on pattern separation can inform test selection and interpretation as we expect that, due to hippocampal dysfunction, TLE will be associated with greater difficulties on tasks including highly overlapping and interfering material than tasks in which material is distinct.

## 7. Consolidation

The hippocampus is critical for consolidation in declarative memory, which refers to the stabilization of long-term memory and enables retention of information over time. There are two types of consolidation: (1) synaptic (or cellular) consolidation, which is completed within minutes to hours, applies to all memory systems and species and consists of long-term modification of synaptic proteins, synaptic remodeling, and growth, and (2) system consolidation, which takes place over days or years and pertains to memories that are dependant on the hippocampus initially, but become independent from this structure and “transfer” to the neocortex after undergoing reorganization (for review see [43]). It is well known that individuals suffering from amnesia, such as HM, have impaired retention, even at short delay periods [5]. TLE patients (especially left) often show milder, but significant forgetting after a few minutes or hours [44], which suggests that synaptic consolidation is reduced. Recent studies have also reported accelerated long-term episodic forgetting in TLE (but not semantic), that is, significant forgetting of information following days or weeks despite intact initial learning and retention at shorter delays (30–60 minutes) [45, 46].

Thus, system consolidation and synaptic consolidation within the episodic memory system appeared to be dissociated in TLE. Importantly, this illustrates that current standard neuropsychological assessments may not capture potential hippocampal dysfunction given that no standardized task include delays that are much longer than 30 minutes.

## 8. Prediction: Combination of Investigations

Thus far, we have discussed concepts that have the potential to improve our ability to assess both functional reserve and adequacy of the temporal lobes behaviourally and, ultimately, improve prediction of postoperative outcome (although no studies have assessed this directly in a single cohort). While preoperative behavior (e.g., memory function) is informative, higher predictive validity is obtained when it is combined with certain types of clinical data (e.g., age of onset, presence of mesial temporal lobe sclerosis (MTS), or cortical dysgenesis on MRI) [47].

The intracarotid amobarbital test (IAP) has been used to predict the consequences to memory of planned temporal-lobe resections since the 1960s [48, 49]. This procedure, in which an anesthetizing agent is injected into the cerebral vasculature of one hemisphere, is intended to evaluate risk by evaluating memory encoding abilities of the contralateral hemisphere (i.e., functional reserve) and ipsilateral hemisphere (i.e., functional adequacy) independently. In cases of

failure on contralateral testing or “crossed asymmetry” (i.e., better performance from the ipsilateral than the contralateral test), surgical planning was modified or in some cases surgery foregone in order to minimize cognitive morbidity. However, in recent years, the added value of the IAP has been brought into question, as studies have indicated that there is a relatively high base rate of failure or for crossed asymmetry, particularly associated with dysphasia following dominant-hemisphere injection, without significant postoperative complications [50, 51]. Furthermore, in larger series of “uncomplicated” TLE (i.e., those in whom there was no evidence of significant bitemporal dysfunction), studies employing multivariable regression techniques have found that IAP results have little or no added predictive value when preoperative memory scores and structural MRI findings are considered [52, 53]. Thus, given the questionable utility of IAP in many circumstances and given the invasiveness of the procedure, there is growing consensus that its use must be carefully considered on a case-by-case basis and perhaps used only in circumstances in which the risk of postoperative amnesia is considered high on the basis of all other available evidences [54]. At the same time, there is a rapidly evolving literature on functional MRI (fMRI) for assessing both language and memory capacities, providing a noninvasive alternative to the IAP, to which we now turn.

## 9. Functional Neuroimaging

Although there is an older literature including positron emission tomography and single-photon emission computed tomography imaging in TLE, the majority of studies in which imaging has been used to evaluate cognitive function use fMRI. Functional brain mapping with MRI, in which the blood-oxygen-level-dependent (BOLD) signal provides an indirect measure of the distribution of neuronal elements activated in a task, has been used in cognitive neuroscience since the early 1990s [55, 56]. Its use clinically is a newer phenomenon, starting with attempts to map language and sensorimotor functions in patients with tumours and epilepsy where other methods of evaluating regional involvement in these processes (IAP, stimulation mapping) could be used to validate the fMRI results. It has proven so successful for sensorimotor and language mapping that there are now (since January 2007) billing codes that permit compensation for such procedures in the US healthcare system. Its effectiveness in determining the functional adequacy of mesial temporal structures for supporting memory, the next logical application in epilepsy surgery, is not yet validated as the reliability of prediction vis-à-vis surgical outcome has yet to be established. Here, we discuss some of the relevant research and highlight some of the challenges to functional mapping posed by network dynamics and functional reorganization in epilepsy. We also alert the reader to several excellent recent reviews of some of this material [57, 58].

## 10. fMRI for Language

Functional MRI is now used in many centres for lateralization and localization of language functions so as to avoid

significant postoperative aphasias. Whilst there is no expectation that there will be a huge variation in the “canonical” language regions in the TLE population, the literature does suggest a higher incidence of atypical dominance (or greater engagement of the typically “nondominant” hemisphere) in epilepsy patients. This is particularly true in cases of early brain injury resulting in weaker right-hand dominance, as was previously established by inactivation procedures such as stimulation mapping and the IAP [59, 60]. Of interest, the proximity of a lesion to the primary receptive and expressive regions (Wernicke’s and Broca’s, resp.) in the left hemisphere does not appear to be a predictor of such reorganization [61, 62], suggesting that atypical dominance may reflect a more subtle disruption of language networks. Thus, it is important to map these language networks in individuals even when the planned resection would be considered unlikely to impact the primary regions known to be involved in language processing.

A number of different tasks have been used for language mapping in fMRI, including ones that emphasize expressive functions such as naming and fluency as well as those tapping receptive abilities such as word/nonword decisions or sentence comprehension. Expressive tasks are typically done without overt speech due to concerns about head motion. There is no “standard” paradigm, and while various papers argue the effectiveness of one over another (e.g., [63, 64]), there is a growing acceptance of the use of a panel of tasks that tap both expressive and receptive functions, as combining these improves greater sensitivity and specificity [65, 66]. For lateralization, the most commonly used metric is an asymmetry index (Left – Right/Left + Right) which is typically calculated on the number of voxels that exceed a particular activation threshold. The calculation is performed either on entire hemisphere or on regions of interest in frontal and temporal lobes typically associated with language processing. Although cutoffs vary for classification of dominance, ratios of +0.25 and –0.25 are frequently used to describe left and right dominance, respectively, with intermediate values indicating weaker lateralization. Figure 1 shows activation maps for two TLE patients in whom our fMRI task panel (verb generation, category fluency, sentence completion, and naming to description) demonstrated left or right hemisphere language dominance, illustrating its utility at the individual subject level.

Overall, there is quite good agreement between fMRI using asymmetry indices and IAP results for language dominance [65, 67–69]. In the largest series to date comprised of 100 epilepsy patients, Woermann et al. [70] found over 90% concordance between fMRI and IAP estimates of language lateralization, although classification agreement was somewhat poorer for extratemporal epilepsy in the dominant hemisphere (25% discordance, fMRI suggesting bilateral representation). As with other methods (IAP, dichotic listening), fMRI reveals more atypical language lateralization in individuals with weaker right-hand dominance [71]. Nonetheless, in right-handed patients with left TLE, up to 30% of individuals show bilateral or right hemisphere language organization by fMRI, a rate that is higher than

in healthy controls or patients with right TLE [72–74]. This shift appears to be more prominent in the temporal than frontal lobes, and it is correlated with age of onset of damage or intractable epilepsy in that region [75], suggesting a direct impact of seizures on lateralization. Of note, this may also be a reflection of damage to pathways connecting temporal and frontal brain regions in epilepsy as shown by recent evidence from diffusion tensor imaging (DTI) [76].

Determining whether a particular region is *critical* for language (e.g., a region in close proximity to a structural lesion or an epileptic focus) presents a bit greater difficulty than determination of dominance, as here one must have a means of validating that the task-related activation signifies performance *capacity* rather than mere correlation or association. Correspondence with stimulation mapping provides one avenue for validation that can avoid the consequences of a postoperative aphasia. Rutten and colleagues [77] reported that a combination of tasks (verb generation, sentence comprehension, and picture naming) was highly sensitive for detection of critical sites, based on disruption of speech with direct stimulation. However, as there were “false positives” (regions in which activation was apparent with no speech disruption) in many cases, the authors felt that fMRI could supplement rather than replace stimulation, perhaps to guide stimulation targets. A recent review of the utility of the IAP in contrast to fMRI reaches a similar conclusion [78]. Nonetheless, activation in the dominant temporal lobe has been shown to be correlated with postoperative naming decline following left anterior temporal lobectomy [79] and there are some impressive instances in which fMRI shows interhemispheric dissociation between frontal and temporal lobe language regions which are not identified by IAP [80, 81].

In addition to alterations in hemispheric dominance in patients with TLE, there is evidence of intrahemispheric reorganization of language. Several studies have reported increased prefrontal activation, which may reflect compensatory processes given that it is seen when performance is unimpaired [82, 83]. Such findings suggest alterations in the components and operation of language networks in TLE, and recent studies have examined directly the connectivity of nodes within these networks. Waites and colleagues reported reduced resting-state connectivity amongst frontal and temporal nodes in patients with left TLE [84]. Protzner and McAndrews [85] used partial least square (PLS) analysis, a multivariate technique, to examine networks that support performance on a test of confrontation naming. Critically, the networks were defined by activation during a verb generation task and the criterial naming task performance was measured weeks to months before or after scanning. They found three separate patterns relating brain activation to naming performance, one each for controls, patients with left TLE, and patients with right TLE. Thus, there may be fairly complex patterns of reorganization associated with TLE, and exploration of these may be important in predicting the nature and degree of postoperative changes following epilepsy surgery.

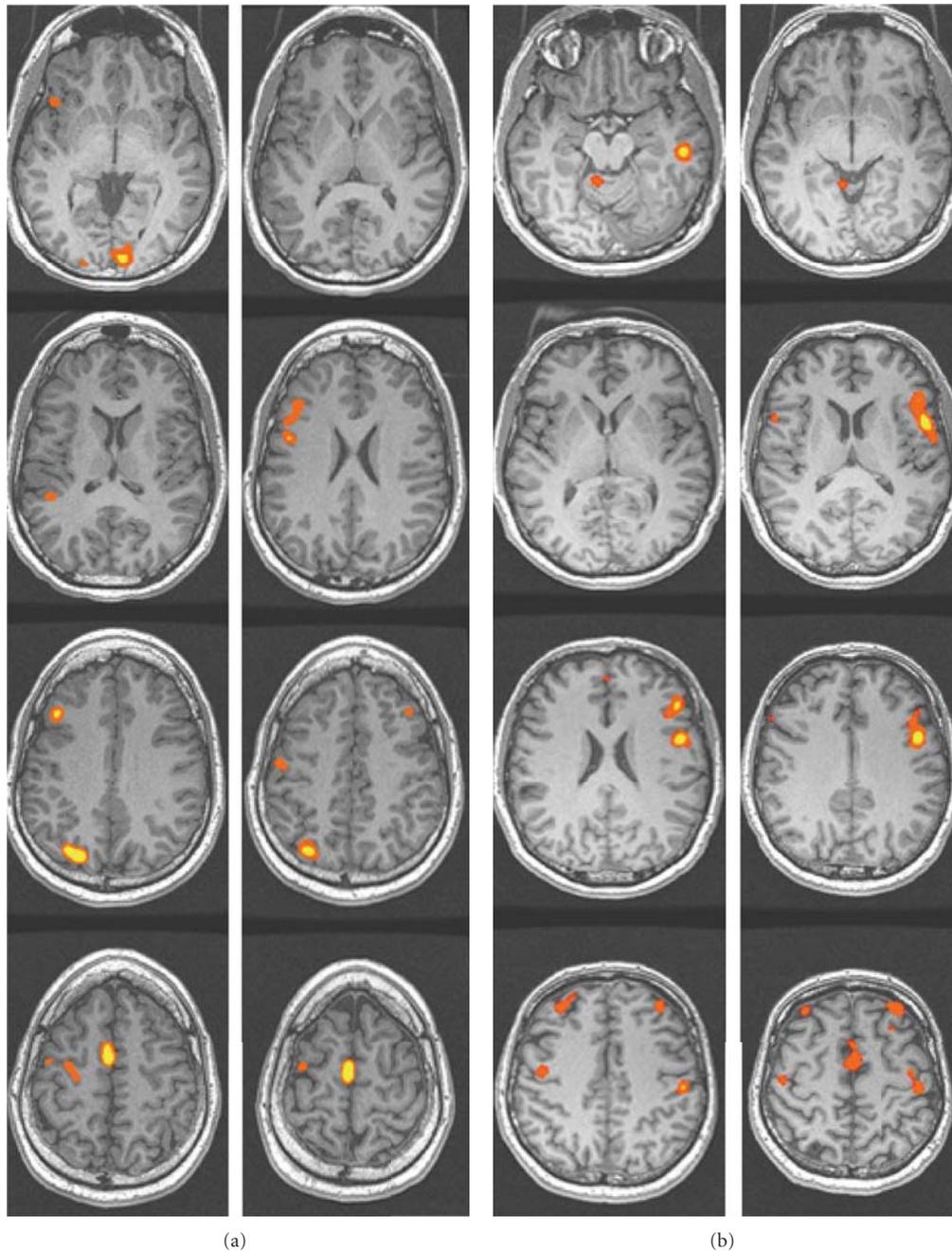


FIGURE 1: Presurgical fMRI for language in patients with TLE. Two individuals with epileptic foci in the left temporal lobe were scanned using a panel of tasks involving 25-second blocks of verb generation, sentence completion, category fluency, and naming to confrontation, alternating with 20-second blocks of fixation. The case in (a) shows left-hemisphere dominance, and the case in (b) shows right hemisphere dominance. In figure, L: left and R: right; threshold is set to  $z > 2.25$ .

## 11. fMRI for Memory

Although the past 20 years of fMRI research in cognitive neuroscience have yielded important insights into brain regions and networks supporting memory processes, its application in a clinical context, particularly in ascertaining the functional integrity of mesial temporal structures in TLE, is limited. There are a number of reasons for this

limitation, including the complexity of memory operations and their relative dependence on specific brain structures: the same area may be involved in support encoding and retrieval but less so for recognition. Like behavioral tasks reviewed above, activation tasks should reliably discriminate between dominant and nondominant temporal lobes and between mesial and lateral temporal (in addition to frontal and parietal lobe) contributions to memory performance.

Yet, even material specificity is less reliably seen with memory activation paradigms than one would expect from the lesion data [86]. Finally, it is important to establish a relationship between functional adequacy of the region to-be-resected and some characteristics of the BOLD signal (i.e., do 3 activated voxels represent a small risk of postoperative decline whereas 20 voxels signify a large risk?). The field is not sufficiently mature to have highly reliable activation tasks with appropriate cutoffs for clinical decision making. However, there have been some important strides in this regard, as we review here.

In attempting to assess functional integrity in the temporal region, one strategy has been to use tasks in which there is typically bilateral MTL activation in controls and assess whether there is reduced activation ipsilateral to the epileptic focus and thus greater asymmetry in TLE patients. A number of studies fulfill those criteria, typically using encoding or retrieval of complex visual material such as scenes, routes, autobiographical memories, and demonstrating reduced ipsilateral activation [87–90]. Of note, there are issues as to their sensitivity to hippocampus versus cortical MTL regions [91]. Another strategy is to use material-specific memory probes that are more likely to preferentially activate one or the other mesial temporal region (e.g., words for the left hemisphere, abstract designs for the right hemisphere); these may also exploit associative or relational memory tasks that have been shown to be particularly good at activating the MTL. For example, Dupont and colleagues using a verbal encoding and retrieval task found reduced MTL activation in patients with left MTS [92]. Using both verbal and visual material at encoding, some studies have consistently reported increased MTL activation in the side contralateral to the seizure focus [93, 94], although as noted above the material specificity can be difficult to demonstrate reliably in healthy controls [86]. Overall, these findings suggest that memory-induced activation may be a sensitive marker of epileptic disturbance.

A crucial concern for fMRI is identifying specific parameters of activation that can characterize the functional integrity of the mesial temporal region, that is, parameters which correlate with other measures of function (e.g., neuropsychological tests, IAP results) and predict memory change following surgery. In that regard, there are some positive results in the literature but perhaps less than one might expect in contrast to the fairly robust language fMRI literature. This may be partly a function of the difficulties posed by signal loss and distortion in the basal temporal region and, importantly, by loss of fidelity caused by postprocessing choices in both metrics and standardization of patient data to normative structural templates [95]. While we must be mindful that it is impossible to know how many null findings there are on this question as they tend to be unpublished and left in “file drawers,” the positive findings stand at least as proof of concept for the clinical utility of fMRI for memory assessment in TLE patients.

Several studies have reported good correspondence between asymmetry in MTL activation and IAP asymmetries [87, 93]. Others have found clinical memory test performance to correlate positively with the magnitude of

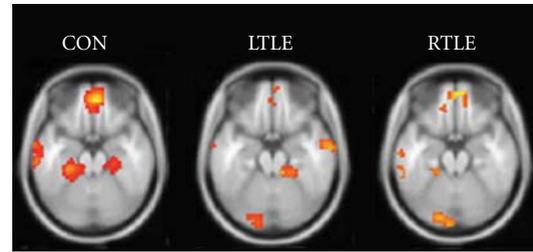


FIGURE 2: Autobiographical memory profiles. fMRI maps illustrate regions demonstrating higher activation for during autobiographical memory recall (retrieving personal memories based on event cues) relative to semantic retrieval (sentence completion). Note that there is less activity in the epileptogenic mesial temporal region for both left and right TLE groups compared to healthy controls ( $n = 10$  per group). In figure, L: left and R: right; threshold set at  $P < .0001$ , uncorrected.

activation in the MTL ipsilateral to the seizure focus [90, 96]. Rabin and colleagues [97] were the first to show that mesial temporal activation (during scene encoding) correlated with postoperative memory performance (on the scene recognition task); increased activation ipsilateral to the seizure focus was associated with greater decline. The crucial validation is, of course, whether activation can be used to predict clinically relevant postoperative memory compromise. There have been several studies demonstrating correlations between activation magnitude in the to-be-resected MTL and the amount of memory change, with greater preoperative activity (expressed either as an absolute magnitude or asymmetry relative to the other MTL) associated with a more dramatic decline in material-specific memory function [96, 98–101]. However, there are also negative instances in which hippocampal activation may be reliable for a given task but does not predict postoperative memory change [102]. Furthermore, the extent to which fMRI parameters provide independent or additional power to the prediction of risk to memory, beyond factors such as neuropsychological test data and measures of hippocampal atrophy, has not been adequately addressed in a sufficient number of studies (see [103, 104]).

Our own work with autobiographical recall in patients with TLE illustrates the complexity of the relationship between functional activation during memory paradigms and clinical indicators. Retrieval of episodes from the personal past is well established as a powerful activator of mesial temporal regions [105, 106], and patients with TLE show marked deficits in recall of details of autobiographical experiences [29, 31]. Furthermore, mesial temporal damage in these patients results in a marked reduction in the affected region as well as the whole autobiographical network [89]. Figure 2 displays newer (unpublished) findings from our clinic in which a second cohort of left and right TLE patients showed reduced activation in the epileptogenic hippocampus as well as other regions in the network. Additionally, Maguire and colleagues showed similar alterations in hippocampal engagement in two other patients with mesial temporal damage from hypoxia [107, 108]. Nonetheless, we have

found relatively poor correspondence between the magnitude or extent of hippocampal activation and performance on clinical memory tests and even some negative correlations in certain tasks (unpublished observations). Of course, it is entirely possible that there is a nonmonotonic function relating activation to clinical impairment in TLE. Indeed, at least one study has reported increases in MTL activation in TLE patients associated with dysfunctional tissue [109]. Sperling and colleagues have observed this in other cases of mesial temporal damage in that patients with very mild cognitive impairment show hyperactivation in the MTL whereas patients with more severe memory deficits show hypoactivation compared to controls [110, 111].

More recent analyses of functional activation patterns have begun to focus on connectivity and network characteristics, rather than focal activation as an important determinant of the effects of TLE on memory. Our study of autobiographical recall demonstrated a significant change in connectivity throughout the autobiographical network, in that patients with left TLE showed reduced connectivity with mesial temporal regions and enhanced connectivity between anterior and posterior midline regions [89]. Of interest, several studies involving patients with left TLE have shown strong correlations between *language* asymmetry and memory change [102, 112], suggesting that a more widespread pattern of dysfunction is reflected in memory deficits found in epilepsy. Indeed, it is likely that a full appreciation of functional competency, and thus the likelihood of functional impairment following surgery, requires consideration of brain networks supporting memory and language rather than focusing exclusively on MTL activation. As noted above, we found that TLE patients and controls activated the same networks in a language task but that there were subtle differences in the network components associated with performance on a clinical test [85]. Wagner and colleagues found that preoperative signal coupling between the ipsilateral hippocampus and superior temporal gyrus during a resting state scan was negatively correlated with disease duration and positively correlated with postoperative decline in memory [113]. Of interest, the primary resting state network, known as the default mode network (DMN), is largely coextensive with the networks involved in autobiographical recall and internal mentation [114] and researchers have begun to examine how connectivity in DMN components may relate to clinical parameters (e.g., seizure duration, cognitive deficits) in TLE [115–117].

## 12. Conceptual and Methodological Caveats in fMRI

There are a number of important limitations of functional activation techniques that require consideration. First, activations reflect correlations between some characteristic of the underlying neural substrate and behavior but this does not mean that an activated region is essential in performing the relevant task. Thus, convergence with other methods (stimulation, inactivation, and lesion) is crucial in making such inferences. Second, the careful selection of

tasks is imperative, particularly as studies typically use a “subtraction” method that attempts to eliminate influences from all but the critical process, yet identification of the appropriate “control” conditions may be quite complicated [118]. Also, the magnitude of these correlations can be artificially inflated in reports, when additional inferential statistics (such as correlations of activation magnitude with behavior) are performed on regions identified in a first-pass analysis, the so-called “double-dipping” phenomenon [119]. As noted above, there may be a very complex relationship between magnitude of activation (or another BOLD parameter of interest) and clinical status and there may also be a function of a host of factors (estimates of structural integrity, etiology of and duration of disease state, and cerebral reserve) that we are only beginning to address in our analyses. The influence of differential task performance is also a crucial variable in that the impact of inadequate task performance on differential activation is exceptionally difficult to assess [120]. The use of task-independent patterns of connectivity, such as those characterized by the DMN, may mitigate some of these methodological problems, but this is unlikely to permit exploration of the full range of cognitive capacities of interest in presurgical planning. Finally, we do not know the extent to which seizures, mesial temporal sclerosis, or antiepileptic drugs may compromise (either globally or locally) the neurovascular coupling that is crucial for observing a BOLD effect [121]. Despite these caveats, fMRI holds considerable promise, with no significant risk to patients, to substantially enhance our knowledge of how language and memory networks change in TLE. Furthermore, there is considerable clinical promise in that one can derive the positive predictive value of the mapping techniques in regard to risk to memory given that results are not used in surgical decision making, unlike the IAP for which test results constrain the treatment offered.

## 13. Conclusion

Neuropsychological assessment remains a critical part of surgical planning for TLE, and it is evolving in precision of diagnosis/prediction by incorporating novel concepts and techniques from cognitive neuroscience and functional imaging. This evolution will be shaped by our appreciation of the fact that even a focal seizure disorder can have widespread effects on anatomy and function and acknowledgement that TLE may represent a paradigm case of subtle functional reorganization that requires us to be informed about the integrity and degeneracy [122] of networks supporting complex cognitive operations.

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## Clinical Study

# Extrahippocampal Desynchronization in Nonlesional Temporal Lobe Epilepsy

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Received 12 May 2011; Revised 14 September 2011; Accepted 25 September 2011

Academic Editor: Warren T. Blume

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Although temporal lobe epilepsy (TLE) is traditionally associated with both hypersynchronous activity in the form of interictal epileptic discharges and hippocampal sclerosis, recent findings suggest that desynchronization also plays a central role in the dynamics of this pathology. The objective of this work is to show the imbalance existing between mesial activities in patients suffering from mesial TLE, with normal mesial structures. Foramen ovale recordings from six patients with mesial TLE and one with lateral TLE were analyzed through a cluster analysis and synchronization matrices. None of the patients present findings in the MRI presurgical evaluation. Numerical analysis was carried out in three different situations: awake and sleep interictal and also during the preictal stage. High levels of desynchronization ipsilateral to the epileptic side were present in mesial TLE patients. Low levels of desynchronization were present in the lateral TLE patient during the interictal stage and almost zero in the preictal stage. Implications of these findings in relation with seizure spreading are discussed.

## 1. Introduction

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy, where the epileptogenic area is located at some part of the temporal lobe. Mesial TLE (MTLE) refers to those cases where the suspected source of epileptogenic activity is located in the mesial area of the temporal lobe [1], and lateral TLE (LTLE), instead, where the focus is located in the lateral side. MTLE is often associated with structural lesions and/or functional deficiency in one or several (dual pathology) mesial structures of the temporal lobe, with hippocampal sclerosis (HS) as the most common underlying abnormality [2]. However, pathological findings of damage in the amygdala and parahippocampal region, which in turn is subdivided into the entorhinal cortex (EC), perirhinal cortex (PC), and parahippocampal cortex (PPC), are also reported [3, 4]. A significant minority of MTLE patients have no pathological findings on magnetic resonance imaging (MRI), even though lateralization may be correctly performed by neurophysiological methods [5, 6].

Normal underlying mesial structures play a key role in our understanding of the pathogenesis of MTLE, as they oblige us to ask whether mesial sclerosis (MS) is either the cause or the effect in MTLE [7].

Pathophysiology in MTLE can be explained according to two models: (1) the “focal” model suggests that a single pathological region in the mesial temporal lobe is responsible for seizure origin, establishing a link between the presence of MS and the region of seizure onset [8]. (2) The “network” model states that seizures in MTLE result from an alteration of limbic network, which implies atrophy in other structures different from hippocampus [9]; this model suggests that the abnormal interaction between EC, hippocampal formation, and subiculum may be responsible for the seizures [10].

In a high percentage of MTLE patients (60%–80%), clinical seizures cannot be eliminated by drug treatment. In such cases, surgery is the only curative/palliative alternative. Even with the advent of imaging techniques that are now routinely applied in the preevaluation of drug-resistant TLE patients, neurophysiological assessment remains the main

diagnostic method at the time of locating epileptogenic areas. Besides traditional electroencephalography (EEG), invasive and semi-invasive neurophysiological methods are justified in most cases when imaging techniques fail in the localization/lateralization of the epileptic focus. Traditional neurophysiological analysis, whether noninvasive, semi-invasive, or fully invasive, depends mainly on the analysis of interictal epileptogenic discharges (IED), which are the hallmark of epileptic activity [11]. However, IED appears in the so-called irritative area, which often does not coincide with the true epileptogenic area. Thus, ictal neurophysiological patterns, such as spikes and sharp waves, must be studied in order to obtain a correct diagnosis. Moreover, as we have recently highlighted [12], analysis of IED in a neurophysiological signal, although very valuable, can only account for a very low percentage of the full information carried by a pathological signal. In order to obtain such recordings, v-EEG (EEG combined with an invasive technique and video recording) is used in most centers. This approach requires hospital admission for several days in order to record and analyze a suitable quantity of seizures to locate the focus.

In this work we analyze foramen ovale electrodes (FOEs) recordings in seven TLE patients with normal presurgical MRI, without taking into account IED activity. Very recently we have shown [12] the existence of interictal mesial synchronization imbalance in TLE patients, mostly with pathologic findings in MRI studies. In the present work, by using part of the already developed methodology, we extend the preceding work in several directions.

- (a) We analyze, for the first time, both interictal and ictal mesial synchronization in TLE patients.
- (b) We use here a homogenous sample of seven nonlesional TLE patients, in order to discard the causality relation of lesion-desynchronization.
- (c) Six out of seven patients presented MTLE, as assessed by previously evaluating FOEs ictal IED analysis; the remaining patient presented LTLE, thus, the issue of mesial synchronization imbalance against mesial or lateral TLE is also addressed.

By analyzing records of ictal and interictal activity in a homogenous sample of nonlesional TLE patients we were able to provide new information regarding the synchronization imbalance in this pathology, as we will show below.

## 2. Methods

**2.1. Patients.** The study sample comprised seven patients (six women). Mean age was  $39.2 \pm 9$  years, and time of these intractable epilepsies was  $21.4 \pm 13.7$  years. The Ethics Committee of Hospital de la Princesa approved the study, and all the patients gave their informed consent. Patients were evaluated before surgery according to the local protocol, as published elsewhere [13, 14], namely, interictal single-photon emission computer tomography (SPECT), MRI 1.5 T, scalp EEG, and v-EEG using 19 scalp electrodes according to the international 10–20 system. None of the patients

presented pathologic findings in the presurgical MRI studies, and, in some cases, this was corroborated by histopathology.

Table 1 shows the clinical information and results of the presurgical studies (SPECT, MRI, and v-EEG) routinely performed in the sample. During the v-EEG recording, antiepileptic drugs were progressively discontinued from the second day to the fourth day (approximately one-third of the dose per day). Six-contact platinum FOEs [15–17] (AD-Tech, Racine, USA) with 1 cm center-to-center spacing, were inserted bilaterally under general anesthesia. Correct implantation was assured using fluoroscopic imaging in the operating room. The most rostral electrode in the foramen ovale was termed FOE no. 1 and the most occipital electrode FOE no. 6.

**2.2. Signal Analysis.** Digital EEG and FOE data were acquired at 500 Hz, filtered at 0.5–60 Hz for both scalp and FOE recording, and exported at 200 Hz to ASCII format (XLTEK, Canada). Artifact-free epochs lasting around 60 minutes were selected for interictal analysis. Multivariate nonoverlapping temporal windows of 2048 data points were used. In the cases of pre-seizure and seizure analysis, multivariate records of 512 data points were used in order to achieve better temporal resolution; 512 points at 200 Hz yield temporal windows of approximately 2.5 seconds each. All derivations in scalp and FOE electrodes were referenced to  $(Fz + Cz + Pz)/3$ , thus 28 electrodes were used:

$$\text{Fp1, F3, F7, T3, C3, P3, T5, O1.} \quad \text{Left scalp} \quad (1a)$$

$$\text{Fp2, F4, F8, T4, C4, P4, T6, O2.} \quad \text{Right scalp} \quad (1b)$$

$$\text{Lf1, Lf2, Lf3, Lf4, Lf5, Lf6.} \quad \text{Left FOE} \quad (1c)$$

$$\text{Rf1, Rf2, Rf3, Rf4, Rf5, Rf6.} \quad \text{Right FOE} \quad (1d)$$

Postprocessing calculations were performed using *Fortran* and R. Interactions between areas covered by electrodes were quantified using the Pearson correlation coefficient [18]. Other nonlinear measures, such as phase synchronization [19], provide similar results [12]. We converted correlation values,  $-1 \leq \rho_{ij} \leq 1$ , between each pair of electrodes  $i$  and  $j$ , into distances,  $0 \leq d(i, j) \leq 1.4$ . Distances serve in the construction of dendograms and provide a more intuitive notion of desynchronization, a central issue in this work. The greater the distance between two recorded areas, the more desynchronized the corresponding neurophysiological activity is. We use the distance matrix to construct dendograms by applying the classic agglomerative single-linkage algorithm.

In order to quantify the degree of synchronization between FOEs on each side, we summed up the distances between pairs of FOE,  $d(i, j)$ , for the left and right sides, and divided the result by two (due to the symmetric character of the distance matrix):

$$\text{AS}_L = \frac{1}{2} \sum_{i=1}^6 \sum_{j=1}^6 d(i, j), \quad \text{AS}_R = \frac{1}{2} \sum_{i=1}^6 \sum_{j=1}^6 d(i, j). \quad (2)$$

We termed the measure defined above average synchronization (AS), which turns out to be a simple yet robust measure

TABLE 1: Clinical data. Gray-shaded row, patient no. 6 is the only case of lateral TLE.

Patients characteristics					Presurgical studies			
No.	Freq	Age	Duration of epilepsy	Gender	SPECT	NMR	v-EEG (inter/ictal)	Diagnosis
1	d	37	6	Male	LM	Normal	RM/RM	R M TLE
2	w	42	28	Female	aLM	M asym	Bi M/LM	L M TLE
3	w	51	40	Female	aMBi (L>R)	*	Bi M/RM	R M TLE
4	m	34	20	Female	aLM	Normal	LM/LM	L M TLE
5	d	24	1	Female	aRM	Normal	Mult/LM	L M TLE
6	w	48	25	Female	aRM	Normal	Mult/Llat	L lat TLE
7	w	39	30	Female	LT	Normal	Bi M/LM	L M TLE

\* Retrocerebellar arachnoid cyst

Freq: seizure frequency; w: weekly; d: daily; m: monthly; irreg: irregular; L: left; R: right; M: mesial; T: temporal; a: anteromedial; Bi: Bilateral; Mult: multifocal; asym: asymmetry; lat: lateral.

of synchronization between all the electrodes on each mesial side. The measure actually is a spatial average over the mesial sites recorded by each FOE.

As we have shown elsewhere [12], interictal synchronization imbalance exists between both mesial sides in TLE patients. This imbalance will be quantified with

$$LI_{AS} = AS_L - AS_R, \quad (3)$$

as a lateralization index.  $AS$  actually quantifies the degree of desynchronization instead of the degree of synchronization. Higher levels of  $AS_L$  imply greater distances between the left FOEs and, thus, higher desynchronization.  $LI_{AS}$  quantifies the imbalance in desynchronized activity between the left and right mesial areas. A positive  $LI_{AS}$  implies higher desynchronization on the left side, and, conversely, a negative  $LI_{AS}$  implies greater desynchronization on the right side.

### 3. Results

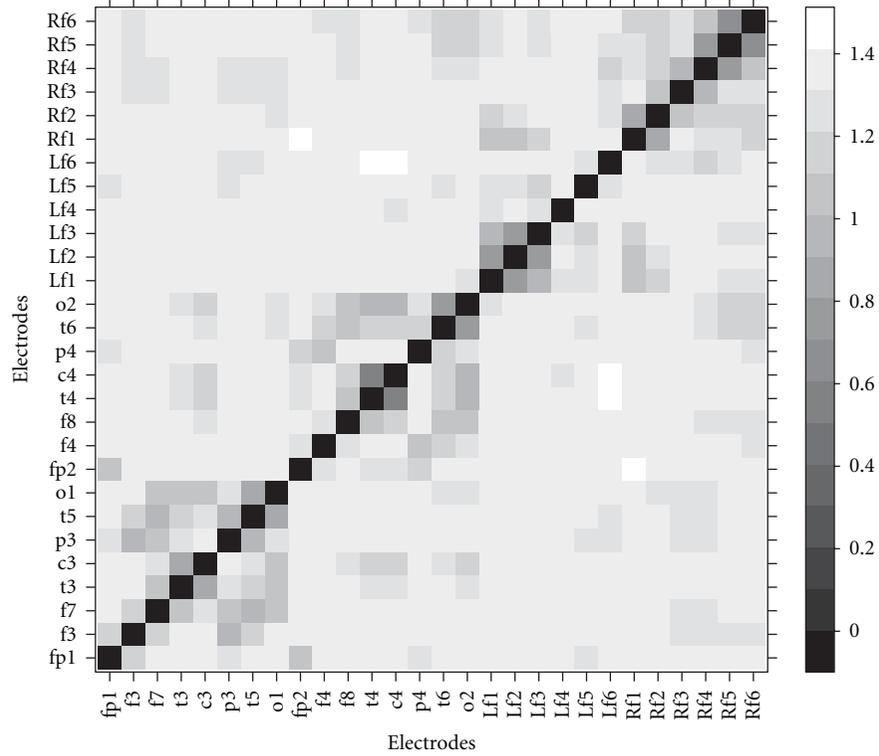
Figure 1 shows a typical distance matrix between each pair of electrodes (patient no. 5). In Figure 1(a), we plot the distance matrix of a single 2.5 sec temporal window during the preictal stage, that is, five minutes before the start of the seizure. Darker areas correspond to higher synchronization or tighter interactions between electrodes: the difference between right FOEs (Rf1–Rf6) and left FOEs (Lf1–Lf6) is apparent. The right FOEs seem to be better synchronized than the left FOEs. On the left temporal side, tighter synchronization was observed only between three electrodes, Lf1, Lf2, and Lf3, which seem to be more synchronized with the right electrodes. On the other side, Figure 1(b) which corresponds to a 2.5 sec temporal window during a seizure, the tight interactions between the entire FOE group are striking.

In order to view the above results in a different but equivalent way, we constructed dendrograms from the corresponding distance matrix of Figure 1. This is displayed in Figure 2. Figure 2(a) shows the dendrogram of Figure 1(a). There are three FOEs on the left mesial side, namely, Lf4, Lf5, and Lf6, and these are “high” in the distance axis, which in turn implies that they are poorly connected with other electrodes. The figure shows that all the mesial electrodes except those

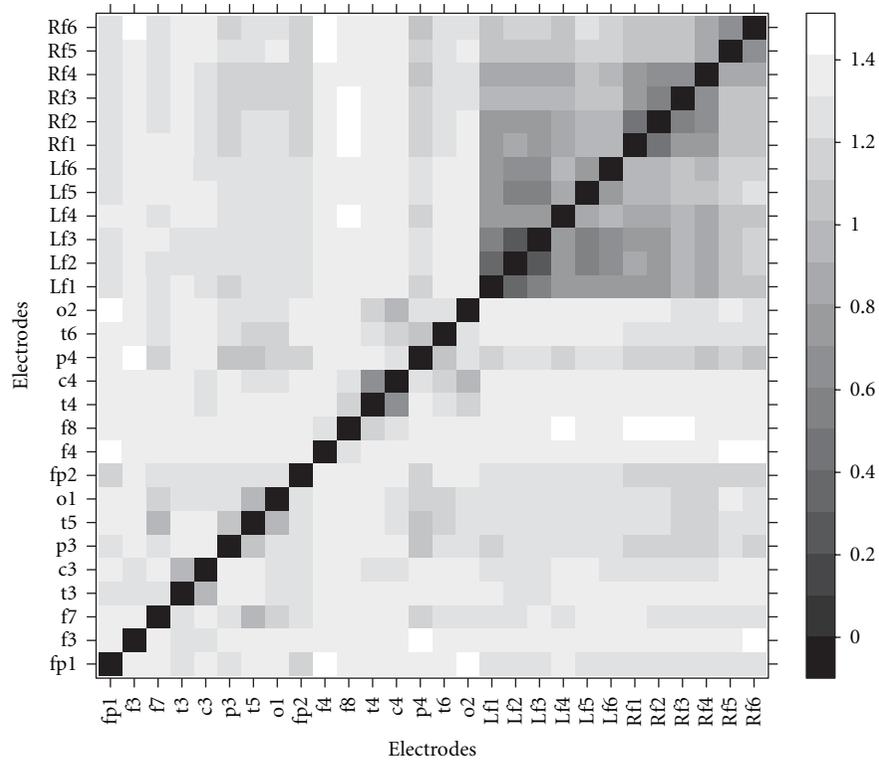
mentioned above are tightly grouped in one or two clusters. Therefore, one can conclude that, in this situation, the left mesial area is more desynchronized than the right one, due to the poor connection of the areas covered by electrodes Lf4–Lf6. Figure 2(b) shows the equivalent situation, but during the seizure. The greater synchronization between all of the mesial electrodes is striking and is seen as the deep position of the entire FOE group in the dendrogram, which in turn is also subdivided into two different clusters, one for the right FOE and another for the left.

In order to follow desynchronization activity during the whole recording for each patient, we used (2) and (3). Figure 3 shows desynchronization activity in patient no. 5 during the period before the onset of the seizure (solid vertical line) and also during the seizure. The upper panel displays the number of channels whose recorded activity was 2.5 standard deviations above baseline activity, as recorded in the first 5 minutes of the interictal record [20]. At onset, activity in the entire FOE group begins to increase, and, after a few seconds, the 12 FOE channels are highly excited. The second panel from the top shows  $AS_L$  with a smooth reduction in desynchronization activity or, equivalently, an increase in synchronization until the end of the seizure. One can observe from this figure that even when the seizure has stopped, the  $AS_L$  does not recover its preseizure value. The third panel from the top shows the  $AS_R$ , that is, desynchronization activity on the right side, whose behavior is similar to that on the left side. The main difference between both sides seems to be the deepest drop in the right desynchronized activity toward the end of the seizure. The last panel shows the difference between both desynchronization measures, that is, (3). Desynchronization activity is greater on the left side than on the right one during the preseizure period. Once the seizure starts,  $LI_{AS}$  behaves erratically, increasing the imbalance toward the positive value in the first part of the seizure, but decreasing and inverting to a negative value (around minute 32) in the second and final part of the seizure.

Figure 4 shows  $LI_{AS}$  for every patient with MTLE, as assessed by ictal video-EEG, that is, patients no. 1, no. 2, no. 3, no. 4, no. 5, and no. 7. During the preseizure period, the imbalance is always ipsilateral to the epileptic side in all



(a)



(b)

FIGURE 1: Typical distance matrix for a particular temporal window. Rf1–Rf6 stands for right FOEs no. 1 to no. 6. Rf1 is the most rostral electrode. Lf1–Lf6 stands for left FOEs no. 1 to no. 6. Lf1 is the most rostral electrode. The other labels are consistent with the standard 10–20 nomenclature. Lower distances (darker) imply tighter interactions. (a) Preseizure stage in patient no. 5. (b) Seizure stage in patient no. 5.

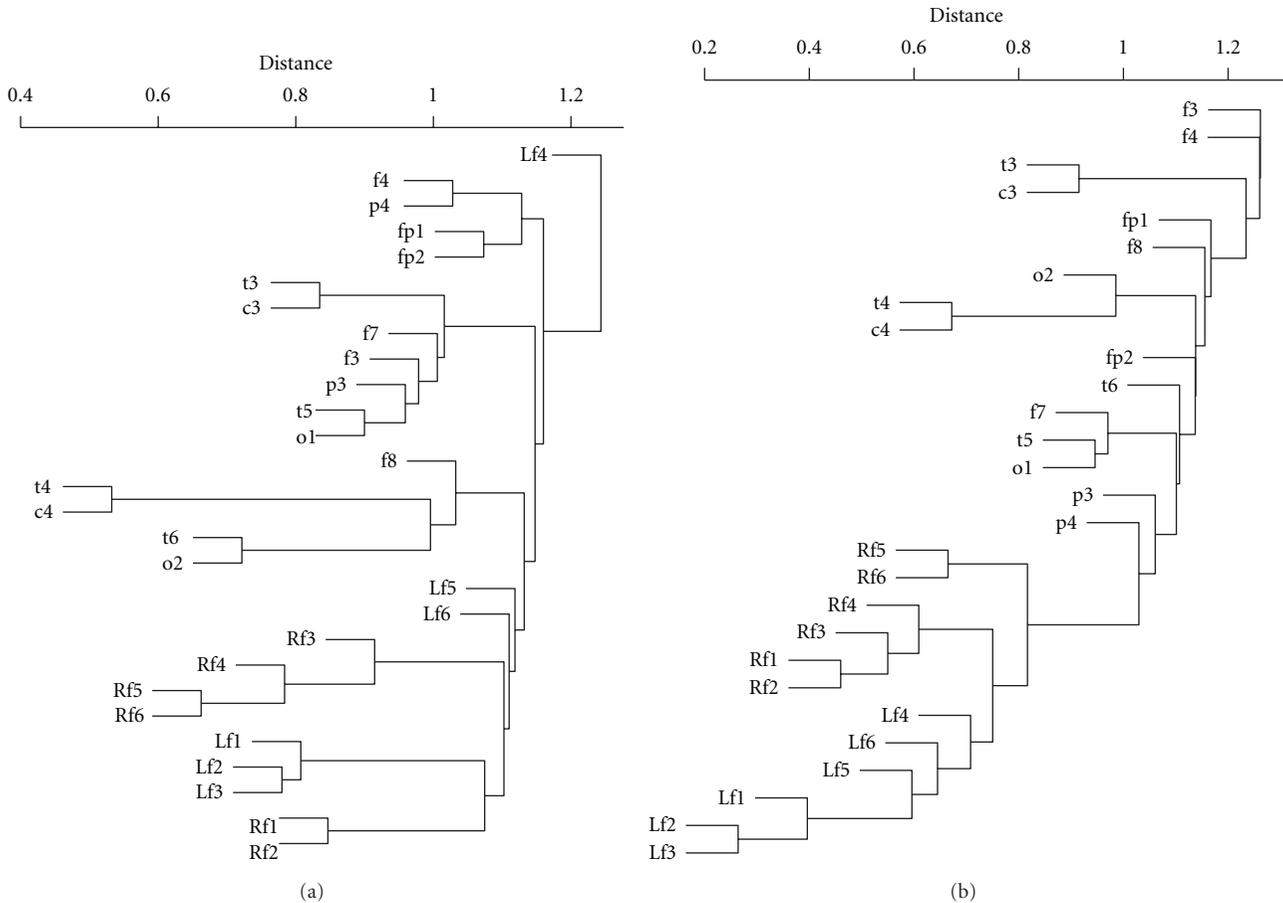


FIGURE 2: Dendrograms (see text) constructed using the distances matrix from Figure 1. (a) Preseizure stage in patient no. 5. (b) Seizure stage in patient no. 5. Lf4, Lf5, and Lf6 correspond to desynchronized activity.

cases. Patients no. 1 and no. 3 are right MTLE, and patients no. 2, no. 4, no. 5, and no. 7 are left MTLE. Although it is difficult to extract a typical pattern of evolution of  $LI_{AS}$  during the seizure from these six cases, some suggestions may be made. For instance, it seems that there is a difference between right and left temporal seizures. In left-sided cases, desynchronization increases ipsilaterally at seizure onset. The most prominent case is patient no. 4, with an abrupt increase in the imbalance around minute 14. Patient no. 7, however, displays a rapid drop before the beginning of the increase. Nevertheless, in all four cases, the imbalance during the seizure seems to begin with an increase in the imbalance followed by a decrease, which seems to end with a reversal of the imbalance, that is, minute 32 for patient no. 2, minute 16 for patient no. 4, minute 35 for patient no. 7, and minute 32 for patient no. 5.

On the other hand, patients with left MTLE (no. 1 and no. 3) do not show any significant change during the seizure, except for the high variability observed.

Figure 5 shows the  $LI_{AS}$  for patient no. 6, which, accordingly with the video-EEG evaluation, is a lateral left TLE. The difference between this LTLE case and those of MTLE is apparent. Little imbalance exists prior to onset, with  $LI_{AS}$  crossing zero imbalance randomly. During the seizure,

desynchronization was initially greater on the right side, although it suddenly became negative around minute 21.

We calculated mean values of  $LI_{AS}$  for each complete FOE recording and for each patient in three different situations. During the interictal stage, we used recordings of approximately one hour, during both the awake and sleep states. We also used a preictal recording of ten minutes prior to the seizure onset. Figure 6 shows the main results. Two cases are missing, namely, patient no. 3 (sleep) and patient no. 7 (awake). The recordings in these cases were inappropriate for the numerical analysis we performed. Except for case no. 6—LTLE—the imbalance  $LI_{AS}$  always coincided with the v-EEG evaluation, which is the gold standard for lateralization in TLE. It is noteworthy that  $LI_{AS}$  correctly lateralizes in each different situation, although with a different power. For the case of patient no. 6, however,  $LI_{AS}$  yielded a right imbalance, although with a much lower value, which in the case of the preictal stage is almost zero.

#### 4. Discussion

We showed the existence of desynchronized activity in mesial structures ipsilateral to the epileptic side in MTLE patients. The only patient with LTLE showed little or no imbalance

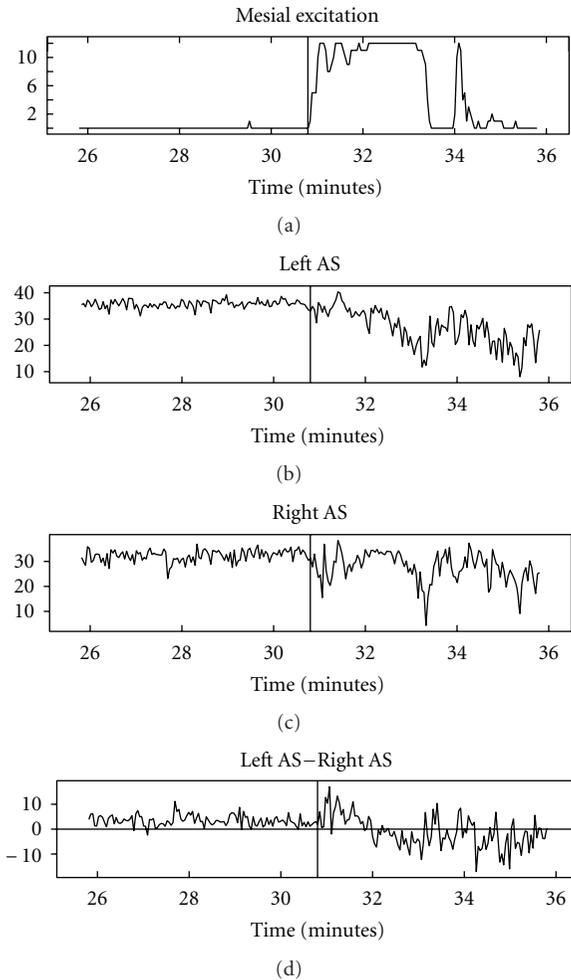


FIGURE 3: Preictal and ictal desynchronization activity in patient no. 5. Upper panel: Number of channels with activity greater than 2.5 standard deviations of baseline activity. Second upper panel: Left AS, as defined in (2), that is, desynchronized activity in the left FOE during the preictal and ictal stages. Third upper panel: Right AS, as defined in (2), that is, desynchronized activity in the right FOE during the preictal and ictal stages. Lower panel:  $LI_{AS} = \text{Left AS} - \text{Right AS}$ , desynchronization imbalance, as defined in (3). In every panel, solid vertical line marks seizure onset.

in desynchronized activity. Our findings came from a cluster analysis of FOEs records in a sample of normal MRI patients.

Our study, however, was subject to a series of limitations. First, none of the patients presented relevant findings in the MRI studies. MRI in our hospital is routinely performed using a 1.5 T device, and the images are visually inspected by expert neuroradiologists. New advances in MRI technologies, such as increased strength of magnetic fields to 3T, improve diagnostic information compared with standard 1.5T studies [21, 22]. In addition, volumetric and quantitative postprocessing image analysis yields better information [2, 23] in some cases. However, it is also true that visual inspection of standard MRI images by a dedicated epileptologist expert, as was the case in our center, can

account for 80–90% of hippocampal atrophy [2, 24]. Second, little attention was paid to the detection of abnormalities in mesial structures other than the hippocampus, mostly due to the tradition of regarding hippocampal sclerosis as the main cause of mesial epilepsy. Nonetheless, several authors report that abnormalities in the EC have been found in TLE patients with [4] and without [25] hippocampal abnormalities. We may resume the above comments stating that no abnormalities in the hippocampus and extrahippocampal areas in our patients were found, at least at the level of routine presurgical evaluations carried out in an average epilepsy center.

The results presented here are based on recordings of FOEs activity. These semi-invasive electrodes, which are introduced into the cisterna ambiens, record activity from extrahippocampal areas. It is reasonable to assume that the most anterior three to four electrodes record activity from EC, because this area forms the lateral wall of the cisterna ambiens [26]. Probably, the rest of the electrodes pick activity up from parahippocampal or perirhinal cortex, though the most frequent epileptiform activity arises from the most facial area [27].

Although it is difficult to define “normal” synchronized activity, we were able to demonstrate the existence of higher levels of desynchronization activity ipsilateral to the epileptogenic side than the contralateral one. As anticipated in the past [28, 29], a decrease in synchronization facilitates seizure onset; therefore, desynchronization facilitates seizure onset in one of these nonhippocampal structures. The state of desynchronization activity could be regarded as a state of increased susceptibility for pathological synchronization, thereby representing a possibly lowered threshold for seizure activity [28, 29]. This point is important in regard to the seizure’s dynamic. In studying the seizure evolution, low levels of synchronization, assessed by measuring zero-lag correlated activity at the seizure onset, were reported [20], although without a definite explanation. Two hypotheses were advanced [20]: whether desynchronized neuronal activity during seizure spreading is due to delays in reaching different cortical areas or the initial ictal desynchronization is caused by the already desynchronized preictal activity. Our results clearly favor the second hypothesis, implying that interictal desynchronization would be essential for initial ictal desynchronization, at least in the mesial cases. In the unique case with LTLE, mesial desynchronized activity achieves similar levels at both sides and therefore plays no role in the seizure onset. This would be expected because the seizure onset zone, as located by v-EEG in this LTLE patient, is at the lateral side of the temporal lobe.

Traditionally, the functional connectivity underlying seizure generation in MTLTLE highlights the importance of a circuit composed of the EC, parahippocampus, and hippocampus, with special emphasis on the last one. Once epileptogenic activity arises at some part of this circuit, it spreads to other structures, such as the amygdala or neocortex. However, recent anatomical findings and our own electrophysiological results place the hippocampus in a comparable position as the EC and amygdala, thus establishing a functional network of interactions. A deficit in communication between these areas, for instance, lowering levels of

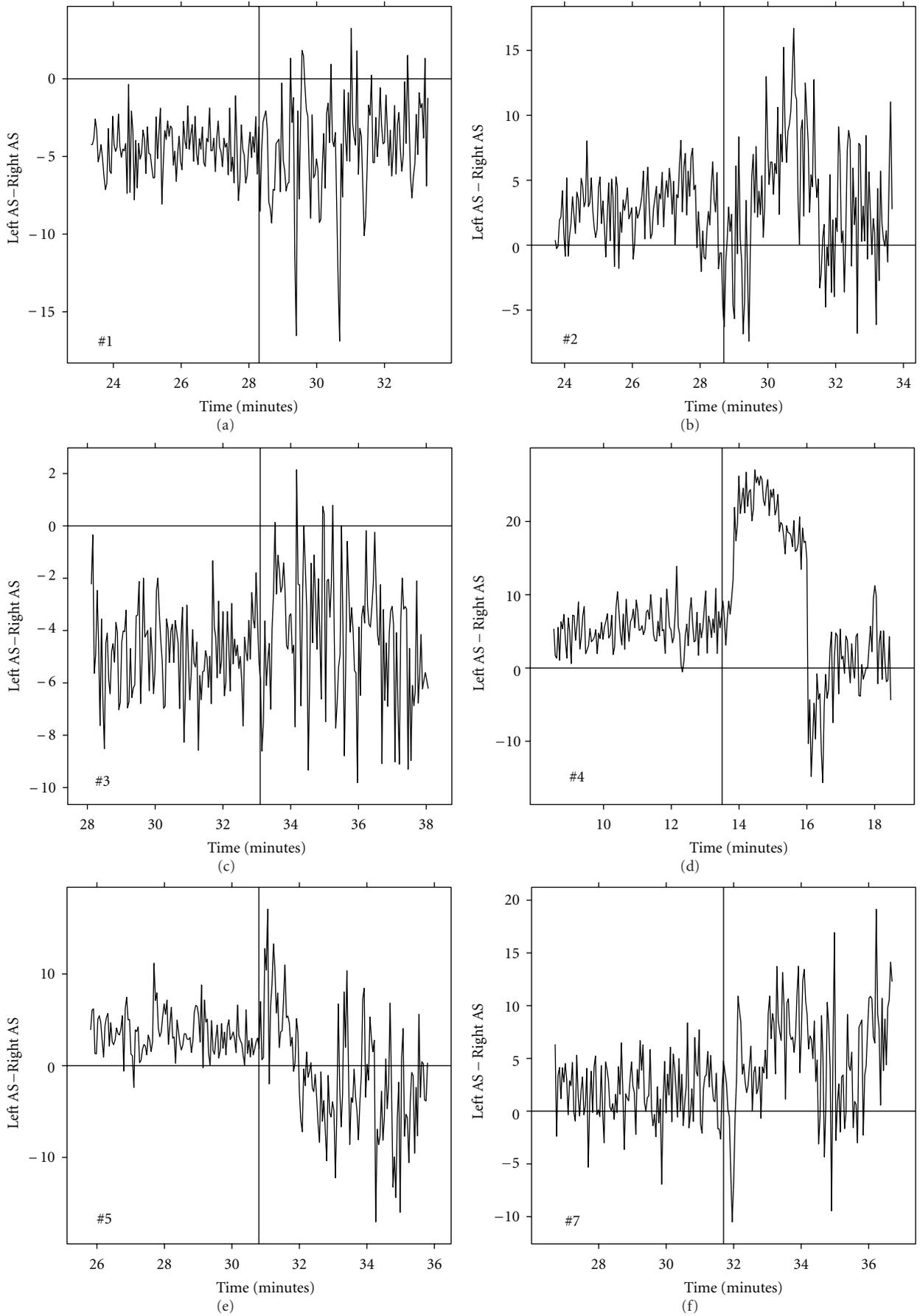


FIGURE 4: Desynchronization imbalances, as quantified by (3) for every mTLE patient.

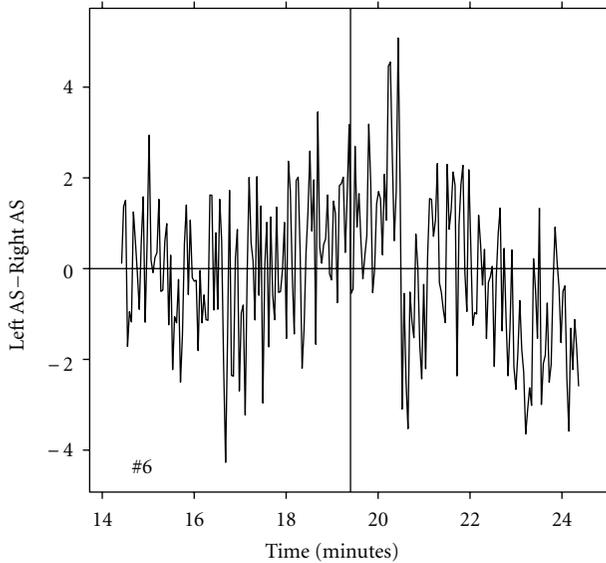


FIGURE 5: Desynchronization imbalances, as quantified by (3) in the only case of lateral TLE (patient no. 6).

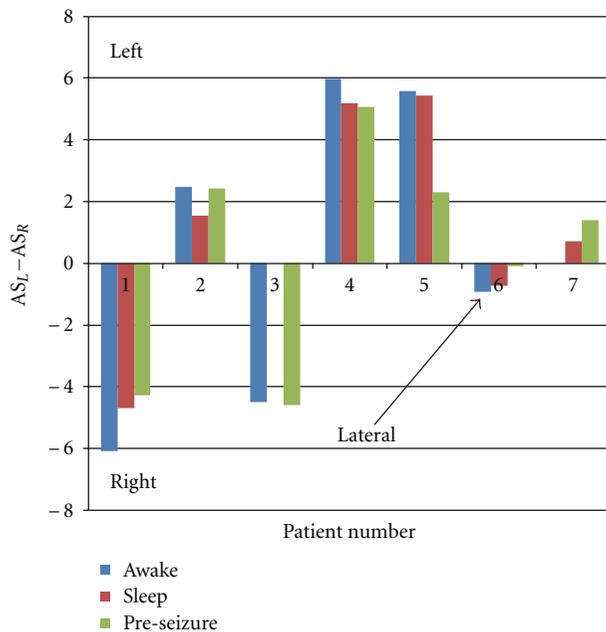


FIGURE 6: Average values of  $LI_{AS} = \text{Left AS} - \text{Right AS}$ , for every patient in three different situations. Blue bar corresponds to awake interictal stage, red bar to sleep interictal stage, and green bar to the pre-seizure stage.

synchronization between them, would promote epileptogenic activity. Once anomalous information is generated in this network, it would then spread to other mesial and lateral structures, reaching the neocortex (and thalamus) and becoming generalized. Failure in the network would be due to underlying structural pathology, such as hippocampal sclerosis or EC atrophy, which is the case in lesional TLE. In normal MRI patients, as in the case studied here, failure

in the network may be due to abnormal communication between underlying normal structures.

Our results are important from two points of view. First, the lateralization power displayed in cases of MTLE was achieved with a semi-invasive methodology, and second the methodology described here would reduce analysis time drastically. In one or two hours of interictal activity, it would be possible to draw reliable conclusions regarding lateralization, without the need to record actual seizure activity.

## Author Disclosures

Jesús Pastor, Eduardo G. Navarrete, Rafael G. Sola and Guillermo J. Ortega have nothing to disclose.

## Acknowledgments

G. J. Ortega is grateful to Rosario Ortiz de Urbina, head of Fundación Investigación Biomédica Hospital de la Princesa for her encouraging support. This work has been funded by grants from Fundación Mutua Madrileña, Instituto de Salud Carlos III, through PS09/02116 and PI10/00160 projects, and PIP no. 11420100100261 CONICET. G. J. Ortega is member of CONICET, Argentina.

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## Review Article

# A Review of the Epidemiology of Temporal Lobe Epilepsy

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Received 22 July 2011; Revised 6 October 2011; Accepted 5 November 2011

Academic Editor: Seyed M. Mirsattari

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Partial-onset epilepsies account for about 60% of all adult epilepsy cases, and temporal lobe epilepsy (TLE) is the most common type of partial epilepsy referred for epilepsy surgery and often refractory to antiepileptic drugs (AEDs). Little is known about the epidemiology of TLE, because it requires advanced neuroimaging, positive EEG, and appropriate clinical semiology to confirm the diagnosis. Moreover, recently recognized incidentally detected mesial temporal sclerosis in otherwise healthy individuals and benign temporal epilepsy indicate that the true epidemiology of TLE is underestimated. Our current knowledge on the epidemiology of TLE derives from data published from tertiary referral centers and/or inferred from population-based studies dealing with epilepsy. This article reviews the following aspects of the epidemiology of TLE: definitions, studies describing epidemiological rates, methodological observations, the interpretation of available studies, and recommendations for future studies.

## 1. Introduction

Epidemiology is the study of disease frequency, its determinants, natural history, and burden of illness in populations [1]. There are many shortcomings in the understanding of the epidemiology of epilepsy mainly related to methodological problems. Some of them are diagnostic accuracy, case ascertainment, and selection bias [2]. Information regarding the epidemiology of temporal lobe epilepsy (TLE) is scanty with few studies and review articles in this subject [3]. This article reviews some of the published evidence in the area and analyzes the methodological obstacles to perform epidemiological studies in this type of epilepsy. This article explores the following aspects; a review of the available definitions for TLE, measures in epidemiology, and a brief review of the well-known epidemiological rates in epilepsy. The article finishes with the description and analysis of the available epidemiological studies in TLE.

## 2. Definition of Temporal Lobe Epilepsy

Standardized definitions are crucial for epidemiological research. The International League Against Epilepsy (ILAE) defines epilepsy as “a condition characterized by two or more

recurrent epileptic seizures over a period longer than 24 hours, unprovoked by any immediate identified cause” [4, 5]. This definition has been used in several epidemiological studies with great success and has helped to understand the burden of epilepsy in different countries [6–8]. A modification in the definition was suggested by Fisher et al. [9] in 2005. The new definition requires the occurrence of at least one seizure plus a clear predisposing factor [9]. This modification could have practical consequences because the prevalence of epilepsy can be overestimated.

TLE was included in the classification of the ILAE in 1989 under the group of localization-related symptomatic epilepsies. The definition offers a tentative description based on suggestive clinical features (dividing seizures in simple and complex partial seizures) plus ictal and interictal electroencephalogram (EEG) findings [10]. The definition suggests the use of some findings in additional tests to help in the diagnosis, such as the presence of hypometabolism in proton-emission tomography scan [10]. The classification of the ILAE also identifies seizures coming from the amygdalo-hippocampal area (mesiobasal limbic or rhinencephalic) and seizures coming from the lateral temporal area [10]. The latter is a form of TLE which is often referred to as neocortical TLE (nTLE).

The classification released by the ILAE in 2010 recognizes some diagnostically meaningful forms of epilepsy such as mesial temporal lobe epilepsy (mTLE) with hippocampal sclerosis (HS) that was not included in the previous classifications [11]. mTLE was defined as a symptomatic focal epilepsy that can be subcategorized as limbic epilepsy (versus neocortical epilepsy) [10] and is one of the most common types of epilepsy referred for epilepsy surgery, often refractory to antiepileptic drugs (AEDs). This classification also suggests the removal of the term “symptomatic” and uses the term “focal.” It also adds the terms genetic, structural, and unknown etiology which may help to create broad categories to better classify some patients. Finally, as Wiebe [3] pointed out, the previous and current classifications of the ILAE do not rate the diagnosis of TLE and the other types of seizures or syndromes according to the diagnostic certainty, for example, definite, probable, and possible. Also, there is no weight for diagnostic features specifying major or minor criteria.

In general, the positive points of the previous and current classifications are as follows: the diagnosis is based on typical clinical description, there is recognition of anatomical areas, the addition of mTLE with HS which is a common type of syndrome, and the inclusion of some specific features such as genetic, structural, and unknown that may help to classify some etiologies in patients with TLE. The negative aspects of the available classifications are the exclusion of MRI criteria and video-EEG findings to diagnose and classify patients, especially for patients with no findings in the routine EEG despite a potential clinical description of TLE. The current classifications also do not include diagnostic categories such as definite, probable, and possible. The latter aspect is a significant disadvantage for the development of large epidemiological studies in TLE.

### 3. The Main Measures in Epidemiology of Epilepsy

In order to perform epidemiological studies in epilepsy, the ILAE recommends the following measures [3]. (a) Point prevalence is the total number of patients with epilepsy in a given population at a specified point in time. (b) Period prevalence is the number of patients with epilepsy in a given population during a defined time interval. (c) Lifetime prevalence is the number of patients with a history of epilepsy, regardless of treatment or recent seizure activity. (d) Incidence is a measure of the risk of developing some new condition within a specified period of time. (e) Incidence proportion (also known as cumulative incidence) is the number of new cases within a specified time period divided by the size of the population initially at risk. (f) The standard mortality ratio (SMR) is the ratio of observed deaths to expected deaths in a defined population. It is age- and gender-adjusted to a standard population and is the most widely used measure of mortality.

### 4. Epidemiology of Epilepsy

**4.1. Prevalence.** The prevalence of epilepsy in the developed countries ranges from 4 to 10 cases per 1,000 [1]. Studies

in the developing and tropical countries have reported a higher prevalence rates of epilepsy, ranging from 14 to 57 cases per 1,000 persons [12, 13]. Higher prevalence rates of epilepsy in the developing countries is probably related to the methodological aspects of those studies, although in some regions in the world, specific infectious diseases are frequent causes of epilepsy such as neurocysticercosis [13].

**4.2. Incidence.** The median incidence rate of epilepsy in the developed countries ranges from 25–50 per 100,000 person years while in the developing countries it ranges from approximately 30–115 per 100,000 person years [14]. In the developed countries, the incidence of epilepsy tends to exhibit a U-shaped curve with highest rates in the children and the elderly. This same pattern has not been found in the developing countries, where the incidence of epilepsy appears to peak in early adulthood.

**4.3. Mortality.** SMR in epilepsy ranges from 1.2 and 9.3 and depends on study methods and population [15–17]. Overall, the information that proves that mortality is increased in patients with epilepsy versus different type of controls is very solid and comes from well-designed controlled studies [15–17].

## 5. Epidemiology of Temporal Epilepsy

Unfortunately, there are few epidemiological studies in TLE. The majority of the studies have been generated in referral centers providing biased estimates.

The best available epidemiological data was provided by the Hauser and Kurland [18]. This initial epidemiological study explored different epidemiological markers of epilepsy in the community of Rochester Minnesota from 1935 to 1967. All the cases were assessed by experts in the Mayo Clinic which was the sole provider of neurology service including EEG to that community. The incidence rate of TLE was 10.4 per 100,000 between 1945 and 1964 and 6.5 between 1935 and 1944. In the same periods of time, corresponding incidence rates of epilepsy in the whole population were 54.3 and 34.7, respectively. In the same study, the calculated prevalence of TLE in 1960 was 1.7 per 1,000 people, with a corresponding rate of epilepsy in the whole population of 6.2 cases. In further studies published by Hauser et al. [19, 20], in the same community, estimates of prevalence and incidence of partial epilepsy were reported, but not for TLE.

Other estimates regarding the prevalence of epilepsy have been obtained from tertiary referral centers. Semah et al. [21] published a very important study where 2,200 patients with epilepsy attending a tertiary care center were classified according to the criteria of the ILAE. In this study, 1369 patients (62.2%) had localization-related epilepsy. From these cases, 66% had TLE, 24% of the cases frontal epilepsy, 2% parietal, 3% occipital, and 3% multilobar. From the whole cohort, 24% had temporal epilepsy. The rest of the patients had either generalized epilepsy (21.5%) or undetermined whether partial or generalized (16.3%). The study also compares rates of intractability between partial and generalized epilepsy being the first one more intractable.

Semah et al. [21] stated the difficulties to localize the epileptogenic zones in some patients and the classification was difficult to use.

A study of Manford et al. [22] produced estimates from a different source. In this study, 275 general practitioners identified all patients older than one month in whom a new diagnosis of definite or possible epileptic seizures was made during 3 years of recruitment. The practices of those family physicians were located around the country in urban and rural areas to avoid demographic sources of bias. Patients were followed at six months, and then every year with followup between 4 and 7 years. Details of hospital and specialist assessments and results of investigations were obtained. From 1995 patients that were included in that cohort, only 594 (21%) patients were classified as having definite epileptic seizures. The authors had significant problems to identify the localization of the epileptogenic area as many patients did not have video-EEG telemetry. Two hundred and forty five (41%) patients were classified as having localization-related epilepsy. Only 3 cases were classified as clear nTLE, 9 overlap between TLE and frontal lobe epilepsy (FLE), and 40 cases were diagnosed as TLE but the researchers could not distinguish between nLTE and mLTE. The overall percentage of cases with TLE from the group of focal cases was 21% and from the whole cohort was 9%.

Finally, studies from surgical centers describe the frequency of TLE and report different rates compared with other sources. For example, Wass et al. [23] reported 291 patients who had epilepsy surgery, 73% were TLE cases and 27% extratemporal. Guldvog et al. [24] described the seizure outcomes of 64 patients, 34 (53%) had TLE and 30 (47%) in other locations. Keene et al. [25] reported 64 patients, 44 (69%) were temporal resections, 16 (25%) extratemporal, and 4 (6%) hemispherectomies. Rougier et al. [26] reported 100 resections, 76% were temporal, 23% frontal and 1% parietal. Finally, Daniel and Chandy [27] reported the surgical outcomes of 141 patients, 102 (73%) patients had temporal resections and 39 (27%) had extratemporal resections. All the studies in surgical centers provide similar rates which are significantly higher than other sources.

Regarding mortality which is a very relevant outcome in epilepsy, we do not have any reported estimates in patients with TLE. There are reports from surgical centers with controversial information regarding the improvement of mortality rates in TLE after surgery. Some studies have demonstrated an improvement of mortality rates after epilepsy surgery if patients render seizure-free [28, 29], but these observations are not consistent in all studies [9, 30]. Patients with TLE from epilepsy centers represent very selected populations and they do not accurately reflect mortality in epilepsy in TLE.

## 6. Interpretation of the Published Epidemiological Studies

The available studies describing the epidemiology of TLE provide interesting and varied information. The studies by

Manford et al. [22, 31] provide a unique epidemiological view of TLE. In this study, the patients did not belong to surgical centers or epilepsy centers and were mainly recruited by general practitioners. The overall percentage of patients with TLE from the groups of patients with localization-related epilepsy was 21% and from the whole cohort was 9%. This study clearly indicates that TLE is not the most frequent type of epilepsy if we take into account cases with epilepsy from the community.

On the other hand, there is no doubt that TLE is the most frequent type of epilepsy that is referred to the surgical centers. The majority of surgical series report that TLE represents between 50 and 73% of all cases assessed in epilepsy surgical centers. The high prevalence of patients with TLE in surgical centers is probably related to the better surgical outcome of TLE compared to extratemporal epilepsy and the higher risk of neurological deficits related to excision of functional cortex in extratemporal cases. Because of this reason, more neurologists and more family practitioners possibly refer patients with TLE more frequently for surgical assessment. In addition, some studies have demonstrated that TLE has high rates of intractability and it could be another reason why patients are more referred to epilepsy centers.

The intermediate rates of TLE reported in tertiary referral centers help us to understand the epidemiology of this entity. Semah et al. [21] showed in his study that overall 24% of patients referred to tertiary care centers had TLE. From the group of patients with localization-related epilepsies, TLE was the most frequent with 66% of cases. In contrast to the studies from epilepsy surgical centers where a great majority of cases have TLE and from studies based on community referrals where the rate is low, studies from tertiary centers show an intermediate prevalence of TLE.

The study of Hauser and Kurland [18] is unique in many aspects and the methodology that was used in this study is probably the recommended for a large-scale epidemiological study in TLE. In the study of Hauser and Kurland [18], all the patients were evaluated in the Mayo Clinic, allowing the possibility to have the assessment from the specialist and the use of other tests to classify the patients with the different types of epilepsy. In contrast to many epidemiological studies that assess the overall prevalence of epilepsy and where simple methods can be used such as a questionnaire or simple questions to ascertain the diagnosis of epilepsy to obtain accurate estimates, in the specific case of TLE and other partial epilepsies, it would be necessary to have a clinical assessment by specialists and the use of other tests such as EEG, MRI, and in some cases video-EEG telemetry.

## 7. Future Research

The lack of large-scale epidemiological studies in TLE could be related to real methodological obstacles. Probably the main obstacle is the lack of a clear definition. As was reviewed in this article, the current definition by the ILAE is not easy to apply in large epidemiological studies. Examples of this situation are the studies of Manford et al. and Semah et al. [21, 31], where some patients were not accurately

classified because of the limitations of the definitions already discussed. In the future, a definition that could include a clinical description plus EEG, MRI, and video-EEG criteria should be employed to improve the classification of patients with TLE. Moreover, the definition has to be easy to apply in large populations such as the ILAE definition of epilepsy.

In the earlier epidemiological studies, very little if any neuroimaging was done; it was not yet available. With the expanded use of neuroimaging in the diagnostic evaluation of most patients with seizures and the improvement in imaging technology, we are getting a better understanding of the role of structural lesions in patients with TLE. Few studies have explored the presence of specific imaging findings related with TLE, such as MTS in normal population or in patients with benign forms of TLE [32, 33]. In the future, epidemiological studies using MRI are going to be critical in order to understand better the epidemiology of TLE.

Another challenge for future epidemiological studies in TLE is the selection of the population. As we reviewed in this article, a cohort for epidemiological studies on TLE should be based on a community where a hospital with major resources to investigate patients is available. This is necessary considering that many cases cannot be diagnosed only with the clinical history and they will require other specialized tests.

Finally, a significant problem to develop a large epidemiological study is the low incidence and prevalence of TLE. The study of Hauser and Kurland [18] shows that the rates are low and the necessity of a large sample size for epidemiological studies could be not feasible in many settings.

## Acknowledgment

J. F. Tellez-Zenteno receives grants from the University of Saskatchewan and the Royal University Hospital Foundation, Saskatoon, Saskatchewan, through the Mudjadik Thyssen Mining Professorship in Neurosciences.

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## Review Article

# Epilepsy, Mental Health Disorder, or Both?

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Received 12 September 2011; Accepted 2 November 2011

Academic Editor: Warren T. Blume

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Temporal lobe epilepsy (TLE), a subset of the seizure disorder family, represents a complex neuropsychiatric illness, where the neurological presentation may be complemented by varying severity of affective, behavioral, psychotic, or personality abnormalities, which, in turn, may not only lead to misdiagnosis, but also affect the management. This paper outlines a spectrum of mental health presentations, including psychosis, mood, anxiety, panic, and dissociative states, associated with epilepsy that make the correct diagnosis a challenge.

*“Dostoyevsky called himself an epileptic. . . it is highly probable that this so-called epilepsy was only a symptom of his neurosis and must accordingly be classified as hystero-epilepsy—that is, as severe hysteria”*  
Z. Freud. Dostoyevsky and Parricide, 1928

## 1. Introduction

Seizures are common in the general population. The incidence of a first, unprovoked seizure in Rochester, Minn, was measured at 61/100,000 person-years [1]. According to the Global Campaign Against Epilepsy (GCAE) [2], epilepsy, defined as recurrent, unpredictable, and typically unprovoked seizure activity, is estimated to affect 50 million people worldwide with the incidence of 40–70/10,000 per year [3], affecting mostly children, since approximately two thirds of the seizures start in the early years of life. By the Epilepsy Foundation statistics, the incidence rises again in the elderly, with the prevalence of 3% by the time a person reaches 75 years of age [4]. This suggests that in patients who are in their 30s to 40s, the onset of the recurrent generalized tonic-clonic seizures may be secondary, arising from a continuation of simple partial seizures, frequently signifying the underlying focal CNS pathology, or general medical condition, such as an altered endocrine or metabolic states.

Decades ago epilepsy was considered a nosological entity within the realm of psychiatric illness, but now the diagnosis

and treatment assignment is left up to neurologists by default, necessitating expertise or at least familiarity with similar clinical presentations related to other medical and mental health conditions. Extensive collaboration or shared care with internists and psychiatrists therefore makes clinical sense, but unfortunately not always possible.

The diagnosis of epilepsy is a clinical one, with the electroencephalography (EEG) findings supporting the diagnosis if positive, but not excluding it if negative [5, 6]. Up to 20% of patients with the clinical diagnosis of epilepsy would have a normal EEG, whether as 2% of the general population could have characteristic spike-and-wave EEG abnormalities. Routine EEG, still the first choice in ambulatory setting, is augmented with continuous EEG (cEEG) monitoring and video-EEG telemetry, which is crucial for confirming the diagnosis of a seizure disorder where there are diagnostic uncertainties or where treatment decision is based on such confirmation [7]. The role of these diagnostic modalities varies from supportive to irreplaceable, for example, in differentiating psychogenic nonepileptic seizures (PNESs) when compared

to other available diagnostic procedures [8]. Patients, presenting with features of a psychiatric illness, often require much more complex approach. Mirsattari et al. recently showed [9] that, even in absence of routine EEG abnormalities and normal head computed tomography (CT) scan, the comprehensive assessment including brain magnetic resonance imaging (MRI) and video-EEG telemetry could be of a paramount importance. Telemetry input is difficult to underestimate when deciding to discontinue antiepileptic drugs (AEDs)—in one study the telemetry monitoring resulted in changing the management in 74% of cases [10].

Indeed, clinical presentations could be easily mistaken for the variety of medical and surgical conditions, including head injury, febrile seizures, meningoencephalitis, and tumors. Other conditions that could be commonly misdiagnosed for epilepsy include but are not limited to hypoglycemia, sleep disorders, migraines, transient ischemic attacks (TIAs), paroxysmal movement disorders, and transient global amnesia (TGA), just to name a few [11, 12]. CT of the brain appears of a limited value, but MRI could be of a diagnostic assistance in identifying mesial temporal sclerosis (MTS). MTS is the most common cause of TLE. It is characterized by atrophic hippocampus with histological picture of neuronal loss and gliosis, which manifests with an increased signal on T2/fluid attenuated inversion recovery (FLAIR) MRI sequences and decreased signal on inversion recovery sequences [13, 14]. early single-photon emission tomography (SPECT) studies were found not to be helpful, specifically in diagnosing TLE, at times leading to false lateralization [15], but ictal SPECT and SISCOM (subtraction ictal spect coregistered to MRI) have been found to provide complementary diagnostic information in the presurgical investigation of medically intractable TLE patients in epilepsy monitoring units (EMUs). The recent advances in diffusion tensor imaging (DTI) appear promising in delineating the disease substrate [16]. Magnetoencephalography (MEG) reflecting the state of electrical activity within the neurons offers better accuracy in localizing the focus of epileptogenic activity compared to EEG due to the elimination of artifacts from the surrounding tissues and high temporal resolution. It is used in some centres for presurgical evaluation and was found to be an important diagnostic modality in “inconclusive” cases [17]. Positron emission tomography (PET) [18] scanning has been transformed from a confirmatory tool of assessing aberrations in glucose metabolism to a rather precise instrument of specific ligands tracing/uptake, assisting in localizing and understanding the neurochemical basis of CNS pathology. Finally, with the help of the combination of functional MRI (fMRI) and EEG, it has become possible to construct a specific brain “mapping,” invaluable in making surgical decisions in patients with epilepsy. The combination of imaging techniques with EEG, targeted at different physiological levels of brain architecture, appears most promising [19].

Despite all the above mentioned advances in imaging, clinical decision-making and EEG continue to be the cornerstone of the diagnostic approach. When the plausible “organic” cause is apparent, the onset of partial or generalized seizures, while considered secondary to general medical

condition, may still suggest epilepsy, or at least make it part of the differential diagnosis. The diagnostic path then could swing to the epilepsy as a “diagnosis of exclusion,” but on the other hand, acute onset of panic attack, especially without any overt triggers, could be misleading. Furthermore, if one adds PNES (which could be viewed as part of the conversion disorder) to the clinical presentation of anxiety, the diagnosis of “true” epilepsy may not be even considered. In the busy emergency departments (EDs), this scenario could easily lead to referral to psychiatrists, if the noncontrast head CT and lab results appear within normal limits.

There have been years of debate whether or not mental health problems experienced by patients with TLE are separate comorbidities or integral parts of the same pathophysiological process. If some disorders, particularly affective, could be attributed to global emotional response to chronic and debilitating illness (i.e., apprehension of seizures, stigma, social isolation, etc.), the symptoms of psychosis on the other hand would be more difficult to explain. It does therefore appear that both typical and atypical clinical presentations with, at times, layers of psychiatric symptoms evolving gradually or sporadically over the course of a seizure disorder might have the common pathophysiological mechanisms, that have not precisely been identified yet.

## 2. Temporal Lobe Epilepsy (TLE)

Seizure-like activity, at some point experienced by many, may not necessarily represent a seizure disorder per se, unless the clinical manifestation continues to unfold further in time with repeated pattern of the neurological manifestation, including abnormal sensation, motor abnormalities, level of consciousness, dysregulation of an autonomic nervous system, affective, behavioral changes, or a combination of all.

Temporal lobe seizures, the single most common adult seizure type [20], are also called “complex partial seizures” or “psychomotor epilepsy,” which could be defined as a chronic neurological condition with recurrent seizures as main characteristic feature. In fact, it should probably be viewed as a spectrum of seizure disorders, rather than an isolated nosological unit, with at least two subtypes, namely, mesial temporal lobe epilepsy (MTLE) and lateral temporal lobe epilepsy (LTLE) with the epileptogenic focus on the outer temporal lobe surface. The condition nevertheless often appears “fluid,” with both types coexisting and/or generating each other. This type of a synchronized neuronal activity appears somewhat unique because of a presence of aura and so-called “twilight” state of consciousness with poor recollection of preceding events.

Classically, the presentation of TLE would include some form of aura, occurring in up to 80% of patients with epilepsy, manifesting by somatosensory psychiatric autonomic symptoms or their combination. This is followed by ictal, postictal, and then interictal states. Screening for automatisms (or semipurposful seemingly automated movements), frequently observed in ictal state, should become norm in every clinical patient encounter—this is

commonly missed only because a witness might not necessarily consider it relevant to report. Examples include lip-smacking, chewing or swallowing, picking at buttons, or other repetitive hand movements. Patients would often appear semireactive to their environment, picking up nearby objects such as telephones or pencils but in a trance-like state with likely no recollection of the events. Speech output may also be automatic or semiresponsive, perseverative at times. Usually, a postictal period of either confusion or dysphasia occurs, the duration of which varies from minutes to hours, but rarely days, and sometimes inversely proportional to baseline cognitive abilities. Other features that suggest a diagnosis of temporal lobe originating seizures include short duration (1-2 minutes), early onset, and a history of childhood febrile convulsions [21]. Sleep-onset panic attacks [22] and the lack of response to typical panic disorder treatments should also raise questions.

It is believed that up to 30% of patients with epilepsy have some form of a psychiatric condition [23]. Psychiatric manifestations of epileptic seizures have been known for years, both for idiopathic cases and those describing patients with seizures with mental health abnormalities following traumatic brain injuries [24]. One recent survey on comorbidities in epilepsy [25] found that neuropsychiatric conditions such as anxiety, depression, bipolar disorder, ADHD, sleep, and movement disorders were more likely to be self-reported by patients with epilepsy than those without it.

Misdiagnoses, namely, labeling secondary psychiatric syndromes with primary psychiatric diagnoses, usually derive from limited understanding of the diverse manifestations of epileptic seizures and could probably be grouped into

- (i) psychosis/schizophrenia,
- (ii) unipolar depression or bipolar disorder,
- (iii) anxiety and/or panic disorder,
- (iv) cognitive decline and behavioral aberrations.

### 3. Psychosis

Psychosis can be defined as an altered mental state with the presence of either or the combination of hallucinations, delusions, and thought disorganization to the extent of altering one's capacity to function. Pathological substrate in psychosis involves the same limbic structures in TLE with or without involvement of the frontal and parietal lobes, the combination of which results in discrete psychotic phenomena [26]. The inner relationship between psychosis and epilepsy appears rather complex, but, from the practical standpoint, it may be important to distinguish these symptoms to a particular TLE phase, that is, during aura, ictal (during the event), postictal (after the event), interictal (in-between seizures), and iatrogenic, representing anticonvulsants sideeffects [27].

The prevalence of psychoses in patients with epilepsy is about 2 to 7% in the general population but measured at approximately 20–60% of those seen in psychiatric departments [28]. Psychosis, the exact prevalence of which is difficult to estimate, can be related to each seizure event

or present in a persistent fashion, fully simulating schizophrenia or schizoaffective disorder if coupled with affective dysregulation. The clinical presentation strongly suggestive of schizophrenia may be so convincing, especially if patients present only with psychotic features [29], that in one study when formally applying criteria for schizophrenia, half of the patients with epilepsy and psychosis could have been easily diagnosed with schizophrenia alone [30]. To make matters worse from the diagnostic standpoint, there also appears to be a cohort of patients with both epilepsy and schizophrenia concurrently existing [31]. Under the circumstances, it would be prudent to pay specific attention to the onset of the first symptom or sign and the response (if any) to anti-convulsant or antipsychotic medication. Even then it may not provide enough evidence to differentiate reliably.

Indeed, not only these two conditions share seemingly the same neuropsychiatric features, but the order of onset of each of these raises the famous “chicken and egg” question. In an attempt to answer the question which of these two separate entities comes first, Adachi et al. [32] came to the conclusion that because of common features and linear distribution of time intervals, so-called “psychosis-epilepsy” and “epilepsy-psychosis” represent the same condition. If true, it seems plausible that since psychosis is a purely clinical entity, the pathophysiologic mechanism responsible for generating these symptoms may be disease independent, that is, appear secondary to electric or chemical disruptions, whether idiopathic, caused by metabolic abnormalities or the host of other offenders. Not all patients with TLE, however, show these abnormalities. There is some evidence that the age of epilepsy onset (earlier age) predispose patients to develop psychotic symptoms, mostly interictally [33, 34]. Other predisposing factors include the presence of borderline intellectual functioning [35] and a family history of epilepsy or psychosis [36]. As for the psychiatric premorbid factors, high prevalence of mood disorders in first- and second-degree relatives, rather than potentially predisposing personality traits, schizotypal, and paranoid in particular, was reported [37].

Half a century ago in a classic text, Slater et al. [38] stated that there were no definite shifts in personality and affective dysregulation in TLE patients, exhibiting hallucinations and delusions, accounted for 3/4 of the studied population. Interestingly, there was also no uniform psychotic presentation in both patients with TLE and schizophrenics without epilepsy. Some could be attributed to the course of illness, whether relapsing-remitting or progressing. The negative symptoms, however, were thought to appear more predominantly in patients with TLE, which were deemed independent of past affective disorders and resulting in greater neuropsychological deficits [39]. Other authors [40] suggest that TLE psychosis lacks the negative symptoms of schizophrenia with more benign and variable course. From the clinical standpoint therefore, it would be safe to assume that just the presence of mostly negative or positive symptoms is neither specific nor sensitive. Since psychosis is a manifestation of the brain dysfunction (symptom) and not a separate disease category, duration of it offers no significant assistance in deciding the secondary process

versus psychiatric illness—in both cases the duration could be highly variable as well as a severity.

Irrespective of the clinical caveats, psychosis in TLE may have either relapsing-remitting course (concurrent with seizures), chronic (involving interictal phase), or combinatory with various complexity and expressiveness of thought disorder or perceptual abnormalities. Preictal states, as well as ictal phase in TLE, may present as an “umbrella” of altered sensorium, including

- (i) illusions (apart from pure illusion phenomenon experiences by many disease-free individuals, distortions of vision aka micro-, macro-, or palinopsia),
- (ii) visual (lines, abstract images, geometric shapes, or colors that appear similar to migrainous aura, localizing to the occipital lobe [41]),
- (iii) auditory (music, often repetitive; voices, at times distorted or muffled [42]),
- (iv) olfactory or gustatory hallucinations,

which may not necessarily lead to loss of consciousness, but may represent either an isolated seizure or a part of it, with or without further progression to motor abnormalities or dissociative states. More complex hallucinations with experiential phenomena can follow [43], comprising dream sequences, flashbacks, and brief or prolonged profound affective symptoms such as sadness, happiness, fear, or anxiety. Patients, usually unresponsive, may demonstrate complex behavior, including seemingly purposeful activity (walking, dressing, chewing, or even repeating phrases). Patients may retain partial responsiveness [44], another strong potential for misdiagnosis. Finally, Kraft et al. [45] described complex ictal psychotic phenomena such as forced thinking, thought withdrawal and insertion.

The specifics of symptoms and their timing seem dependent on the spread of the seizure focus in each individual, but it is worth noting that the particular features of complex partial seizures must be absent before an ictal cause for psychosis is ruled out. The wide variability in presentation and relative low frequency make systematic evaluation of these phenomena problematic, but identification of seizure activity leading to anticonvulsant treatment tends to result in psychiatric improvements [45] although, to the best of our knowledge, there are no randomized, controlled studies outlining this issue. Because of the frequently observed motor abnormalities, ictal psychosis may not necessarily present a diagnostic dilemma.

Postictal psychosis is also common, accounting for 25% of epileptic psychoses [46], and would usually follow the prolonged seizure activity with generalized tonic-clonic seizures in particular. Because this seizure type is easily recognized by physicians and lay-people alike, there is usually no difficulty in identifying the cause. The uncertainty arises when these events do not seem related, even though rarely there is a lucid interval of one to six days prior to the onset of psychosis. Kanner et al. [47] reported 10% of patients with history of depression as predictive factor, experiencing postictal psychosis with the median duration of 18 hours, which corresponds to the findings of others. As to the specifics of

the presentation, it varies from grandiose and religious delusions with elevated moods [48] to mixed manic-depressive like psychosis or bizarre behavior [49]. From the practical perspective, confusion in emergency rooms in respect to the differential diagnosis stems from convulsions not being witnessed, or with appearance of the mental health problems in patients following a nonconvulsive seizure. Thus, in an attempt to delineate the differential path, applying DSM IV criteria per se might not be sufficient—one needs to take into account the past medical and mental health history, pace of the development of psychotic symptoms, fluctuations on the level of consciousness, and, finally, the responsiveness or lack of thereof to antipsychotic medications.

Interictal psychoses seem most troublesome to differentiate from a pure psychiatric illness. Many authors would again argue that the distinction between the neurologic and psychiatric boundaries in these individuals is arbitrary or artificial [45], since the judgment is based solely on clinical observation. Schizophrenia-like psychosis in epilepsy is not that common but well documented [38]. These individuals present quite similarly to paranoid schizophrenia with perceptual abnormalities, with a mean latency of about 14.1 years after onset of epilepsy although with a wide range. Clinically, factors that distinguish these patients from having pure schizophrenic illness were reported to include a typically better premorbid function, a preservation of affect, religious, moral, or ethical interests [50, 51], absence of negative symptoms, formal thought disorder, and catatonia [29, 52]. A study of 282 epilepsy patients with psychosis compared to 658 epileptic controls concluded that earlier age at onset of epilepsy (mean 12.8 versus 14.6 yrs), a family history of psychosis (5.5% versus 0.3% in controls), complex partial seizures or generalized tonic-clonic seizures, and borderline intellectual functioning were predictors for developing interictal psychosis [53]. The clinical utility of the data is debatable as the absolute differences between groups appear small. Case reports of patients with this overlap of symptoms highlight the difficulties in both diagnosis and management, even though anticonvulsants tend to improve clinical outcomes [54, 55]. The global outcome in epileptic schizophrenic patients tends to be worse, perhaps reflecting organicity in their illness [31].

Another caveat deserving consideration is so-called “forced normalization” or “alternative psychosis” phenomenon, associated with normalized EEG secondary to anticonvulsants (phenytoin, carbamazepine, ethosuximide) but with exacerbation of psychotic symptoms [56], manifesting mainly in paranoid delusions or other symptoms, including depression, mania, anxiety, and lasting for days or weeks. Lastly, in patients with medically intractable TLE, surgical approach may precipitate the onset of the psychotic features [57]. This process could be qualitatively different from the previously seen signs of psychosis (if any), and, in other cases, psychiatric condition would just remain unchanged with postoperative seizure improvement [58].

Summarizing, symptoms and signs of psychosis may appear at any phase of the epileptic disorder and require meticulous history taking and trials of medication to speculate on exact diagnostic modality.

#### 4. Psychogenic Nonepileptic Seizures (PNESs)

PNESs represent the whole cluster of a seizure-like disorder, either occurring separately and independently from epilepsy or complementing it. It could be defined as manifestation of similar if not identical signs of seizures in absence of paroxysmal neuronal discharge. Symptoms that are consciously produced for conscious reasons (i.e., malingering), those consciously produced for unconscious reasons (forms of factitious disorder), and physiologic seizure-like activity secondary to medical conditions belong to separate categories. Unconsciously produced symptoms for unconscious reasons, as in conversion disorder, which include a great variety of neurological presentations, appear more appropriate description of this pathological state. Ironically, even though this phenomenon probably represents one of those cornerstone diagnostic modalities that act as a pivotal point in swinging patient care between specialties, neither neurologists nor psychiatrists have any reliable tools for diagnosis and management.

Emergency department physicians are facing these challenges on a regular basis, especially when psychogenic seizures (frequently labeled as “pseudoseizures”) are the only visible clinical manifestation. Frequently, giving the benefit of the doubt and acting out of the worst possible scenario for the sake of safety, these presentations could be diagnosed and treated as epilepsy if no apparent physiological explanation exists. Unfortunately, years could pass before the diagnosis is made—according to one study [59], the time between the onset of symptoms and diagnosis could exceed several years—the laboratory, electrophysiological, and imaging studies searching for the cause usually take extensive amount of time and resources.

In an attempt to clinically differentiate psychogenic from nonpsychogenic seizure activity, one needs to bear in mind that classic grand mal tonic-clonic presentation with tongue biting, urinary incontinence, and complete unresponsiveness during the ictal phase is rare in PNES. Clonic muscle jerks in PNES are often symmetrical with the eyes closed, falls rarely involve serious body injuries, benign automatisms are rare, and postictal confusion, if present, does not reach the level commonly seen postictally in patients with TLE. Length of psychogenic seizures frequently exceeds 5 minutes [60]; these patients would more likely have a history of chronic pain or fibromyalgia [61], depression and dissociative states [62]. Other factors include history of childhood sexual, emotional or physical abuse [63], history of unipolar depression or anxiety disorders [64], along with somatoform and conversion disorders [65].

One could easily see psychogenic seizures as part of conversion disorder, which includes a whole array of neurological presentations involving motor, sensory, and coordination abnormalities, difficult to diagnose in emergency settings and even more difficult to treat. Stigma of having a mental health condition, shame, and denial may make the therapeutic alliance with these patients problematic [60], and with an absence of evidence-based therapeutic approach showing significant benefit [66, 67], patients may fall in-between family physicians, psychiatrists, and neurologist

with minimal, if any, relief. In terms of management, a recent review [68] suggests different types of cognitive behavioral therapy (CBT) as a preferred treatment modality. This was echoed by a pilot study by Goldstein et al. suggesting CBT as more effective in reducing the frequency of seizures than standard medical care alone [69].

#### 5. Dissociative Symptoms

Strictly speaking, by the DSM IV criteria, dissociative disorders embrace several subtypes: depersonalization disorder, dissociative amnesia, dissociative fugue, dissociative identity disorder, and “not otherwise specified” or NOS disorder. DSM V working group (<http://www.dsm5.org/>) suggests to include derealization disorder in the first category and add substance-induced dissociative disorder as a clearly defined subgroup. Dissociative symptoms, if not viewed in the context of epilepsy, are usually associated with the mind compartmentalizing unpleasant or severely traumatic memories from consciousness, thus associated with posttraumatic stress disorders (PTSD), acute stress or conversion disorder. In simple terms, all dissociative states to some extent embrace the disconnection of self from the surroundings as a protection mechanism.

This phenomena may occur as an aura, during preictal or immediate postictal states, with or without affective component or anxiety. In patients with TLE, there is some evidence [54], echoed by others [70], that the presence of dissociative states, defined by the Dissociative Experience Scale (DES), is predictive of psychogenic or pseudoepileptic rather than epileptic seizure occurrence. Other authors [71] suggest the sole presence of dissociative symptoms indicative as responsible for nonepileptic seizures, but under condition of a presence of memory impairment, psychological traumas/PTSD, personality, or affective disorder. The literature reflecting psychiatric overtones in TLE outlines dissociative symptoms primarily in context of psychogenic seizures, with evidence that the presence of dissociative states may have a negative impact on psychogenic seizure outcome [72].

#### 6. Anxiety and Panic

Anxiety in humans is a natural response required for adaptation and as such is not pathological by itself. However, when the sense of worry or apprehension becomes excessive (compared to what would be experienced by most under the circumstances) or uncontrollable, it starts to affect the quality of life and from that point requires professional attention. In fact, in combination with unipolar depression, it is anxiety with or without panic that frequently motivate patients to seek help not the mood. There is a clear distinction between a fear and anxiety with the latter reflecting rather apprehensive response to unknown, internal, or conflictual situation. Pathophysiology of anxiety includes dysregulation of inhibitory neurotransmitters (GABA specifically) [73], as well as dopamine, epinephrine, and serotonin, coupled with impaired secretion of corticotropin-releasing hormone and cortisol. Literature suggests that severely affected patients,

with refractory epilepsy, high seizure frequency, would more likely to have multiple comorbidities, including anxiety [74]. At least half of patients with chronic epilepsy would have either affective or anxiety disorder [75] with TLE patients affected more often.

DSM-IV-TR criteria for anxiety disorders appear somewhat soft, perhaps reflecting the clinical reality of the anxiety disorders crossing over with each other, with common features of pathological apprehension in all of them. Generalized anxiety disorder (GAD), panic disorder (PD), obsessive-compulsive disorder (OCD), and different phobias are part of the anxiety spectrum. A classic presentation of simple partial seizures of the mesial temporal lobe easily meets DSM-IV criteria [76] for panic attack: abrupt discrete episode of intense fear or discomfort, reaching maximum intensity within minutes and associated with autonomic arousal, somatic, and mental state symptoms. Muscle tension, “stomach butterflies,” hypervigilance, fear of losing control, feelings of getting “crazy,” and so forth and as well as psychotic symptoms could be experienced in any phase of epileptic disorder. The seizure typically begins with an aura, commonly accompanied by a visceral sensation (epigastric rising sensation, uneasiness in a chest, stopped or racing heart) and by an overwhelming sense of fear, which in fact, does appear most frequently ictally [77]. Other common auras include derealization, such as *déjà vu* (sense that current events had already happened in the past with an ability to predict immediate future); *jamais vu* (sense of unfamiliarity despite familiar surroundings), and, less commonly, depersonalization (sensation of being positioned outside of the body). Palpitations, cold sweats, tremulousness, lightheadedness, and nausea may follow. Fear of having a panic attack, called “reactive,” may not be readily distinguishable from other egodystonic feeling of generalized elevated apprehension, not associated with panic attacks. In addition, extreme isolated fear of having a seizure adds to the clinical complexity because, if severe, may qualify for a separate clinical category. Phobias in TLE could be subdivided in two major categories: fear of seizures or consequences of such (possibly resulting in agoraphobia) and unrelated phobias [78].

To qualify for DSM-IV criteria of a panic disorder, attacks must be recurrent, unexpected, and followed by 1-month duration of either persistent concerns, worries about the implications, or a change in behavior, all of which are understandable and predictable responses in this setting. If the diagnosis of epilepsy is not considered at all, likely in the setting of scarce history of seizures, the exclusion for “caused by a general medical condition” may not be applicable, resulting in psychiatric rather than antiepileptic management. Often, however, the same medication could be used for both patients cohorts, but for the different reasons (e.g., mood stabilizers) and secondary improvement of psychiatric symptoms may drive the diagnosis further from neurological. To differentiate panic disorder from epilepsy, one must attempt to elicit a detailed seizure history. It does appear of a paramount importance because the key differentiating clinical features may not necessarily be volunteered neither by patients nor by witnesses. Another reason for poor history is a simple lack of awareness due to the retrograde or

anterograde amnesia. If awareness was retained, the patient may give some or all of the history, thus classifying an event as a simple partial temporal lobe seizure. It is, however, more common for awareness or memory function to be disrupted, diagnosed then, if witnessed, as a complex partial seizure.

## 7. Mood

Affective disorders in TLE are important comorbidities primarily because of suicide potential in all forms of it, including gesture, ideation, or successful attempt, which accounts from 10% to 15% in patients versus 1–1.5% in general population [79, 80]. According to Harden and Goldstein [81], the prevalence of depression appears 5 times more frequently in patients with controlled seizures and 10 times in those with uncontrolled. It is not known whether the depression in these patients could be viewed primarily as part of the primary CNS pathology or as an understandable response to the epileptic disorder with all the hardship of every day coping. Even though some skepticism exists as to the “functional” nature of the affective disorder, there is evidence [82] that controlling the frequency of seizures dramatically improves quality of life, possibly via secondary alleviation of a depressed mood. On the contrary, apparently manic episodes are seen much less often [83].

Affective disorders in patients with TLE have the prevalence of up to 80% based on data gained from a structured interviews along with self-ranking scales [84]. The cause of it is more likely multifactorial, from purely psychological factors [85] to biological [86]. Latter is believed to include hypometabolism in extratemporal regions, hippocampal dysfunction or atrophy, and 5-HT1A-receptor-binding abnormality among other factors [87–90]. Pharmaceutical management, specifically anticonvulsants, may alter affective states as well [91], but it is not known whether or not they may potentiate the depression or just act as cofactors. Based the population-based study [92], there is some evidence that depressive symptoms preceding the onset of epilepsy may be seen up to seven times more frequently among the patients versus the control group, which on one hand suggests involvement of the same anatomical structures in both processes (at least on the functional level), and on another, makes the possibility of interdependency of severity plausible. As Kanner pointed out [93], the presence of a psychiatric illness, depression in particular, may be associated with additional difficulties in seizure control, thus making this form of TLE more treatment-resistant.

Clinical presentation of a mood disorder can appear at any time (preictal, ictal, postictal, interictal), taking many forms from simple irritability and anger to flat affect, guilt, anhedonia, chronic suicidal ideation, and suicide attempts. Interictal dysphoric disorder, known as baseline mood flattening in epilepsy, encompasses many features characteristic for DSM IV criteria for depression, but paradoxically with an addendum of euphoria. Kula et al. found [94] that the established interictal dysphoric disorder in 54.8% of cases showed a “clear-cut” relationship with epileptic seizures. The importance of this mild (in comparison with major

depressive disorder) condition lies in its prevalence and, correspondingly, extended drain on quality of life.

## 8. Cognitive or Behavioral Decline

Not surprisingly, patients with severe intractable epilepsy have worse clinical outcome, with cognitive decline as part of it. A retrospective analysis of 136 patients apart from cognitive deficit itself showed a direct dependency between the frequency of tonic-clonic seizures and level of cognitive impairment [95].

Typical absence seizures, or petit mals, usually first seen in school-age children, while representing a generalized disorder, rarely lead to any convulsions. They are characterized by sudden impairment in awareness, often with a motionless blank stare and cessation of ongoing activities. Duration is typically seconds with a rapid return to baseline and, importantly, there without aura or postictal state [96]. Specifically because of that, observers would not necessarily suspect any seizure activity in these patients—the signs of momentary disorientation, confusion, “not listening,” and any form of the compensatory behavior could be easily attributed to one of the mental health conditions.

Absence status epilepticus is another form of paroxysmal abnormality with continuous or nearly continuous absence seizure activity, but with a slightly different presentation, characterized by variable slowness in behavior and mentation, either fluctuating or constant. Despite seemingly complex and unusual presentation, only the US, its incidence was estimated at 65,000–150,000 cases per year [97]. Clinical presentation varies from mild forms to stupor or coma and can easily be mistaken for catatonia. Patients seem apathetic and lethargic as they can still eat, drink, dress themselves, and follow simple commands [98]. Quite often there are some physical clues such as oromotor or manual automatisms that may be present—examples include semipurposful repeated chewing motions, picking at buttons, or rubbing the nose. During these episodes, intermittent and subtle myoclonic jerks of the eyelids can be seen, quite commonly in children, with the cheek and jaw being additionally involved in adults. Myoclonic jerks as a response to various stimuli (such as sudden noises or lights) are less common. Absence status can last from half an hour to days and rarely leads to generalized tonic-clonic seizures. Unlike convulsive seizures, the act of continued absence status is not thought to cause direct permanent sequelae.

Diagnostic difficulties in this realm are experienced not only by neurologists or psychiatrists, but by physicians of different specialties; it may be seen in a variety of medical conditions, for example, as a complication of general anesthesia [99], reaction to antibiotics [100], or being associated with MELAS, where apart from paroxysmal activities, confusion, paranoid delusions, and behavioral shifts can be observed [101]. Psychiatric manifestations, apart from behavioral, cognitive aberrations, and psychosis, may include memory deficits [102]. In mentally delayed, typical or atypical absence seizures are common, but their recognition can easily be overlooked. An unexplained and significant cognitive

or behavioral decline in this population demands further investigations, EEG, or telemetry in particular.

Patients with apparent dementia or other various forms of cognitive decline may turn out having electrical paroxysms. In one study, three patients with gradual memory deterioration over years were referred to a dementia clinic with a tentative diagnosis of Alzheimer's disease (AD). Their workup included an EEG, which identified epileptiform activity in two and waveform abnormalities in the third patient. Neuropsychological scales revealed a reversal of their initial decline above their baseline scores once treatment with anticonvulsants was initiated. However, they did not reach scores for their age equivalents [103].

Neurodegenerative diseases are the recognized epilepsy risks, accounting for 20% of known etiology [1]. The varied EEG abnormalities seen in these clinical conditions cloud clinical interpretation unless clear epileptiform activity is noted. Although anticonvulsants may cause cognitive impairment as a sideeffect (as in most recent report on topiramate) [104], treatment anecdotally improved cognitive status. There may not be a clear-cut algorithm to follow, but clinicians must be aware of epilepsy presenting as AD, or of epilepsy complicating AD, and that in both scenarios anticonvulsants may have an impact on the quality of life.

## 9. Personality and Life Style

Apart from the presence of the disease, the duration of illness could have further impact on patients' life. Hermann et al. [105] reported that in comparison with the healthy controls, patients with long standing TLE experience chronic emotional and behavioral distress, resulting in significantly poorer quality of life.

To reiterate, apart from biological substrate responsible for personality traits yet to be identified, people with TLE frequently has an altered life style, adjusted for best performance under the circumstances. The latter include psychological burden of social stigma, having seizures, ongoing expectations of such, interictal declines in functioning, and a necessity to take medication for seizure control, often, for life. This starts in the childhood but does affect different age group differently. In one study [106] of 118 children with epilepsy, deterioration in energy levels, attention, and language were less pronounced in older children, who on the other hand were found more affected by decreased self-esteem and anxiety. Families with these children are understandably stressed with the peak emotional response at the onset of the disease [107], with ongoing struggle made worse by unpredictable nature of illness and, with time, behavioral abnormalities [108]. Academically, children with epilepsy appear to do worse, which could also be psychologically detrimental [109]. It was found that higher parent education acts as a self-esteem protective factor in children with processing speed decline [110]; however, little is known about any interventions that may assist early in life to help these young patients function overall better in both social and environmental dominions. Recent study by Rodenburg et al. [111] clearly shows the necessity of early

screening for the psychological problems, paying specific attention to the family issues, social functioning in the transition into adolescent years, and unmet needs.

Adolescents, particularly with childhood onset of epilepsy, continue to be at higher risk of comorbid psychiatric conditions, including affective disorders with increased suicide risks [112]. As time goes by and adolescents turn into young adults, they frequently discover self ineligible for certain jobs, for example, those associated with operating a heavy machinery, public transportation, and so forth. In addition, many, depending on the severity of illness, found themselves crippled by inability to drive, which makes them more dependent than the same age others. The impact of epilepsy on social functioning was found profound and greater than, for example, migraine [113], even though both are chronic neurological conditions and both observe elements of episodic but complete disability.

Many patients with TLE remain unemployed, facing social or personal isolation [114, 115]. Having said that not all carrying the diagnosis of epilepsy are equally affected, severity of a disease, including the presence of comorbidities and/or psychiatric symptoms and signs [116], predictably affects the prognosis. Recently, authors from Spain [117], based on cross-sectional multicenter epidemiological study, revealed 58% employment and 10.9% unemployment rate, with occupational incapacity (12.5%) higher in patients with partial seizures, twofold affecting those with refractory epilepsy. Indeed, the number of medications to keep seizures under control and quantity of seizures add to unemployment risk [115].

Personality in general terms could be defined as a combination of emotional, attitudinal, and behavioral pattern of responses to the environment, not necessarily immediately obvious to an individual. Personality traits, seen in patients with epilepsy (if one assume they do exist) may affect social and occupational interactions further [118]. Manchanda [119], citing current consensus rejecting the term, gave a brief description of “epileptic personality,” which does not seem to follow any particular pattern, but at the same time suggesting that the serious social maladjustment could be precipitated or potentiated by such. Interictal behavioral traits were described decades ago [120] and included circumstantiality, dramatization, excessive mental “chewing” (viscosity, hyperreligiosity), and altered sexual behavior. Controversial views, however, persist up to this point [121, 122].

Swinkels et al. [123] showed higher dimensional scores for the epilepsy patients in cluster C personality traits (dependent and avoidant in particular) along with development of maladaptive personality traits, dependent on the duration of the disease. Again, this could be attributed to consequences of having chronic medical condition, but patients with, for example, asthma, did not observe the same tendencies [124]. In TLE patients with left or bilateral seizure foci, a clinically notable elevation of the “viscosity” or, in other words, tendency to be over inclusive, circumstantial, repetitive, and clingy was observed [125]. Other authors [126] suggest that the structure of seizures matters; experience of auras were attributed to the development to both cluster B and C personality traits; avoidant traits were

reported in patients with PNES [127]. Attempting to further delineate various discrepancies in opinions, Locke et al. [128] undertook a study of 79 patients subjecting them to the battery of neurophysiological testing, concluding that there is no evidence to suggest any specific personality changes despite the burden of chronic and unpredictable illness, naturally affecting both mood and behavior.

## 10. Treatment

Management of epilepsy is generally effective, by either medical or surgical means, with the rate of success related to the type and cause of seizure. Since treatable, recognition of an underlying seizure disorder obviously has significant implications. Occasionally, initial misdiagnosis possesses only mild repercussions, as in the case with benign occipital lobe epilepsies being mistaken for migrainous auras [41, 129–131]; however, completely omitting a possible diagnosis of epilepsy in differential may have devastating effects on the lives of afflicted individuals, as the alternate diagnosis is often schizophrenia [38, 45, 51, 132–135], affective disorders [21, 136–139], or (recently becoming more apparent) Alzheimer’s disease [103]. Apart from that, there is data that SSRIs or antipsychotic medications may increase seizure risk by affecting the metabolic rate of neurotransmitters [140].

As to the pharmaceutical management of the associated with TLE psychosis, it usually depends on its severity. For example, postictal brief psychosis may not require any intervention, unless delusional beliefs or perceptual abnormalities threaten to alter the behavior. In interictal psychosis, if not affected by anticonvulsants, atypical antipsychotics may be given, preferably not those changing seizure threshold. Affective disorders are suggested to address starting with SSRI and/or CBT with electroconvulsive treatments (ECT) as last resort [141].

## 11. Summary

A great variety of epileptic presentations can meet DSM-IV criteria for schizophrenia, brief psychotic disorder, panic attack, generalized anxiety, major depressive disorder, dissociative disorders, dementia, and other conditions under the umbrella of “mental health disorders.” According to set criteria, the symptoms cannot be caused by a general medical condition, but the mimicry of epilepsy syndromes can be so convincing, that seizure may not be even considered.

The increasing frequency of case reports suggests that the number of misdiagnoses are not necessarily declining and there are many yet to be discovered. Additionally, epilepsy and psychiatric disorders are not mutually exclusive diagnoses and could easily coexist. Overlooking either diagnosis in a patient afflicted with both may lead to treatment failures.

The outpatient EEG is not a sensitive test since seizure activity is typically episodic, subtle abnormalities can be easily missed, and imaging is commonly unremarkable. Clinicians must rely on their knowledge of varied presentations to consider epilepsy and whether investigations and consultation with the professionals in other subspecialties

are warranted. In difficult cases, referral to an epilepsy monitoring unit for cEEG and video recordings are essential to increase the sensitivity and specificity of the diagnosis. DSM V, to be released in the near future, should identify typical seizure characteristics as exclusion criteria.

Finally, greater collaborations between the disciplines of neurology and psychiatry are required to improve the care for patients that share some characteristic features of the both illnesses but they do not exclusively fall in one or the other camp.

## Acknowledgments

The authors would like to thank Dr. A. Burhan and Dr. R. Manchanda for critical appraisal of this paper.

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## Review Article

# Depression in Temporal Lobe Epilepsy: A Review of Prevalence, Clinical Features, and Management Considerations

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Received 4 July 2011; Accepted 10 September 2011

Academic Editor: Warren T. Blume

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Depression in temporal lobe epilepsy has been established as a frequent occurrence, and various possible mechanisms for this significant comorbidity have been posited. However, there is still little to guide a clinician in the recognition and management of depression in patients with temporal lobe epilepsy. This is in part due to the lack of consistent findings in earlier studies, which was likely partly due to variabilities in methodology, sampling, and diagnosis of both temporal lobe epilepsy and depression. However, in recent years, significant effort has been made to address these issues and provide a framework for diagnosis and management of depression in this population. The following is a review of the literature, with special emphasis on clinical phenomenology of depressive symptoms, described bidirectional risk between depression and temporal lobe epilepsy, and treatment strategies in the context of potential drug interactions with antiepileptic drugs.

## 1. Introduction

Temporal lobe epilepsy (TLE) is the most frequent of the epileptic disorders. Interictal depressive symptoms, and interictal major depressive episodes, are quite common in epilepsy in general but appear to be particularly linked to TLE [1]. This link between these two disorders has been a source of great interest to both neurologists and psychiatrists for many years and has generated an expansion of knowledge in both fields that has been used to better understand not only these two disorders, but the relationship of mood, cognition, and temporolimbic function in other related conditions as well [1].

Despite this, a review of the literature reveals that there is limited cohesive guidance regarding the prevalence of depression in TLE patients and the clinical features by which diagnosis can be made, nor are there universally accepted guidelines for the management of depression in this population. Difficulties in study design, variable sample populations, and the challenges of confirming temporal lobe focus in some patient populations are all possible contributors to this gap. However, many established authorities in this field have been making significant efforts to overcome these issues

and move towards a cohesive approach to diagnosis and management of depression in the TLE population.

## 2. Prevalence of Depression in Temporal Lobe Epilepsy

Although there have been many studies examining the frequency of depression in temporal lobe epilepsy patients, it has been difficult to establish a clear pattern with respect to prevalence, particularly in comparison to other types of epilepsy [2]. Historically, depressive symptoms have been considered to be more frequent in epilepsy with a temporal lobe focus than in extra-TLE or generalized epilepsy [3–8]. However, several other studies have not been able to document any such differences [2, 9–17].

Several explanations for this have been proposed. Firstly, concomitant or additive mechanisms may play a role in the development of depressive symptoms in sufferers of TLE. Rodin et al. [7] noted that many patients with TLE have more than one seizure type, and that the number of seizures rather than the location of the focus may be more relevant. Two later studies confirmed that frequency of seizures were more

significant in predicting depressive symptoms than focus location [18, 19]. Other risk factors have also been identified, such as age of onset and laterality of temporal lobe focus that may also place patients at higher or lower risk than location of focus alone [20, 21]. Similarly, frontal lobe dysfunction in addition to temporal lobe dysfunction may be an important risk factor in developing depression in TLE patients [2]. Additionally, Swinkels et al. [2] described significant methodological differences among the various studies examining prevalence rates of depression in epilepsy, including small sample size, lack of control groups, variable and often non-standardized diagnostic instruments, and variability in the study population (inpatients, outpatients, surgical patients, etc.). Finally, Adams et al. [15] observed that many studies assessing psychiatric symptoms in epilepsy predate the advent of technology such as video electroencephalogram monitoring and magnetic resonance imaging, which may make characterization of the underlying lesion more unreliable. All of the above may be contributing to the fact that although there is a plethora of studies dedicated to the assessment of prevalence of depression in temporal lobe epilepsy, consensus has yet to be achieved.

Nevertheless, a handful of recent studies have attempted to rectify some of the above issues and have provided some interesting data. Sanchez-Gistau et al. [16] studied 308 patients that were carefully classified as having epileptiform foci that was temporal or extratemporal in localization. These patients were then administered the Structured Interview for DSM-IV Axis I Psychiatric Disorders (SCID-I), and results were compared using a multivariate analysis. Of the TLE group, 22% had a lifetime prevalence of Major Depressive Disorder, and 14.6% had previous one-year prevalence of this disorder. Extra-TLE sufferers had a lifetime prevalence of 14.6% and a previous one-year prevalence of 6.5%. Of all the psychiatric disorders assessed (mood disorders, psychotic disorders, somatoform disorders, substance abuse disorders, and anxiety disorders), only previous-year prevalence of major depressive disorder was significantly different between the two groups, with TLE sufferers having a higher rate of major depression. Adams et al. [15] followed 319 individuals with focal epilepsy over an 11-year period. The epileptic site, laterality, and type of the lesion were confirmed with video electroencephalogram monitoring and MRI scans. The patients were assessed by the study neuropsychiatrist using DSM IV diagnostic criteria prior to their epilepsy diagnosis being made and were reviewed by a second neuropsychiatrist to confirm diagnostic concordance. The overall prevalence of depression in the study participants was 32.6%. No significant differences were found in the prevalence of depression between TLE patients (31.2%) and extra-TLE patients (37.9%), nor between left or right-sided lesions. Of note, patients with nonlesion focal epilepsy exhibited a higher rate of depression (41.6%) compared to those with a lesion on MRI, regardless of temporal or extratemporal focus. Swinkels et al. [17] assessed 67 TLE patients and 64 extratemporal lobe focus patients for depression using the Beck Depression Inventory and the Composite International Diagnostic Interview. No significant differences were noted between the two localization groups, but rates of psychiatric symptoms were

higher in patients with more frequent and prolonged seizures.

In summary, the question of whether a temporal lobe focus of epilepsy assigns a higher prevalence of depression to patients is not yet fully answered. Earlier studies were divided on this issue, but variability in methodology, patient samples, accuracy of identification of epileptic focus, and in diagnostic tools used for assessment of depression all made comparison of the data difficult. Additionally, this variability in results may also represent multiple factors at play in the development of depression beyond simply localization of epileptic focus, such as frequency and length of seizures, age, and comorbid dysfunction across multiple areas.

### 3. Clinical Characteristics of Depression in Temporal Lobe Epilepsy

Although this survey of the available literature did not uncover studies of the natural history of depressive symptoms in TLE patients specifically, most studies examining the relationship between depressive symptoms and age of onset of epilepsy or duration of epilepsy do not identify clear association with risk of depression [8, 22, 23]. One study did find a potential link between depression and development of seizures in later life [24].

One of the questions that has been raised historically is whether depressive symptoms in the epilepsy and TLE population represent a comorbid mood disorder, with diagnostic characteristics and a natural history similar to major depressive disorder as seen in the general population, or whether these symptoms instead represent a collection of emotional and cognitive disabilities similar but not equal to a major depressive disorder [25–27].

The concept of *interictal dysphoric disorder* was proposed to describe the latter in response to studies suggesting that a significant portion of epilepsy patients with depressive symptoms would not have met criteria for Major Depressive Disorder as typically described in diagnostic schedules [28, 29]. For example, Kanner et al. [30] examined patients with refractory seizures and depressive symptoms and found only 29% met DSM IV criteria for Major Depressive Disorder. Initially proposed by Kraepelin, then later Bleuler, this concept originally described a pattern of symptoms consisting of prominent irritability, euphoria, anxiety, anergia, insomnia, and pain. These symptoms are described to have a chronic, relapsing and remitting course, but to respond well to antidepressants [31]. A more specific range of symptoms had been described by Blumer et al. in their Neurobiological Inventory for Epilepsy, which was a reformulation of earlier inventories that were meant to define the TLE personality characteristics [25, 29]. Two categories of symptoms have been described: *depressive-somatoform symptoms* (depressed mood, anergia, pain, and insomnia) and *affective symptoms* (irritability, euphoric mood, fear, and anxiety) [29]. Anhedonia has also been proposed as a better marker for depression in patients with epilepsy, in part secondary to its independence from physical symptoms associated with medications and chronic illness [32].

However, there have also been many proponents of the belief that there is not sufficient evidence to support a model of psychopathology unique to temporal lobe epilepsy. Kanner and Nieto [33] proposed that the symptoms described in these TLE- or epilepsy-specific psychopathology inventories are quite similar to a stable mood disorder with marked depressive and anxiety features rather than a *de novo* condition. Lishman [34] also concurred that the depressive symptoms described as specific to the TLE population were an artifact of sampling and selective reporting by patients in institutional settings.

Efforts have been made to test the validity of diagnosing depression in this population. Reilly et al. [25] reasoned that the latent variable factors observed to be impacted in depressive disorders (negative attitude, performance difficulty, and somatic elements) could be measured in TLE patients to compare the level of dysfunction across these domains to known quantities in major depression. TLE patients manifested difficulties across these domains that were very similar to that seen in major depressive disorder, suggesting that these symptoms represented a major depressive disorder, rather than a condition unique to TLE. Jones et al. documented the validity of the SCID and MINI (Mini International Neuropsychiatric Interview) by comparing to patient self-report of symptoms of Major Depressive Disorder, and finding very high concordance [35].

In summary, there has been some suggestion historically that depressive symptoms in the TLE population may represent not depression but rather a condition unique to these patients. This concept has been described as interictal dysphoric disorder. However, there now also have been studies that appear to confirm that the DSM IV criteria for major depression are valid in the TLE population, and that the depressive symptoms they experience can be understood as a stable mood disorder.

#### 4. Neuroanatomical Findings of Depression in Temporal Lobe Epilepsy

The various structures of the limbic system have been a focus of interest in understanding both depression and TLE for quite some time. Regions of particular interest for both these disorders include the temporal lobes (particularly the hippocampus, amygdala, entorhinal, and neocortical cortex), the frontal lobes, and important limbic subcortical structures such as the basal ganglia and thalamus, as well as the circuits connecting all these structures [1, 37–40]. Although the hippocampus and amygdala have been the major focus of attention, all of the above structures have been found to share association across these two disorders [1].

In both depression and TLE, hippocampal volumes have been found to be abnormal [1]. In depressed patients with and without TLE, hippocampal volumes are reduced, usually bilaterally or occasionally left sided only [37, 41–45]. In TLE patients, volumes are usually reduced on the side of the epileptic focus [40, 42, 45]. In depressed TLE patients, hippocampal volumes are usually reduced bilaterally. Interestingly, in patients with a left-sided TLE focus, cognitive problems with memory and learning are more marked [46]. Other

studies have confirmed this, linking depression and verbal learning impairments in TLE patients [47]. The suspected cause behind this is dysfunction within the larger language representation in the left hemisphere [46, 47].

The amygdala has also been a source of intense study in the combined field of depression and TLE, given its key role in fear and associated emotions [48]. This structure appears to change as an acute depressive episode becomes chronic, initially becoming enlarged bilaterally, then shrinking bilaterally as the mood disorder becomes chronic [1]. Two studies have found a relationship between escalating amygdala volume and severity of symptoms of depression in the TLE population [49, 50]. Left-sided volume increases of the amygdala and severity of depression symptoms in TLE patients seemed particularly associated with each other [50]. The suspected mechanism for this is hyperactivity of the amygdala in the acute phase of depression in TLE and non-TLE patients, resulting in an increase in volume secondary to increased regional blood flow [1, 49, 50].

The two commonest lesions for the development of temporal lobe epilepsy are mesial sclerosis and the more rare neocortical temporal lesions [1]. Patients with mesial temporal sclerosis have significantly higher rates of depression than those with neocortical temporal lesions, regardless of lateralization [51]. Additionally, patients with mesial temporal sclerosis have a greater frequency of cognitive side effects and mood problems with antiepileptic drugs [52]. Interestingly, Salgado et al. [53] found significantly more widespread grey matter volume loss in TLE patients with depression as compared to their nondepressed fellow patients. This leads to the suggestion that there is a bidirectional relationship between these two disorders [53].

In summary, various important structures of the limbic system have been found to be significantly different in depressed TLE patients in comparison with nondepressed fellow patients. There may be a bidirectional relationship between depression and TLE influencing these structures.

#### 5. Depression after Neurosurgery in Temporal Lobe Epilepsy

Surgery for intractable epilepsy has become increasingly available for patients, resulting in more individuals becoming seizure-free, often thus dramatically improving quality of life [35, 54]. However, there is an emerging recognition that psychiatric complications can occur in the postoperative period, including *de novo* symptoms of depression [54].

The strongest risk factor for depression in the postoperative course is, perhaps not surprisingly, preoperative depression [55–57] and has been reported in approximately 20–30% of patients undergoing surgery [58–60]. Rates of *de novo* depression in TLE patients in the postoperative period range from 5 to 25% [54]. Other risk factors identified include older patients at time of surgery [61, 62], male gender [55], strong family history of psychiatric illness, and poor seizure outcome postoperatively [61]. The highest risk period appears to be in the first 3 months following surgery, with slow improvement at the 12- or 24-month mark [54, 63].

Lateralization has been the focus of many studies, but no clear, cohesive pattern appears to have emerged yet. Several studies suggest that right temporal lobe resections represent a greater risk of postoperative depression [57, 64], while several more support left temporal lobe resection as higher risk for this complication [56, 57], and yet others report no evidence of laterality at all [63]. These ambivalent results are echoed in the literature examining rates of depression following tumor resections [65, 66].

However, some studies have documented what appears to be a bidirectional risk in the relationship between postoperative seizure control and depressive symptoms. Metternich et al. [67] documented significantly lower Beck Depression Inventory scores in patients that were seizure-free postoperatively. Reuber et al. [58] observed that postoperative TLE patients improved significantly with respect to depressive symptoms in comparison to medically managed TLE patients, but only if seizure control was significantly improved. This led them to suppose that depressive symptoms were associated with epileptic activity rather than structural changes.

Finally, Wrench et al. [68] recruited 60 patients undergoing two types of surgery (mesial temporal lobe resection and nonmesial temporal lobe resection) and followed them longitudinally. Preoperatively, 43% of these patients had a lifetime prevalence of depression, with no difference between the surgical groups. Predictive factors for preoperative depression included family history of mental illness and financial dependency. However, in the postoperative phase, the mesial temporal resection group experienced a significantly higher rate of depression, both recurrence and *de novo* [68], suggesting that perhaps disruption of these structures carries a higher risk of depression as a complication postoperatively.

In summary, recurrence and *de novo* development of depression is a risk in TLE patients undergoing surgery, particularly in the first 3 months postoperatively. Although no clear pattern is emerging regarding the relevance of laterality, there is significant evidence to support a bidirectional relationship between depression and postoperative seizure control, where the presence of one can exacerbate the other. This echoes the findings previously described earlier in this chapter, in which each condition may operate as a significant risk factor for the other.

## 6. Antiepileptic Drugs and Depression

Antiepileptic drugs (AED's) have been known to have positive psychotropic effects beyond their antiseizure effect for quite some time [69]. Indeed, many AED's have separate indications for the treatment of psychiatric disorders, including roles as mood stabilizers [70], anxiolytics [71], and in the management of withdrawal syndromes [72]. It is also equally true that many AED's have negative psychotropic effects that can complicate the management of both epilepsy and depression in patients [69].

The AED's associated with the highest risk of occurrence of depressive symptoms in patients with epilepsy are those which act at the benzodiazepine-GABA receptor complex [69]. These include barbiturates, topiramate, and vigabatrin.

Levetiracetam and felbamate appear to represent an intermediate risk of depressive symptoms, leaving the other AED's as either low risk or unknown [69] (Table 1). Unfortunately, a clear understanding of which populations may be at particular risk of developing depressive symptoms while on AED's has yet to be developed [69], and this review of the literature did not produce any studies that endeavored to identify this in the TLE population. However, Mula and Schmitz [69] suggests a general approach of monotherapy if possible, with introduction of any new AED's with slow, careful titration, and careful histories of premorbid and family psychiatric disorders being collected regularly in this patient population [69].

## 7. Consequences of Depression in Temporal Lobe Epilepsy

*7.1. Depression as a Risk Factor for Seizures.* Depression has been acknowledged by the World Health Organization as one of the most significant sources of burden of disease and suffering globally [73]. The impact of this disorder on mortality, morbidity, quality of life, social function, and occupational function have been well described. Similarly, the additive burden of depression in chronically medically ill people has also been well described, both for epilepsy as well as other medical conditions as diverse as COPD, ESRD, cancer, and diabetes. Thus, it is expected that there would be a consequence to be borne by those TLE patients that carry the comorbidity of these two disorders.

However, as previously noted in this chapter, there is strong support for a bidirectional risk existing between these two disorders. In other words, the presence of depression may have a direct impact on TLE symptom severity, control, and possibly even onset.

For example, Forsgren and Nystrom [74] found that there was a seven-fold increase in rates of depression being diagnosed *prior* to the onset of the seizure disorder in patients with newly diagnosed epilepsy when compared to age- and sex-matched controls. This remarkable finding was further raised to a 17-fold increase when patients with a localized onset were studied. Another study found a 3.7-fold increase in frequency of diagnosis of depression preceding the first seizure in older adults with new onset epilepsy [24]. A study of Icelandic children and adults with new onset epilepsy found a similar increase in rates of depression preceding seizure onset (1.7 fold), as well as a 5.1-fold increase in a premorbid history of attempted suicide [75]. In a study of children with new onset seizures, psychopathological symptoms (including anxiety, depression, attention disorders, thought disorders, and somatic disorders) were present at higher rates than controls for 32% of the newly epileptic children [76]. Finally, recent studies have also suggested that psychopathology could be a significant risk factor for infants developing nonfebrile seizures or epilepsy in childhood [77].

Perhaps the most interesting finding of the pattern of mood symptoms predating epilepsy is Alper et al's. [78] study of epileptic patients enrolled in SSRI, SNRI, and mirtazepine treatment trials. Patients on the medications had significantly lower rates of seizures when compared to their

TABLE 1: Positive and negative effects of AED's [36].

Antiepileptic drug	Negative psychotropic symptoms	Positive psychotropic symptoms
Barbiturates	Depression, hyperactivity	Anxiolytic, hypnotic
Carbamazepine/ oxcarbazepine	Irritability	Mood stabilizer, antimanic
Ethosuximide	Behavioral abnormalities, psychosis	None identified
Felbamate	Depression, anxiety, irritability	None identified
Gabapentin	Behavioral problems in children	None identified
Lamotrigine	Insomnia, agitation	Mood stabilizer, antidepressant
Levetiracetam	Irritability, emotional lability	Possible antimanic
Phenytoin	Encephalopathy	Possible antimanic
Pregabalin	Unknown	Anxiolytic
Tigabine	Depression (nonconvulsive status epilepticus)	Possible anxiolytic
Topiramate	Depression, psychomotor slowing, psychosis	Mood stabilizer
Valproate	Encephalopathy	Mood stabilizer
Vigabatrin	Depression, aggression, psychosis	None identified
Zonisamide	Agitation, depression, psychosis	Possible antimanic

matched fellow patients receiving placebo. This last study in particular is suggestive of the potentially exacerbating role that untreated depressive symptoms may have on seizure control.

**7.2. Suicidality in TLE Patients.** Completed suicide is one of the most tragic and feared outcomes of a depressive episode and is always a concern to clinicians when working with patients with significant psychiatric comorbidity. Fortunately, it is a relatively rare event in the general population. Unfortunately, in epilepsy, the rate of suicide is approximately two to five times that of the general population, and this is further elevated to a 25-fold increase among patients with TLE [79, 80]. Not surprisingly, the rate of completed suicide is further elevated up to 32-fold by the presence of a comorbid depressive disorder [79].

This shocking increase has been considered to be primarily influenced by the psychosocial consequences of living with chronic epilepsy [81]. However, recent data would suggest that the situation is more complex than psychosocial consequences of chronic illness alone, and that a part of understanding completed suicide risk in epilepsy may lie in the examination of suicide attempts. A study comparing suicide attempts among patients with epilepsy to comparably handicapped controls with other chronic disabilities found

that 30% of patients with epilepsy had attempted suicide as compared to 7% of controls [80, 81]. This is relevant given the fact that suicide attempts are complex behaviors involving many factors, including impulsivity and executive dysfunction, which can be associated with temporolimbic function [82–86]. Jones et al. [87] found a lifetime prevalence of suicide attempts of 20.8% among 139 outpatients followed at epilepsy centers in the United States. In this sample, the highest rates of attempts were among patients with a lifetime history of a major depressive episode or manic episode, and higher rates of suicidal ideation were also associated with a lifetime history of mood or anxiety disorders. Major depressive disorder was the most frequent psychiatric disorder identified among patients with a history of suicide attempt (51.7%), while anxiety disorders were more strongly associated with suicidal ideation (58.8%) in this sample [87].

This suggests that there are characteristics specific to epilepsy, in particular TLE, which may place patients at elevated risk of completed suicide and suicide attempts, particularly in the context of comorbid depression. Espinosa et al. [88] studied 42 patients with newly diagnosed TLE over a 1-year period and assessed suicide risk via the Plutchik Risk of Suicide scale. They found that 57.1% of their sample scored >7 on this scale, which is the highest risk category for suicide, 28.6% had a past history of suicide attempts, and 45.2% had experienced suicidal thoughts. The study authors also assessed for multiple associated factors including psychiatric comorbidity, past medical and psychiatric history, and neuropsychological deficits. They discovered a significant relationship between higher suicide risk and a higher rate of suicide attempts in patients with a family history of psychiatric diseases, left-sided TLE, current major depressive episode, and higher perseverative responses on neuropsychological testing via Wisconsin Card Sorting Test (WCST). They also found a strong correlation between poor WCST performance and severity of depressive symptoms, implying that the presence of depression likely exacerbates executive dysfunction in a population that already has documented difficulty in this area. Once again, this suggests a bidirectional relationship between depression and epilepsy in the manifestation of suicide risk.

There is an added layer of complexity in understanding suicidality in TLE patients. On December 16, 2008, the US Food and Drug Administration issued a warning about an increased risk of suicidal ideation and behavior among people taking AED's [89]. The agency had performed a review of 119 clinical trials of 11 AED's and noted a 1.8-fold increase in suicidal behavior or ideation in patients taking AED's in comparison to those taking placebo. Although many methodological issues have been identified with this study, it raised concerning questions regarding the use of these drugs in a population known to suffer significant psychiatric comorbidity. As described previously in this chapter, AED's have been documented to produce both positive and negative psychotropic effects, and the FDA's announcement produced a flurry of epidemiologic work to attempt to confirm this increased risk of suicidality and hopefully suggest mechanisms [90]. These questions are still being answered, and the studies' findings have been quite mixed, but results thus far

suggest that if there is an elevated risk of suicidality with AED's, it appears to be very low [69], and that no clear pattern is emerging regarding risk stratification across the various AED's [69, 90]. Additionally, none of these studies have focused on TLE in particular, but rather have included samples that tend to be quite broad both in type of epilepsy and comorbidity of psychiatric illness [90], which in part may explain the variability of findings. Wen et al. [90] noted an interesting trend in their retrospective analysis of patients in the Comprehensive Epilepsy Research Program (CERP) database over a 32-month period. Briefly, they noted that the strongest predictors for the development of suicidality over time were the presence of depressive symptoms or suicidality prior to AED treatment, and that those patients started on new or multiple AED's had less improvement of suicidality over time in comparison with those who had no changes made to their AED regimen. Additionally, they found no significant difference in suicidality between the AED's themselves. This led the authors to suggest that perhaps the findings of the original FDA study were generated by the artifact of patients on AED's improving less than placebo controls with respect to their suicidality symptoms over time.

**7.3. Quality of Life Consequences for Patients with Comorbid Depression and TLE.** Multiple studies in epilepsy in general and TLE specifically have made efforts to examine the relationship between various factors associated with living with epilepsy and the impact on quality of life [91–98]. Kanner [99] reviewed 5 studies in particular that consistently demonstrated that depression was the most powerful predictor of health-related quality of life across multiple domains, even when controlling for factors such as seizure frequency, severity, and other psychosocial variables. Meldolesi et al. [98] studied 106 patients with drug-resistant unilateral temporal lobe epilepsy, administering various standardized quality of life instruments as well as the Beck Depression Inventory and an anxiety scale. They also found depression to be consistently the strongest predictor of lower scores on all QOL domains except seizure worry. This effect was independent of socioeconomic status, gender, lateralization of seizure focus, seizure frequency and severity, and anxiety.

Additionally, comorbid depression appears to be associated with a greater likelihood of adverse events associated with antiepileptic drugs, more frequent visits to physicians, and higher cost of medical care related to the seizure disorder, rather than any cost associated with the psychiatric disorder and its treatment [97–99]. This is an interesting finding in light of the recurring theme woven through the literature of the bidirectionality of depressive symptoms and epilepsy symptoms. Again, the presence of one appears to make the management of the other more of a challenge.

## 8. Management Strategies for Depression in Temporal Lobe Epilepsy

In general, evidence for treatment strategies of mood disorders in epilepsy are lacking, and development of management approaches tend to rely on clinical experience rather

than evidence-based trials favoring one treatment over another [69]. The paucity of data is even more pronounced when examining the literature for TLE-specific depression treatment studies. Not surprisingly then, there are no widely accepted guidelines for the treatment of depression in TLE patients.

However, clinicians can turn to a body of literature that, while lacking in large, double-blinded, and placebo-controlled RTC's, still includes several smaller open label trials, case series reports, and a handful of comparative studies. The bulk of this data does not limit itself to TLE although a recently published comparative study in TLE patients in particular is included in the following discussion.

**8.1. Antidepressants.** There are three main considerations when initiating an antidepressant trial in a patient with epilepsy: exacerbation of seizure control, potential for interaction with AED's, and efficacy of the antidepressant in depression symptom resolution. There appears to be variability between and also within the various antidepressant drug classes although some generalizations can be made from the available literature.

**8.1.1. Antidepressants and Seizure Risk.** The potential for antidepressants to provoke seizures has been a source of concern and possibly a barrier to treatment of depression in patients with epilepsy [100]. The data documenting seizures secondary to antidepressants is derived largely from psychiatric populations, in vitro or animal model studies, or from samples which were not specifically patients with epilepsy [36, 100]. Often, seizures associated with antidepressants are described in cases of toxicity, such as accidental or intentional overdose [36, 100]. This makes it difficult, if not impossible, to generalize findings to epilepsy patients. The situation is further complicated by the fact that animal and human studies suggest that some antidepressants may have an anticonvulsant effect, while some may have a proconvulsant effect, and yet others may have a biphasic effect, in which they are anticonvulsant at lower doses and proconvulsant at higher doses [36]. Mechanisms proposed for the proconvulsant effect include the anticholinergic effect of many antidepressants (particularly at higher doses), as well as the elevation of serotonin and noradrenalin neurotransmission [36]. Anticonvulsant effect may be mediated by the interaction of the antidepressant with other factors, including AED's. For example, fluoxetine has been noted to enhance the anticonvulsant effect of phenytoin and carbamazepine via selective inhibition of serotonin uptake [36].

Tricyclic antidepressants (TCA's) have a wide variety of neurotransmitter related effects, many of which are dose dependent as well. Overall, they are considered proconvulsant, in large part secondary to their significant anticholinergic effect, which is known to lower seizure threshold [36]. As stated previously, some selective serotonin reuptake inhibitors (SSRI's) may actually have an anticonvulsant effect [101–103]. In general, clinical and research experience suggests that the risk of seizures with SSRI's is very low and perhaps not different from placebo, and certainly lower than with

TCA's [101]. A special consideration with SSRI's is the fact that they can promote hyponatremia, which can represent a risk in the precipitation of seizures [36]. Other antidepressants which are considered to be "high risk" for seizures in the general population or in toxicity studies (e.g., bupropion) have been found overall to have an acceptably low risk when prescribed correctly [36].

Overall, the incidence of seizures with antidepressants is less than 0.5%, particularly when used within the recommended therapeutic range and when other risk factors are excluded [36] (Table 2). Given the significant consequences described earlier in this chapter associated with depression in TLE, it would therefore seem that concerns about exacerbating seizure control should not be enough to rule out antidepressants in most TLE patients.

**8.1.2. Interactions between Antidepressants and AED's.** TCA's have, by nature of their longevity, perhaps the most collective clinical experience in many medical conditions, epilepsy included. Amitriptyline, clomipramine, and imipramine are extensively metabolized by CYP 1A2, 2D6, and 3A4 (Table 3). Nortriptyline and desipramine, the metabolites of amitriptyline and imipramine respectively, are metabolized mainly by CYP 2D6. All AED's with enzyme-inducing properties (barbiturates, carbamazepine, and phenytoin) all induce the metabolism of TCA's. However, carbamazepine also reduces protein binding of imipramine and desipramine, resulting in increased free fraction of these drugs, and thus resulting in little need to alter dosing of these two TCA's when coadministered with carbamazepine. Valproate can inhibit the metabolism of TCA's resulting in increased plasma levels at comparable dosage. Overall, coadministration of TCA's and AED's can be done safely and effectively as long as dosing is done slowly and carefully and is accompanied by regular monitoring of blood levels of both drugs [36].

SSRI's are generally more tolerable and safe than TCA's, due in part to their reduced anticholinergic effect and inability to block sodium channels, even in overdose [104]. As a result, these drugs are widely prescribed. Fluoxetine and paroxetine are metabolized by CYP 2D6, sertraline by CYP 3A4, fluvoxamine by CYP 1A2, and finally citalopram by CYP 2C [104]. Paroxetine is an inhibitor of CYP 2D6, fluvoxamine inhibits CYP 1A2, and fluoxetine moderately inhibits CYP 2D6 and 3A4. Sertraline and citalopram do not seem to have significant induction/inhibition properties [105].

Fluoxetine has a high risk of interaction with phenytoin, but less clearly with carbamazepine [36, 106, 107]. Paroxetine and sertraline seem to have low risk of interaction with phenytoin [36, 106]. However, carbamazepine seems to induce citalopram's metabolism significantly, thus reducing plasma concentrations and possibly efficacy of this drug [36]. Paroxetine appears to have little interaction with carbamazepine, valproate, or phenytoin [36]. Fluvoxamine appears to have no effect on carbamazepine levels [36]. However, there is a paucity of evidence on the safety of fluvoxamine coadministration with valproate or phenytoin [36]. Sertraline was found to increase the levels of lamotrigine in two documented cases [36]. Finally, sertraline was found to have no

TABLE 2: Seizure prevalence in psychiatric samples during treatment with antidepressant drugs [36].

Antidepressant	Dosage (mg)	Seizure prevalence (%)
Tricyclic Antidepressants (TCA's)		
Amitriptyline	<200 mg	0.1
	>200 mg	0.6
Imipramine	50–600 mg	<0.1–0.9
Clomipramine	>200 mg	0.5
Tetracyclic Antidepressants		
Maprotiline	150–200 mg	0.4
Mirtazepine	30 mg	<0.1
Selective Serotonin Reuptake Inhibitors (SSRI's)		
Fluoxetine	20–60 mg	0.2
Fluvoxamine	<100 mg	0.2
Sertraline	50–100 mg	<0.1
Paroxetine	20–60 mg	0.1
Norepinephrine Dopamine Reuptake Inhibitor (NDRI's)		
	300 mg SR	0.1
Bupropion	300–450 mg IR	0.4
	>450 mg IR	>0.6

significant effect on carbamazepine levels in a double-blind randomized, placebo-controlled trial of 14 healthy volunteers [36]. Sertraline and clonazepam were also found to be safe in coadministration [36].

SNRI's (venlafaxine and duloxetine) are primarily metabolized by CYP 2D6 [104], but interactions with AED's have yet to be studied [36].

Mirtazepine is a noradrenergic and specific serotonergic reuptake inhibitor (NaSSA) and is primarily metabolized by CYP 2D6. Studies are lacking in this population on interactions with AED's, but this medication has been noted to bind histaminic receptors, resulting in sedation, increased appetite, and weight gain. Given that these are side effects of many AED's, the potential for an additive effect is present [36].

Bupropion is a noradrenergic and dopaminergic reuptake inhibitor (NDRI). Carbamazepine is a potent inducer of the metabolism of bupropion, significantly reducing plasma levels [104]. Bupropion in turn has marked inhibitory properties, increasing levels of valproate and phenytoin [36].

**8.1.3. Efficacy of Antidepressants in TLE.** Again, there is a dearth of evidence-based, controlled trials that attempt to study efficacy of antidepressants in epilepsy in general, and the number of trials specific to TLE found in this review of the literature was a single one.

The earliest controlled trial in patients with epilepsy involved amitriptyline and an antidepressant that no longer exists (nomifensine). At 6 weeks, improvement of depressive symptoms was documented in both drugs, but at 12 weeks,

TABLE 3: CYP450 enzymes inhibition and induction by antidepressants and antiepileptic drugs [36].

CYP isoenzyme	Inhibitors	Inducers	Substrates
CYP 1A2	Fluvoxamine Fluoxetine Paroxetine Tertiary TCA's	St. John's Wort	<i>Antidepressants</i> TCA's Fluvoxamine Mirtazepine Duloxetine
CYP 2C9/10	Fluoxetine Fluvoxamine	Phenobarbital Carbamazepine Phenytoin	<i>Antidepressants</i> Sertraline Fluoxetine Amitriptyline Bupropion <i>Antiepileptics</i> Phenytoin
CYP 2C19	Fluvoxamine Fluoxetine	Carbamazepine Phenytoin	<i>Antidepressants</i> Citalopram Escitalopram Sertraline Clomipramine Imipramine Moclobemide <i>Antiepileptics</i> Phenytoin Mephenytoin Esobarbital Mephobarbital Phenobarbital Primidone
CYP 2D6	Fluoxetine Paroxetine Sertraline Secondary TCA's		<i>Antidepressants</i> Fluoxetine Fluvoxamine Citalopram Escitalopram Duloxetine Paroxetine Venlafaxine Trazodone Maprotiline Mirtazepine TCA's
CYP 3A4	Fluoxetine Fluvoxamine Mirtazepine	Carbamazepine Barbiturates Phenytoin St. John's Wort	<i>Antidepressants</i> Sertraline Venlafaxine Escitalopram Mirtazepine Trazodone TCA's <i>Antiepileptics</i> Carbamazepine Zonisamide Tigabine

nomifensine was superior to amitriptyline. Overall, data about TCA's efficacy in the treatment of depression in epilepsy is largely uncontrolled or anecdotal but appears to support efficacy and tolerability [36].

SSRI's have become the first line of pharmacotherapy in most depressive disorders due to their proven efficacy and benign side-effect profiles. However, efficacy in epilepsy specifically has not been well studied yet. A series of open label studies support some efficacy and tolerability for sertraline, citalopram, mirtazepine, and fluoxetine. In general, SSRI's seem to be effective and well tolerated, but the response rates have been quite mixed across studies, likely due to great variability in sample populations, limited control of comorbid psychiatric disorders, and the occasional presence of cognitive disorders or brain damage in the samples [36].

However, Kühn et al. [108] produced a prospective study of safety and efficacy of citalopram, mirtazepine, and reboxetine (not available in North America) in TLE patients. They performed a post hoc analysis of 75 TLE patients with depression who received standard treatment with one of the above drugs. In general, they found that all the antidepressants were effective in treating the symptoms of depression, and that there were no serious adverse events or drug interactions. However, the dropout rate was significantly higher for mirtazepine than the other two agents, perhaps again because of the tendency of this drug to cause sedation, increased appetite, and weight gain in a population already often prone to these complications secondary to AED's.

**8.2. Lithium.** Although most known for its efficacy in bipolar disorders, lithium is also used as an augmentation strategy for treatment resistant unipolar depression. Unfortunately, even less has been published on the safety and efficacy of lithium in epilepsy than for antidepressants [36].

Coadministration of lithium carbonate and carbamazepine may have a benefit in terms of mood stabilization but appears to be associated with multiple interactions, including hematologic, thyroid, and electrolyte dysregulation. However, lithium appears to be relatively tolerable when administered with valproate, but once again the additive aspects of sedation, weight gain, and tremor were noted. Lamotrigine and lithium appeared to be well tolerated together, though topiramate and lithium was associated with toxicity in at least one case [36].

Lithium also is known to be proconvulsive at higher doses, but this does not seem to be a significant concern at lower doses in epilepsy patients on AED's. However, as lithium is usually administered as an augmentation agent in unipolar depression, the additive risk of serotonin syndrome and lowered seizure threshold of both an antidepressant and lithium being administered to an epilepsy patient must be considered [36].

**8.3. Psychotherapy.** Once again, very little data has been collected on psychological therapies in the epilepsy population, let alone TLE. However, the few studies that exist seem to support the efficacy of cognitive behavioral therapies as useful in the treatment of depression in epilepsy [69].

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## Clinical Study

# Temporal Lobe Epilepsy in the Elderly

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Received 3 August 2011; Revised 20 September 2011; Accepted 9 October 2011

Academic Editor: Seyed M. Mirsattari

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The incidence of epilepsy has bimodal distribution peaking at the extremes of life. Incidence is greater in younger and older age groups (Hauser et al., 1993, Sidenvall et al., 1993, Forsgren et al., 1996, and Olafsson et al., 2005). As the world population ages more elders with epilepsy will be identified. In the high-income countries with longer life expectancy, the number of elders with epilepsy will be even higher. CPSs account for 40% of all seizure types in the elderly (Hauser et al., 1992); however, the proportion with temporal lobe epilepsy (TLE) is uncertain.

## 1. Causes

The specific causes of TLE in the elderly have not been clearly disclosed. With advancing age underlying coexisting factors are more likely to be identified, and the proportion of people classified as idiopathic is less when compared to the younger age groups. Nonetheless, up to half of elderly patients with epilepsy go without an identified cause.

In the under 65-year age group, head trauma, brain tumors, and CNS infections are common associations. Etiology of seizures veers towards a cerebrovascular origin in the elderly [6]. Dementing illnesses have also taken their place as a significant etiology [7].

Idiopathic TLE has been reported in adults with familiar history of epilepsy (mean age of onset: 25.5; range: 11–45 years). This group was also found to have a better prognosis [8]. Similar reports in elderly patients are missing. There are however case reports of mesial temporal lobe sclerosis (MTS) in elderly persons with new onset seizures. These accounts highlight the challenging differential diagnosis overlap with primary cognitive disorders and nonparaneoplastic limbic encephalitis [9]. New onset TLE has also been reported without evidence of MTS [10].

The etiology of hippocampal damage is discussed in a retrospective study of 38 patients with adult onset TLE [11]. The median age at onset was 37.8 years (range: 21.0 to 78.7 years). A total of seven patients, 60 years and older, were included in this report. In all cases, the common fea-

tures encompass frequent CPSs (range <1 to 600 seizures per month) developing over one year (defined as the median time from the initial onset of seizures to the time of assessment). Based on MRI evidence of hippocampal atrophy, history of causative events, concomitant disease, cerebrospinal fluid results, and autoantibodies patients were classified in one of four etiologic categories; secondary hippocampal sclerosis (HS); idiopathic HS; definite limbic encephalitis (LE) and MRI defined possible LE. Eleven patients met secondary HS criteria. Three had presented prolonged seizures and one nonprolonged repetitive seizures. In this subgroup, 36% showed bilateral MRI hippocampal abnormalities. Two patients had experienced a severe head trauma; two, old infarct; one a porencephalic cyst and one neurofibromatosis type I. Only two patients in this subgroup were 60 years and older. One showed bilateral hippocampal atrophy after head trauma and the other was unilateral. The latter reported 500 seizures per month. In the idiopathic HS group, all seven subjects had unilateral hippocampal abnormalities. Four underwent selective amygdalohippocampectomy and histopathology confirmed HS. In this subgroup of idiopathic HS, none of the seven patients were 60 years or older. Definite LE included nine patients with 5 (56%) showing bilateral hippocampal abnormalities on MRI. Six of the nine patients had sequential MRIs with initial hippocampal swelling, followed by normalization and ultimately atrophy and high-intensity signal. In addition to seizures, memory impairment was clinically significant. Four patients had positive voltage

gated potassium channel antibodies (VGKC abs) and one anti-Hu antibodies. The remaining four patients were diagnosed with rectal, small cell lung cancer (SCLC), testicular tumor with Ma2 antibodies, and a uterine leiomyosarcoma, respectively. In this subgroup of definite LE, three patients were 60 years and older. All three showed bilateral MRI hippocampal abnormalities. VGKC abs, rectal cancer, and small cell lung cancer were documented in one patient each. Finally, 11 patients were classified as MRI defined possible LE based on repeated MRIs with initial hippocampal swelling, normalization and atrophy, and absence of malignancy or antibodies (one exception with atypical anti-Hu antibodies). Seven (63%) showed bilateral MRI changes. This subgroup also presents episodic memory impairment and affective disturbances. Two patients, 60 years and older, were included, both with unilateral hippocampal involvement. This report delineates idiopathic and secondary HS as well as paraneoplastic and non-paraneoplastic LE as causative factors of late onset TLE emphasizing bilateral HS in the latter two subgroups, however, not infrequent with secondary HS. Memory impairment was more common with bilateral HS and in all cases frequent CPSs developed over a relatively short period of time. The few elderly subjects included in this series appear to follow these general premises.

A potential etiologic factor of TLE in the elderly is represented in generalized convulsive status epilepticus (GCSE) recognized to occur more often in the elderly with an estimated incidence of 86 per 100000 [12, 13]. A complication of GCSE is subsequent damage to the hippocampus [14, 15]. Mortality after GCSE is significant. Survivors would be at risk of subsequent partial seizures originating after hippocampal damage [16].

## 2. Clinical Presentation

The clinical features of various partial seizure types have been recently reported comparing patients 55 years of age and older (mean  $65.2 \pm 8.53$ ) to a group between 18 and 45 years of age (mean  $33.6 \pm 6.75$ ); each group encompassed 55 consecutive subjects [17]. Diagnosis was based on clinical and/or EEG findings. Partial seizures with loss of awareness and lack of prominent automatisms were classified as dialeptic seizures and in the older group accounted for 60% of all focal seizures and 52% of the younger patients. Partial seizures with prominent mouth and/or hand automatisms happened in 18% of the older patients while in 14% of the younger group. These differences were not statistically significant. The authors did not specifically report on the localization of the origin of these seizures. In this series, baseline characteristics showed some relevant differences. Not surprisingly, the older group had a later age at seizure onset ( $53.6 \pm 20.23$  yrs versus  $23.4 \pm 12.12$  yrs), seizure-free period greater than 1 year (20% versus 8%), and cerebral vascular disease as a risk factor (20% versus 6%). The younger group reported more than one seizure per month (54% versus 28%) and a history of febrile seizures (20% versus 6%). For the older and younger age groups, risk factors included trauma 30% in each group, CNS infection in 6% and 4% and CNS tumor in 8% and

6%. Among the 28 patients that had no recollection of their seizures, 17 (61%) were from the older age group. In total, 9 subjects (18%), all of the older age group, reported subtle perception of transient confusion ( $P = 0.002$ ). The total number of subjects with aura (defined as partial seizures without loss of awareness) was less common in the older age group (54% versus 76%  $P = 0.03$ ). No significant differences could be demonstrated in the comparison of symptoms consisting of auras (psychic, autonomic, abdominal, visual, somatosensory or gustatory, auditory, olfactory, and vertigo) or generalized tonic clonic seizures (GTCSs) occurrence. Approximately one-third of patients in each group had a normal EEG, while 26% of the older group and 20% of the younger group had nonspecific finding. Focal epileptiform discharges were shown in 42% of the older and 23% of the younger subjects. Video-EEG monitoring was limited to a total of 9 patients yielding an additional 10% of older and 8% of younger patients with focal epileptiform and/or focal seizures.

In patients with epilepsy, memory dysfunction is not an unusual complaint. Transient epileptic amnesia is an emerging concept described in middle-aged and older people with an evident response to antiepileptic drug treatment (AED). Subjects with transient epileptic amnesia attacks may go unrecognized. A characteristic feature is prolonged periods of ante- and retrograde memory impairment with a mean duration between 30 and 60 minutes and subsequent amnesia that occurs upon awakening. The male population is more frequently affected. Transient amnesia may be the sole clinical manifestation in approximately one-third of patients. Attacks recur on the average 15 times per year. Hallucinations and automatisms have been frequently reported, while GTCSs are rare. Repetitive questioning is present in up to half of patients requiring differentiation from transient global amnesia. Interictal epileptiform abnormalities may be demonstrated in one-third of patients and ictal electrophysiological correlates have been recorded unilaterally or bilaterally in the temporal lobes. Brain imaging is usually clear, or lesions involve the temporal lobe [18, 19].

Diagnosis is further challenged when symptoms of dementia compound the clinical picture. Alzheimer dementia may present with partial or generalized seizures and nonlocalizing EEG abnormalities. An overlap with memory complaints is obviously expected in this group of cases [9].

The diagnosis of TLE in the elderly poses a challenge (see Table 1). The clinical features are subtle, and patients are unaware of seizures. Memory lapses, brief gaps in the flow of conversation, and blank stare and confusion may be the only clinical manifestations. Clinical features resemble TIA, delirium, congestive heart failure, cardiac arrhythmia, orthostatic hypotension, vasodepressor episodes, metabolic dysfunction with hypoglycemia, hyponatremia, sepsis, or drug toxicity [30].

## 3. Pharmacological Treatment

A small number of randomized controlled trials (RCTs) have been conducted in elderly patients testing the efficacy of

TABLE 1: Differential diagnosis of temporal lobe epilepsy in the elderly.

Temporal lobe epilepsy [19–21]	CPSs are common while auras and automatisms are not as common as in younger age groups. Brief gaps in conversation or periods of confusion may be only manifestation. Patients are frequently not aware of having seizures. Stroke is the most common cause in this age group. However, idiopathic cases have been reported.
Limbic encephalitis (LE) [8, 10]	Rapid progressive short-term memory deficit, with psychiatric symptoms consisting of irritability, depression, sleep disturbances, and hallucinations. CPSs more often than any other seizure types. Repetitive questioning may happen. CSF with increased proteins and lymphocytic pleocytosis. Temporal lobe abnormalities on EEG and MRI. Bilateral MTS not infrequent in nonparaneoplastic or paraneoplastic LE. May evolve to encephalomyelitis, decreased level of consciousness and refractory seizures. Antineuronal antibodies have been associated to underlying malignancy; anti-Hu (SCLC), anti-Ma2 (testis or other), CV2/CRMP5 (SCLC, thymoma), antiampiphysin (breast, SCLC), anti-Ri (carcinoid), anti-VGKC (thymoma, SCLC, other), and anti-NMDA (ovary).
Dementia [22, 23]	Gradual cognitive decline interfering with independence due to; memory, abnormalities; personality or behavioral changes; reasoning and judgment abnormalities; impaired language functions or visual spatial skills. Uncommon partial seizure or GTCs. Intermittent memory lapse that may be confused with CPSs. EEG diffuse slowing more often than focal abnormalities.
Transient ischemic attack [24, 25]	Sudden focal neurological dysfunction resulting from cerebral or retinal ischemia with clinical symptoms lasting less than 24 hours but frequently resolving within one hour. No evidence of cerebral infarction. Early CPSs are very rare after TIA. EEG abnormalities with temporary speech dysfunction and amnesia may represent focal inhibitory seizures.
Transient global amnesia [26]	Sudden transitory anterograde and retrograde memory loss or forming of new memories. Episodes last for less than 24 hours. Same question repeated over and over. A precipitating factor is common. Permanent residual memory gap after recovery. Awareness is spared. No aphasia or apraxia or focal neurological deficits. No seizures and normal EEG.
Delirium [27, 28]	Acute confusional state, altered awareness, fluctuating course, cognitive disturbance and difficulty maintaining attention. In elders hypoactive delirium is more common than hyperactive type. Disorientation, language impairment, and memory deficits. Sleep cycle disturbances or reversal. Intermittent fear, paranoia, anxiety, depression, irritability, anger or euphoria. Common in older and/or hospitalized patients. Frequent multiple predisposing factors. Diffuse slowing on EEG.
Epileptic transient amnesia [10, 29]	Recurrent episodes of memory deficits with long-term forgetting and remote autobiographical memory loss. Oral automatisms and olfactory hallucinations. More common in middle-to-old-aged men. Medial temporal lobe atrophy on MRI and epileptiform abnormalities present. Impressive response to antiepileptic treatment.

AEDs. Studies do not specifically address TLE but serve to evaluate efficacy and safety issues of AEDs in the setting of epilepsy in the elderly.

Recently, a group of 77 people with a mean age of 68 years and partial onset seizures were randomized in a pilot study to topiramate (TPM) 50 mg or 200 mg doses as add-on or monotherapy. Etiology of seizures was identified in 52% of patients. Cerebrovascular causes and head trauma accounted for 40% and 33%, respectively. Seizure freedom was similar with the lower and higher doses (52% and 58%, resp.) as well as seizure frequency (0.26/month and 0.33/month, resp.). More than 60% in both study groups complained of adverse side effects with somnolence, dizziness, and headache being the most common. Overall 18% of patients had to discontinue TPM due to adverse effects [31].

One randomized controlled trial (RCT) tested carbamazepine (CBZ) versus lamotrigine (LMT) in a total of 64 subjects (mean age: 67 years) with partial seizures (simple or complex) with or without secondary generalization presenting on average between 8 and 12 months after stroke. Stroke was classified as cortical in 64% of patients allocated to LMT and 66.7% of the CBZ group. Subcortical strokes were diagnosed in 36% and 33.3%, respectively, in these study

groups. Localization of the origin of the seizure was not reported. Subjects allocated to CBZ reported significantly more adverse effects than LMT leading to study withdrawal (31% versus 3%,  $P = 0.02$ ). On completion of the first year, 72% of patients on LMT and 44% on CBZ were seizure-free ( $P = 0.05$ ) [32].

A total of 590 elderly patients (mean age: 72 years) with newly diagnosed epilepsy with any seizure type were randomly allocated to gabapentin (GBP), LMT, or CBZ. In total, 42% of patients experienced CPSs. The etiology was similar among groups with an approximate one-third due to cerebral infarction. The localization of the origin of CPSs was not accounted for. A mild cognitive impairment or memory problems were present in 35% and 25% of patients, respectively. At 12 months, 46.7% had completed the study. LMT was significantly best retained than CBZ ( $P < 0.0001$ ) or GBP ( $P = 0.015$ ). At one year, seizure freedom was not significantly different between groups (LMT 51.4%, GBP 47.4%, and CBZ 64.3%). The time to first, second, fifth, and tenth seizure in the first year was also similar and no significant statistical differences were demonstrated between groups. Similarly, the overall seizure-free retention rate at one year was 24.9%. Severe adverse effects were reported

in 8.1%. Weight gain was greatest with GBP, while hyponatremia and any rash with CBZ. Of the seven patients requiring hospital admission due to hypersensitivity reactions, one was due to LMT and six to CBZ. Thirty-nine subjects died during the study. In the one case, CBZ was stopped after a hypersensitivity reaction two weeks before death [33].

A total of 150 elderly people (mean age: 77 years) with any seizure type resulting from idiopathic, symptomatic, or cryptogenic epilepsies were included and randomized in a 2:1 ratio to either LMT or CBZ [34]. Cerebral infarction was disclosed in 30% of the LMT group and 38% in the CBZ group. In 79% the daily LMT median dose was 100 mg (range: 75–300 mg), and in 82% the daily CBZ median dose was 400 mg (range: 200–800 mg). Adverse effects forced 41% of dropouts with CBZ and 18% with LMT. Seizure freedom during the 16 weeks of the study period was significantly different favoring LMT over CBZ (39% versus 21%,  $P = 0.027$ ).

#### 4. Surgery

Seizure outcome in 16 patients 50 years and older (mean 55.5 yrs, range 50–72) was compared to 184 younger patients (mean: 32.9 yrs, range: 16–49) undergoing anterior temporal lobectomy (ATL) [35]. All patients had pathologically confirmed unilateral HS and MRI lacked evidence of any other pathology. None of the variables showed to be predictors of the outcome. Following ATL older patients were less often seizure-free than the younger patients (56% versus 79%,  $P = 0.041$ ). Postsurgical complications were more frequent in the older patients (25% versus 4.4%,  $P = 0.009$ ).

Boling et al. reviewed 18 patients 50 years and older with 61% having MTS. The mean age at surgery was 54 years and followed for up to 64 months. Seizure freedom was reached by 61%, and 72% were able to reduce or stop their antiepileptic drugs. This older set of patients underwent multiple comparisons with subjects grouped in decades from ages 10 to 49 years. In the four resulting groups no significant differences could be demonstrated regarding proportions of seizure-free patients [36].

Sirven et al. reviewed a total of 30 patients aged 50 years and older (mean  $54.2 \pm 4.7$ ) and compared them to 340 subjects younger than 50 years (mean  $32.8 \pm 7.7$ ). These groups were followed for  $4.0 \pm 2.7$  years and  $5.0 \pm 2.9$  years, respectively. Seizure freedom was 52% in the older group and 75% in the younger group ( $P = 0.008$ ). A discriminant function analysis disclosed that age at surgery and duration of epilepsy explained the largest fraction of variance. Younger age and shorter duration of epilepsy favored a seizure-free outcome. The authors consider that results could have been impacted by the fact that surgery in the older group was performed in their early 50's with only 5 patients 59 years and older. In this retrospective analysis, MR images were not available for all patients [37].

#### 5. Conclusions

As population grows, an increment is expected in the number of subjects 65 years and older identified with TLE. Countries

with a longer life expectancy are going to be impacted to a greater extent. More often than not a coexisting significant medical condition may be revealed as well as acute or chronic brain involvement. Clinical diagnosis is elusive with subtle presenting features such as recurrent memory lapses or periods of confusion. Nevertheless, the typical signs of CPSs are likely. The undisputable advantage of video-EEG monitoring recognized in the investigation of people with epilepsy is clearly applicable to elderly populations [20–22, 38, 39]. AEDs continue to be the foundation of the medical pharmacological treatment.

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## Research Article

# Postoperative Neuropsychological Outcome in Patients with Mesial Temporal Lobe Epilepsy in Argentina

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Received 11 April 2011; Revised 10 August 2011; Accepted 8 October 2011

Academic Editor: Seyed M. Mirsattari

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The aim of the present study is to compare pre- and postsurgical neuropsychological outcome in individuals suffering from mesial temporal lobe epilepsy (mTLE), in order to evaluate prognosis. The selected thirty-five patients had medically mTLE and had undergone an anterior temporal lobectomy (ATL). Neuropsychological evaluation was performed in three different stages: before ATL, 6 months after resection, and a year afterwards. Neuropsychological protocol evaluated attention, verbal memory, visual memory, executive function, language, intelligence, and handedness. There was a significant improvement ( $P = 0.030$ ) in the group with visual memory deficit after surgery, whereas no changes were observed across patients with verbal memory deficit. No changes were observed in language after surgery. Executive function showed significant improvement 6 months after surgery ( $P = 0.035$ ). Postoperative outcome of cognitive impairments depends on baseline neuropsychological status of the patients with TLE. In our case series, deficits found in patients with mTLE after ATL did not result in a subjective complaint.

## 1. Introduction

Neuropsychological evaluation is a very important tool to characterize cognitive aspects in patients with epilepsy and to determine the topography of the epileptogenic zone [1–4].

In a previous study conducted by our group [4], patients with mesial temporal lobe epilepsy (mTLE) [5] displayed a neuropsychological profile characterized by material-specific verbal/visual episodic memory, executive function, and speech impairment. In most cases, memory deficits correlated with the lesions detected by MRI [4]. These findings were similar to those reported by other authors.

A high percentage of patients with TLE syndrome benefit from temporal lobe resection [6]. In the history of epilepsy surgery, neuropsychological evaluation played a major role to understand some aspects of cognition. There are several publications concerning the prognosis of cognitive functions

among patients undergoing epilepsy surgery [3, 7, 8]. Verbal memory deficits were observed after left temporal lobectomy (TLY). On the other hand, visual memory deficits were found after right TLY. These findings are similar to those described in published studies conducted among English populations.

The aim of the present study is to compare pre- and postsurgical neuropsychological outcome in individuals suffering from TLE in order to evaluate prognosis across a Spanish-speaking population.

## 2. Materials and Methods

The selected thirty-five patients with mesial temporal sclerosis (MTS) were treated at the Epilepsy Center of the Hospital Ramos Mejía. All the studied patients had MTS on their MRI [4].

The type of surgery performed consisted of resection of the anterior temporal lobe, as well as a resection of the anterior mesial temporal structures including the anterior third of the hippocampus (Standard Anterior Temporal Lobectomy, ATL). Lateral temporal neocortex and mesial structures were removed at approximately 3 cm from the temporal pole within the dominant hemisphere, and up to 4.5 cm in the nondominant hemisphere.

Fifty one percent of the patients underwent a left TLY and 49% ( $n = 17$ ) underwent a right TLY.

The neuropsychological protocol used in this study was the same that was previously published by our group. The verbal tests were validated for the Spanish language [1, 4, 9].

Neuropsychological evaluation was performed in three different stages: before surgery, 6 months after resection, and a year afterwards.

- (i) Attention: Forward and Backward Digit Span, WAIS, and Trail Making Test part A.
- (ii) Verbal memory: Rey Auditory Verbal Learning Test (RAVLT) and List Learning Test.
- (iii) Visual memory: Rey-Osterrieth Complex Figure Test (RCFT).
- (iv) Executive function: Wisconsin Card Sorting Test (WCST), Trail Making Test Part B. Verbal Fluency (FAS).
- (v) Language: Boston Naming Test (BNT), Token Test (TT).
- (vi) Intelligence quotient (IQ).
- (vii) Handedness: Edinburgh Questionnaire (EHQ).

Patients who had an IQ below 70 were excluded from the study.

### 3. Statistical Analysis

The results of the neuropsychological evaluation were compared with the normative according to age, sex, and formal education. For each patient the raw values of each data of the cognitive tests were normalized to a  $Z$  score. Patients were classified as “normal” when all the tests presented values superior to a  $Z$  score  $-2$  (two standard deviation below normal values), or “abnormal” when some of the results were inferior to a  $Z$  score  $-2$ .

In a second stage of analysis, we divided results obtained in RAVLT, RCFT, WCST, FAS, and BNT, into three groups: Baseline with ( $n = 35$  patients), 6 months with ( $n = 35$  patients), and a year from surgery with ( $n = 14$  patients), due to a loss of followup in the rest of the patients.

We used raw values. We did not compare them with normative scores. We compared means as follows:

- (i) baseline/6 months:  $n = 35$  patients,
- (ii) baseline/year:  $n = 14$  patients,
- (iii) 6 months/year:  $n = 14$  patients. In order to match the number of patients in each group to compare two samples, we decided to form two groups with 14 patients.

TABLE 1: Patients profile.

Gender (F/M %)	45/55	
Age (average years)	$36.1 \pm 8$	
Time of epilepsy evolution	$21.1 \pm 12$	
Education (average years)	$10.6 \pm 4$	
Handedness (R/L)	94/6	
RTLY/LTLY (%)	49/51	
	HE	70
MRI lesion (%)	HE plus	18
	Tumor	9

HS: Hippocampal Sclerosis. RTLY: Right temporal lobectomy. LTL: Left temporal lobectomy.

Were used ANOVA and Chi-Square tests for the analyses, to compare dependent and independent variables in a sample of normal distribution and to test the independence of two variables together, by presenting data in contingency tables.

## 4. Results

**4.1. Patient Demographics.** All patients had drug-resistant mTLE.

The average age of the study population was  $36.1 \pm 8$  years.

The average evolution time of epilepsy was  $21.1 \pm 12$  years.

The average education was  $10.6 \pm 4$  years.

Forty-five percent of the study population was women. Ninety-four percent of the study population was right handed, and the remaining 6% was left handed.

All patients underwent standard ATL.

70% of the patients had hippocampal sclerosis (HS), 18% had HS plus temporal pole dysplasia, 9% presented a low degree tumor, and 3% had cavernoma.

Postoperative categorization of the seizures (Engel scale) [10] was 85.7% Class I, 8.5% Class II, and 2.8% Class III. This was observed one year after surgery (see Table 1).

**4.2. Neuropsychological Outcome.** In the preoperative assessment, (28.5%) out of 35 patients showed a normal neuropsychological evaluation, while 25 patients (71.4%) showed significant deficit on any of the tasks.

At six months after surgery, there was an increase in the percentage of patients with normal neuropsychological test scores (13 patients, 37.1%)

A year after the surgery, the neuropsychological evaluation was completed in 14 patients. There was a similar tendency in the outcome observed 6 months afterwards, because 5 patients (35.7%) out of 14 patients presented a normal neuropsychological evaluation, where one of them was abnormal at baseline. Nine patients (64.2%) out of 14 patients show significant deficits on at least one of the tasks.

**4.3. Intelligence Quotient (IQ).** The average of the total IQ score prior to surgery was  $91.7 \pm 13$ , (73–125). Six months after the surgery, the average of the total IQ score was

TABLE 2: Memory outcome after anterior temporal lobectomy based on the side of the surgery.

		RTLY N = 17		
		Baseline N = 17	6 months N = 17	12 months N = 4
Memory deficit	Normal %	41.1	47	50
	VIM %	35.2	23.5	0
	VEM %	11.7	17.6	50
	B %	11.7	11.7	0
		LTLY N = 18		
		Baseline N = 18	6 months N = 18	12 months N = 9
Memory deficit	Normal %	16.6	27.7	33.3
	VIM %	11.1	0	11.1
	VEM %	66.6	61.1	44.4
	B %	5.5	11.1	22.2

RTLY: Right temporal lobectomy. LTLY: Left temporal lobectomy. VIM: Visual memory. VEM: Verbal memory. B: both memories.

$93.5 \pm 12$  (74–125). A year after the surgery, the average of the total IQ score was  $93.7 \pm 12$  (80–125). Therefore, changes were nonsignificant.

**4.4. Memory.** Baseline evaluation of these 35 patients was included in a previous paper. In that study we found deficits in delayed recall, on RAVLT and RCFT. Therefore, the present analysis was conducted primarily in consideration of those data [4].

Results of memory evaluation for each patient, compared with normative, were as follows.

**4.4.1. Left Temporal Lobectomy Group ( $n = 18$ ).** At baseline, twelve patients (66.6%) presented verbal memory deficits, and two patients (12%) had visual memory deficits. One patient (5.5%) had both types of memory deficits. Three patients (16.6%) did not present any memory deficits.

Six months after surgery, no significant changes were observed.

A year after surgery, the tendency was the same as observed at 6 months after surgery (Table 2).

**4.4.2. Right Temporal Lobectomy Group ( $n = 17$ ).** At baseline, two patients (11.7%) presented with verbal memory deficits, and six patients (35.2%) had visual memory deficits. Two patients (11.7%) had both types of memory deficits. Seven patients (41.1%) did not present any memory deficits.

Six months after the surgery, no significant changes were observed.

A year after the surgery, only 4 patients were evaluated (Table 2).

When we compared the raw data means, we found a significant improvement ( $P = 0.030$ ) in the group with visual memory deficits (Table 3).

**4.5. Language.** In the preoperative evaluation, 26 patients (74.2%) had speech impairments, while in 9 patients (25.7%) language assessment was normal.

Deficits were mostly observed in the naming. The most significant finding was BNT. No significant impairment was observed in the listening comprehension (Token Test).

There were no significant changes 6 months and a year after the surgery (Table 3).

**4.6. Executive Function.** Before surgery, 9 patients (25.8%) presented with deficits in the Wisconsin Card Sorting Test (WCST). The most frequent alterations were planning and difficulty in mental flexibility to switch strategies, and preservative errors. Verbal production capacity and mental flexibility (FAS) were abnormal in 5 patients (14.2%).

Six months after surgery, significant improvement was observed in 6 patients (17%) ( $P = 0.035$ ) in the evaluation with WCST (Table 2). Verbal production capacity (FAS) did not show significant impairment. 11 patients (31.4%) showed deficits.

A year after surgery, there were no alterations in the assessment of WCST, while on FAS, all patients improved significantly ( $P = 0.026$ ) (Table 3).

## 5. Discussion

A high percentage of patients with TLE syndrome benefit from temporal lobe resection [6]. In the history of epilepsy surgery, neuropsychological evaluation played a major role to understand some aspects of cognition.

Following the order previously set out in this study, we will proceed to discuss the results of postoperative evaluation.

Regarding IQ, the average of the total score shows no significant improvement 6 months after the surgery and remains stable 12 months afterwards. This has been noted by other authors [11], who point to an overall slight improvement, that might depend on multiple factors such as the absence of seizures, the improvement in the patients' overall quality of life, or simply practice effects.

Memory analysis was performed by discriminating between verbal/visual memory.

Verbal memory deficits were the most frequent findings in patients with left mTLE, while in patients with right

TABLE 3: Analysis of raw data of RAVLT, RCFT, BNT, WCST, and FAS tests, at baseline, 6 months, and a year after anterior temporal lobectomy.

	MEAN	N	P
<b>RAVLT</b>			
Baseline	6.8	35	0.706
6 months	6.55	35	
Baseline	6.57	14	0.692
Year	7.07	14	
6 months	6.57	14	0.692
Year	7.07	14	
<b>RCFT</b>			
Baseline	14.6	35	0.796
6 months	14.86	35	
Baseline	15.93	14	0.086
Year	19.07	14	
6 months	17.5	14	<b>0.03</b>
Year	19.07	14	
<b>BNT</b>			
Baseline	39.51	35	0,631
6 months	38.8	35	
Baseline	39.21	14	0.92
Year	39.43	14	
6 months	40.36	14	0.753
Year	39.43	14	
<b>WCST</b>			
Baseline	4.57	35	0.268
6 months	4.97	35	
Baseline	4.5	14	0.378
Year	5.07	14	
6 months	4.29	14	<b>0.035</b>
Year	5.07	14	
<b>FAS</b>			
Baseline	23.03	35	0.098
6 months	18.97	35	
Baseline	25.38	14	0.081
Year	29.77	14	
6 months	20	14	<b>0.026</b>
Year	29.77	14	

BNT: Boston Naming Test, WCST: Wisconsin Card Sorting Test, RAVLT: Rey auditory learning verbal test, FAS: verbal fluency, RFCT: Rey figure copy test.

mTLE, visual memory deficits were frequent observation, but less consistent findings. Memory deficits were most frequently observed in delayed recall of both verbal and visual material. These findings are consistent with lesions in the mesial temporal structures, which seem to be critical for encoding [4].

Significant improvement of visual memory was observed at 6 and 12 months on delayed recall, whereas verbal memory analysis showed no significant changes.

In most cases, patients with normal memory at baseline showed no significant changes after ATL.

After left ATL, patients presented significant verbal memory deficits, whereas after right ATL, visual memory deficit was less consistent, deficits on verbal memory (contralateral to the resection), and remained unchanged or slight improvement [3].

Chelune described the “functional adequacy” phenomenon as the functional adaptation of the tissue to be resected in the ipsilateral temporal lobe to the lesion, and “reserve capacity” as the mnemonic capacity of the hippocampus contralateral to the lesion [8]. Thus, those patients who do not present with a memory deficits preoperatively would have an unfavorable prognosis, since “functionally” healthy tissue may be resected, while patients who display memory deficit prior to surgery would have a better prognosis.

As regards language, no significant changes were observed in the postoperative evaluation.

The detection of deficit in the BNT brings about several conclusions. One is the theory that suggests a connection between the hippocampal system and its relationship with the language formation process at the phonological and semantic levels, as well as its relationship with comprehension and production, which reveals a deficit in the retrieval of stored information in the lexical-semantic system [12].

Recently, the same author described the role of the hippocampus in the association of external stimuli with its semantic content. Thus, the damage caused by epilepsy in the lateral and mesial regions of the temporal lobe would affect the neocortical and hippocampal functions involved in the storage and retrieval of such information, leading to a semantic memory deficit [13, 14]. Another hypothesis holds the existence of atypical areas within the anterior and basal regions of the temporal lobe as a result of neural plasticity mechanisms [15–17].

Thirty percent of our patients displayed deficits in the Executive Function, thus implicating the function of the frontal lobe. This has been noted by other authors, and numerous hypotheses have been suggested. One of the theories holds the possibility that the temporal discharge propagation towards the frontal lobe may interfere with the executive function.

Another plausible theory is that memory deficit may alter the results of the tests assessing frontal function [18–20]. In our population, a significant improvement was observed after surgery, which is consistent with other observations.

## 6. Conclusions

To our knowledge, this is the largest study involving Spanish-speaking patients.

The postoperative prognosis of cognitive impairments depends almost entirely on the patient’s prior condition.

In the group of patients with executive function deficits in baseline, there was a significant postsurgical improvement.

Patients who manifested postoperative deficits after ATL did not result in a subjective complaint, and the patients who did not display a cognitive deficit preoperatively remained stable.

Neuropsychological evaluation turns out to be an important tool in the diagnosis and followup of medically intractable TLE patients after TLY.

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## Review Article

# Temporal Lobe Epilepsy in Children

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Received 10 June 2011; Accepted 21 August 2011

Academic Editor: Seyed M. Mirsattari

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The temporal lobe is a common focus for epilepsy. Temporal lobe epilepsy in infants and children differs from the relatively homogeneous syndrome seen in adults in several important clinical and pathological ways. Seizure semiology varies by age, and the ictal EEG pattern may be less clear cut than what is seen in adults. Additionally, the occurrence of intractable seizures in the developing brain may impact neurocognitive function remote from the temporal area. While many children will respond favorably to medical therapy, those with focal imaging abnormalities including cortical dysplasia, hippocampal sclerosis, or low-grade tumors are likely to be intractable. Expedient workup and surgical intervention in these medically intractable cases are needed to maximize long-term developmental outcome.

## 1. Introduction

The temporal lobe plays a vital role in epilepsy and is the most frequent lobe involved in focal onset seizures. Temporal lobe epilepsy in children and infants has clear clinical features which make it distinct from the fairly homogeneous syndrome seen in adults.

Reported studies of temporal lobe epilepsy (TLE) in children are heavily biased towards those with medically intractable epilepsy, and few studies focus on cohorts who are newly diagnosed. This paper will address pediatric-specific aspects of TLE, including clinical semiology in young children, pediatric epilepsy syndromes involving the temporal lobe, medical and surgical management, associated psychiatric and cognitive disorders, and long-term outcomes.

## 2. Epidemiology

The overall incidence of new-onset epilepsy in children ranges from 33 to 82 per 100,000 children per year, and approximately half- to two-thirds of these children have focal-onset seizures [1–6]. However, the exact incidence of TLE is not known, as the specific lobe of onset is not specified in most incidence studies. Compared to adults, focal seizures in children are more likely to arise from extratemporal foci. Simon

Harvey et al. identified 63 children with new-onset TLE over a 4-year period in the state of Victoria, Australia (population 4.4 million) [7]. In our 30-year cohort of new-onset epilepsy in children, 276/468 (59%) had nonidiopathic focal epilepsy. Of these, 20 (7.2%) had a focal lesion on MRI in the temporal region (10: mesial temporal sclerosis, 1: malformation of cortical development, 2: ischemia/gliosis, 1: tumour, and 4: vascular malformation), while 17 (6.1%) had normal imaging and a single focus of epileptiform discharge in the temporal region. Therefore, it was determined that TLE was responsible for 8% of all pediatric epilepsy, and for 13% of all focal seizures in our cohort [1].

## 3. Semiology of Temporal Lobe Seizures in Children

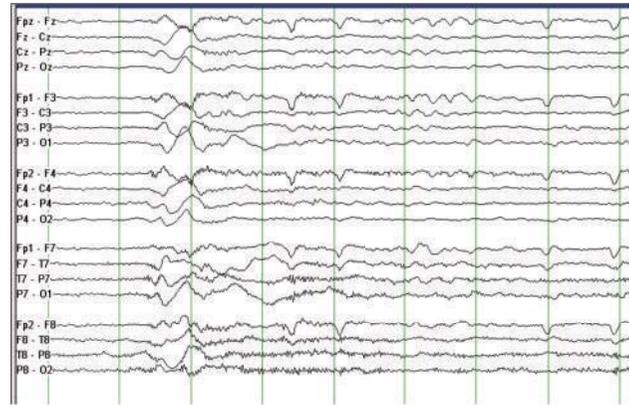
One of the defining characteristics of TLE is its unique semiology. These features, which have been studied extensively in adults, can help clinicians to localize seizures to the temporal region prior to capturing interictal/ictal epileptiform discharges. Such information is particularly valuable when evaluating patients with medically intractable epilepsy. When concordant with structural magnetic resonance imaging and electroclinical data, seizure semiology can facilitate the identification of candidates for successful surgical interventions

[8]. The semiology of temporal lobe seizures in children has previously been investigated, although less robustly than in adults. Like adults, children with TLE are more likely to demonstrate specific semiologies when their seizures arise from specific portions of the temporal lobe (e.g., mesial, lateral, or insular). However, in contrast to adults, the semiology of TLE in children can be profoundly affected by age and brain development. Such changing semiology can present a challenge to physicians attempting to identify (and effectively treat) children with TLE.

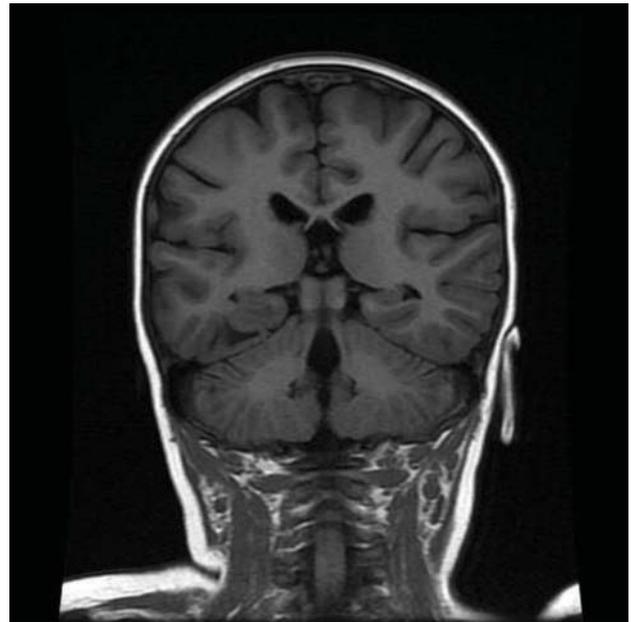
**3.1. Semiology of TLE in Infants and Toddlers (Age 0–3 Years).** Some of the most difficult temporal lobe seizures to identify utilizing semiology alone are those arising in infants and toddlers. Unlike older children, infants and toddlers are more likely to display seizure semiologies reminiscent of extratemporal and generalized epilepsies. Previous studies have documented an inverse relationship between the occurrences of ictal motor manifestations and age [9–14]. Such motor manifestations include tonic, clonic, myoclonic, and hypermotor seizures, and epileptic spasms [9, 10, 14]. Despite their unilateral origin, such movements can appear bilateral and symmetric, complicating attempts to lateralize seizure onset [9, 13]. They can also be easily mistaken for frontal lobe seizures [9, 13]. The likely reason for the increased motor manifestations of TLE in infants and toddlers is the presence of focal pathology in the setting of incomplete CNS myelination [14, 15]. This is particularly pertinent with regards to the limbic system, which is resistant to synchronization in an immature state [10, 16–19]. The occurrence of epileptic spasms in young children with temporal lobe pathology is likely secondary to rapid secondary generalization of focal onset seizures via dysfunctional cortical-subcortical interactions (particularly involving the thalamus, basal ganglia, and other brain stem structures). This can result in the generalized semiologic and EEG appearances, making identification of the ictal-onset zone problematic (Figure 1) [20, 21].

One of the hallmarks of TLE in adults is the occurrence of automatisms. Although automatisms can be seen in infants and toddlers with TLE, they are typically simpler than those observed in older children and adults [9, 10, 12, 22–25]. These simpler automatisms include oroalimentary (lip smacking), gestural (hand fumbling), and blinking movements [9, 12, 24, 25]. This difference may arise from the limited repertoire of voluntary fine motor gestures in young children. Once such gestures develop later in life, they can be incorporated into complex automatisms [9, 22]. Given the lack of well-developed verbal communication skills in children aged 0–3 years, it is usually impossible for clinicians to properly assess for auras at seizure onset [9, 12, 26]. Rather, the earliest signs of such seizures in infants and toddlers may be behavioral arrest, staring, and lip cyanosis [25].

**3.2. Semiology of TLE in Preschool and Early School-Age Children (Age 3–6 Years).** In contrast to infants and toddlers, preschool and early school-age children with TLE have better developed lateralizing motor manifestations with their



(a)



(b)

FIGURE 1: This 2-year-old girl had onset of infantile spasms at the age 6 months, which were refractory to three antiepileptic medications. During the clusters of spasms, she had head drops, nonforced head turn, and eye deviation to the right, with elevation of both upper extremities. Her EEG (a) shows a generalized sharp wave followed by high frequency and low-amplitude activity during the spasm (50 microvolts/mm, 30 mm/sec). Her coronal FLAIR MRI (b) shows a lesion in the right temporal region, which was found to be a ganglioglioma. She has remained seizure-free since surgery.

seizures [9, 10]. This age group is more likely to demonstrate dystonic posturing, versive/nonversive head turning, and eye/mouth deviation [9, 23, 25, 27]. Dystonic posturing, eye/mouth deviation, and versive head turning have been found to lateralize to the contralateral hemisphere in this population, with correct lateralization in 75–100% of cases [23]. Nonversive early head turning correctly lateralizes to the ipsilateral hemisphere in 80% of cases in this age group [23].

In preschool and early school-age children with TLE, more complex automatisms can be observed. These include

the oroalimentary automatism seen in younger (age 0–3 years) children in addition to staring, looking around, and/or hand clapping [9, 10, 23, 25]. However, more complex automatism are still less likely to be observed in this age group versus older children (age >6 years) and adults [23, 25]. They are also less likely to correctly lateralize to the ipsilateral hemisphere than in older children (50% versus 100%) [23].

Although children between the ages of 3 and 6 years with TLE are more likely to note auras at seizure onset than their younger counterparts, this can still be difficult to assess (given the subjective nature of such symptoms). Rather than asking children with presumed TLE about auras, it may be more prudent for clinicians to ask parents/caregivers about behaviors associated with such phenomenon. For example, a child who consistently cries or runs to a parent/caregiver at seizure onset may be experiencing ictal fear; this frequently localizes to the mesial temporal region [28, 29]. Conversely, children who demonstrate stereotyped unilateral ear plugging at the onset of seizures may be experiencing an auditory aura localizing to the contralateral superior temporal gyrus [30].

**3.3. Semiology of TLE in Older Children and Adolescents (Age >6 Years).** Beyond the age of 6 years, children with TLE display much of the same seizure semiology as their adult counterparts. Some older children with TLE will report a prodrome hours (or potentially even days) prior to seizure onset. Such prodromes can consist of headaches, irritability, insomnia, personality changes, and/or a sense of impending doom [28]. However, children with TLE are less likely to experience such prodromes versus those with generalized tonic-clonic seizures [28]. Auras are common in older children with TLE (particularly mesial temporal lobe epilepsy) [25]. The most common aura reported by older children is an epigastric-rising sensation [28]. Other auras include olfactory, gustatory, somatosensory, auditory, visual, and other visceral (oropharyngeal, abdominal, genital, and retrosternal) alterations in self-perception and psychic (*déjà vu*, *jamais vu*, and/or a dreamy state) phenomena [28]. Such auras often yield the most useful information when attempting to localize seizure onset correctly. Seizures associated with macropsia, micropsia, macroacusia, or microacusia typically arise from the lateral temporal region [28]. Olfactory and gustatory hallucinations characteristically arise from the uncus [28]. Even emotions such as fear, strangeness, or embarrassment can represent simple partial seizures, sometimes originating from the amygdala [28].

Compared to children age 0–6 years, older children and adolescents with TLE are more likely to demonstrate automatism with their seizures [10, 23]. Such automatism include oroalimentary (lip smacking and swallowing) and gestural symptoms (picking, fumbling, and aimless movements) [28, 31]. When involving a single extremity, automatism are a reliable lateralizing sign to the ipsilateral hemisphere; one study even reported 100% accuracy in lateralization in this age group [23]. Children age >6 years can also display tonic or dystonic posturing of an extremity (particularly the arm) with TLE, providing the seizure involves the motor strip [28]. Such posturing can assist clinicians in correctly

lateralizing seizure onset to the contralateral hemisphere [28, 32]. However, care must be taken not to assume temporal localization with such posturing, as it can also arise from a seizure focus in the frontal lobe [28].

When seizures arising from the temporal lobe in children result in loss of consciousness, it is believed that there has been bilateral limbic involvement [28]. Complex partial seizures of temporal lobe onset can last for several minutes, which is typically longer than complex partial seizures arising from extratemporal (e.g., frontal) regions [28]. Such seizures are also more likely to secondarily generalize than similar seizures in younger children [10, 23]. Postictally, children with complex partial seizures of temporal lobe onset can display confusion, disorientation, fatigue, headaches, and continued automatism [28]. Such behaviors can last for minutes to hours and can be difficult to clearly delineate from ictal phenomena [28]. However, they tend to be briefer than similar postictal behaviors demonstrated by adults with new onset TLE [27].

#### **3.4. Abdominal Epilepsy of Temporal Lobe Onset in Children.**

A semiology of TLE which is more common in children versus adults is abdominal epilepsy. These seizures, which are typically accompanied by impairment of consciousness, are accompanied by abdominal pain and emesis [28]. The discomfort is usually periumbilical, colicky, and severe and can be accompanied by headache, dizziness, syncope, and temporary loss of vision [28, 33]. The duration of abdominal pain is usually limited to 10–15 minutes and may be associated with sweating, stomach growling, salivation, and flatus [28]. Such a diagnosis can be difficult for clinicians to make, ultimately requiring prolonged video EEG monitoring to establish [28].

**3.5. Autonomic Effects of Childhood TLE.** Another potentially useful marker of TLE in children is autonomic (cardiac and respiratory) changes. The most commonly observed autonomic change in temporal lobe seizures in children is ictal tachycardia. This occurs with roughly equal frequencies in children versus adults [34] and can be observed in up to 98% of all childhood temporal lobe seizures [35]. This is particularly true if they are of right hemispheric onset [35]. In contrast, ictal bradycardia is rare in children, occurring in less than 4% of monitored seizures [36]. Such seizures are typically extratemporal in onset [35, 36].

One of the most dramatic autonomic disturbances that can occur during temporal lobe seizures in children is hypoxemia and/or apnea. Nearly half of all children and one-fourth of their seizures captured in inpatient monitoring units are characterized by desaturations <90% [36]. Such desaturations were not trivial, with nearly one-third (32.1%) falling to <60% [36]. Ictal hypoxemia in children is not specific for TLE and is more likely to be observed when partial seizures secondarily generalize [36]. However, in younger children (age 2–6 years), apneic attacks may be the sole manifestation of TLE [28, 37]. Such hypoxemia/apnea could theoretically exacerbate bradycardia induced by carotid chemoreceptors, causing further respiratory suppression.



FIGURE 2: This EEG shows interictal left temporal spikes recorded from a 13-year-old boy with left temporal lobe epilepsy due to mesial temporal sclerosis (10 microvolts/mm, 30 mm/sec).

#### 4. EEG Features of TLE

The scalp EEG in patients with TLE is important for making the initial diagnosis of epilepsy, as well as localizing seizure onset. The value of scalp EEG is improved by ensuring a sleep recording during routine EEG. Furthermore, localization of seizure onset is improved through the use of additional EEG electrodes, either sphenoidal or inferolateral temporal, as well as closely placed electrodes [38–41].

**4.1. Interictal EEG Features of TLE.** The interictal EEG in TLE is typically characterized by temporal spike or sharp-wave discharges and temporal intermittent rhythmic delta activity (TIRDA). Temporal spike or sharp-wave discharges are highly epileptogenic discharges that are maximal over the anterior temporal region and may prominently involve the ear leads (Figure 2). There is often increased activation of spike and sharp-wave discharges during drowsiness and sleep, with nearly 90% of patients with temporal lobe seizures showing spikes during sleep [42]. The spike-wave discharges may occur independently or synchronously over the bilateral temporal regions. However, most patients with bitemporal interictal EEG patterns are found to have unilateral temporal lobe seizures [39].

TIRDA has also been seen in patients with TLE. Like the spike and sharp-wave discharges, TIRDA is also most prominent during drowsiness and NREM sleep (Figure 3). It is characterized by rhythmic trains of low- to moderate-amplitude, monomorphic delta frequency slow waves over unilateral or bilateral temporal regions. The monomorphic slow waves are without clinical correlate and must be differentiated from the polymorphic delta activity that would be seen with a focal lesion over the temporal region. TIRDA has the same epileptogenic significance as temporal spike and sharp-wave discharges [42].



FIGURE 3: Left temporal intermittent rhythmic delta activity (TIRDA) in a 12-year-old boy with temporal lobe epilepsy. TIRDA consists of rhythmic trains of low-moderate amplitude monomorphic delta frequency slow waves and is most commonly seen during drowsiness or sleep (15 microvolts/mm, 30 mm/sec).

**4.2. Ictal EEG Features of TLE.** The temporal lobe has the lowest threshold for seizures. However, it is important to note that scalp ictal and interictal EEG recordings in children may be poorly localizing, even in TLE, due to incomplete or abnormal brain maturation. A focal lesion can present with generalized or multiregional epileptiform discharges in infants and young children (Figure 1). Similarly, the ictal EEG in a focal seizure of anterior temporal lobe origin may initially demonstrate lateralized or generalized scalp EEG changes [43].

Typically, the scalp EEG during a temporal lobe seizure will demonstrate moderate- to high-amplitude rhythmic paroxysmal activity that is maximal over a unilateral temporal region (Figure 4). This may progress to generalized rhythmic slowing that is maximal on the side of seizure onset [44]. Prior to seizure onset and postictally, there may be increased interictal temporal or bitemporal spike wave activity. Postictally there may also be focal temporal or generalized arrhythmic slow wave activity. This must be distinguished from continuing seizure activity.

#### 5. Differential Diagnosis

Temporal lobe seizures and temporal EEG discharges are seen in several pediatric epilepsy syndromes. Seizures may be due to structural abnormalities, either congenital or acquired. Classically, mesial temporal lobe seizures are seen with hippocampal sclerosis, often preceded by a history of prolonged or atypical febrile seizures. Mesial TLE with hippocampal sclerosis has been identified as a distinctive constellation in the most recent epilepsy syndrome classification [45].

However, nonlesional temporal lobe syndromes must also be recognized, including autosomal dominant lateral TLE, idiopathic partial epilepsy with auditory features, familial mesial TLE, and partial reading epilepsy.

Autosomal dominant lateral TLE, also known as autosomal dominant partial epilepsy with auditory features, is associated with mutations in the leucine-rich, glioma-inactivated 1 (LGI1) gene in approximately 50% of families

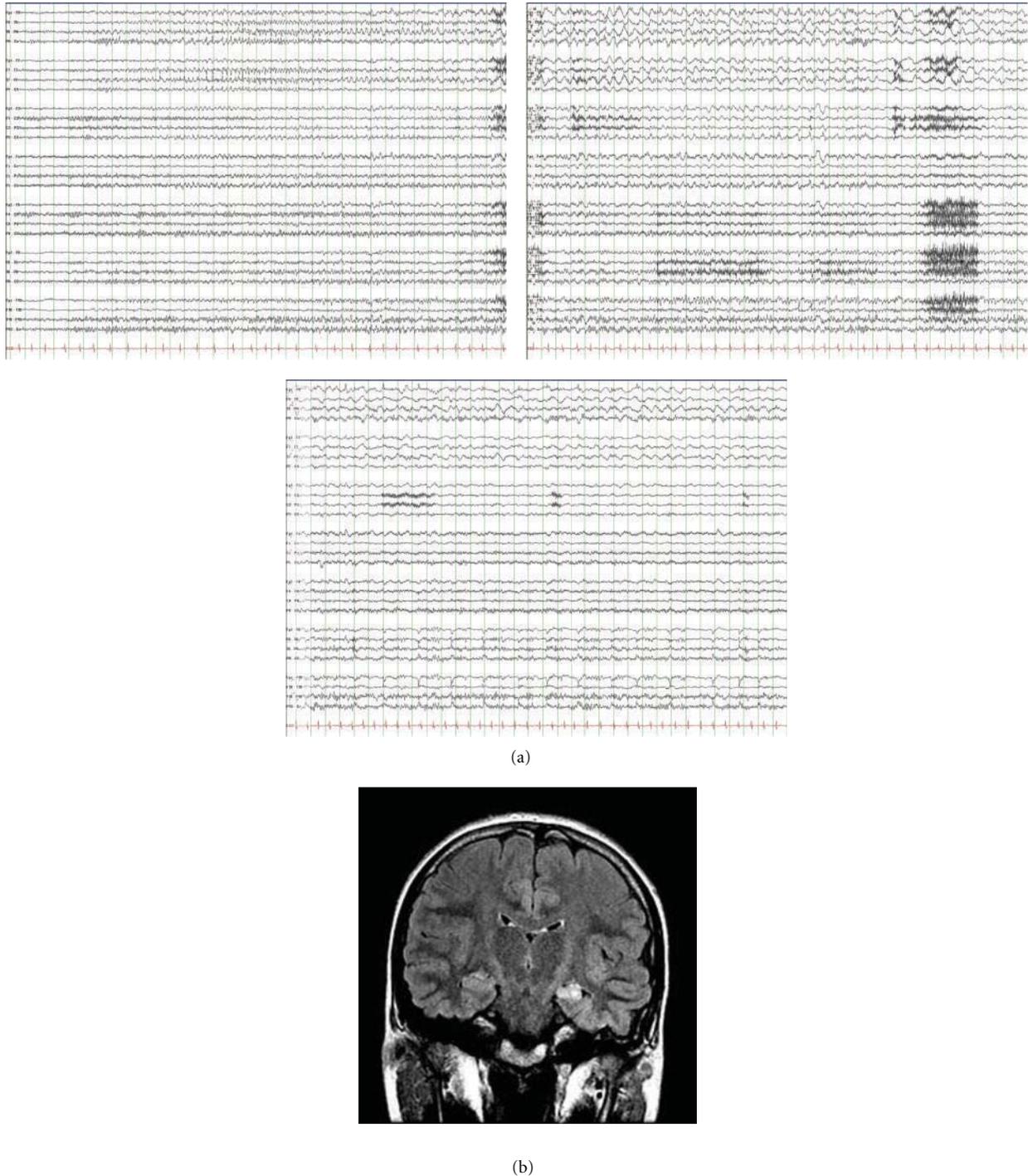


FIGURE 4: (a) shows 3 consecutive pages of EEG illustrating the onset of a left mesial temporal seizure in a 13-year-old girl with a history of a prolonged febrile convulsion at the age of 18 months (10 microvolts/mm, 15 mm/sec). Her coronal FLAIR MRI (b) shows left mesial temporal sclerosis. Her seizures were intractable to medical therapy, but she became seizure-free after surgery.

[46, 47]. Median age at onset is in late adolescence (range 1–60 years), and the focal seizures have prominent elementary auditory auras. Aphasic seizures are seen in 17% of cases and secondarily generalized seizures in 90%. Neuroimaging is usually normal and the clinical course is benign, with most patients achieving good control with antiepileptic medica-

tions. Epilepsy with similar features can be seen without family history and without LGI1 mutations [48].

In review of 100 individuals from 20 families, Crompton et al. characterized the clinical features of familial mesial TLE, which they propose is inherited in a polygenic (rather than autosomal dominant) manner [49]. Median age at



(AEDs). Therefore, both medical and surgical treatments will be discussed.

**6.1. Medical Management.** The goal of epilepsy management is long-term seizure freedom with minimal or no unacceptable side effects. Despite the availability of new antiepileptic drugs, there is no single AED that has proven superior efficacy in the management of focal seizures [74]. The choice of which drug to use depends on the individual patient characteristics and medication side effect profile. While newer drugs (e.g., oxcarbazepine, levetiracetam, lamotrigine, topiramate, etc.) are considered to have improved side effect profiles compared to older AEDs (phenytoin, phenobarbital, and carbamazepine), some of the newer medications carry greater risk for cognitive impairment (topiramate, zonisamide) or behavior problems (levetiracetam).

Furthermore, many children continue to have seizures in spite of adequate AED treatment. If two or more appropriate AEDs at adequate doses and duration have failed to control seizures, the probability of seizure freedom is low and diminishes progressively with further unsuccessful medication trials. Among newly diagnosed adults with epilepsy without prior medication trials, 47% to 50% became seizure-free with their first AED, 11% with their second drug, and less than 3% with their third monotherapy or with combination of two drugs [75, 76]. In children, the response to medication is more favorable. Carpay et al. found that 51% of children whose first medication failed for lack of efficacy had a good response to a second agent [77]. However, the likelihood of achieving a remission of longer than one year with subsequent drug regimens was only 29% after two medications failed, and 10% after three medications failed. In a separate study by Berg et al., among children whose seizures persisted despite trials of two AEDs, only 38% achieved a 1-year remission and 23% achieved a 3-year remission at last contact [78]. In children with cryptogenic or symptomatic focal epilepsy, the outcome may be more concerning; only 29% of children became seizure-free with a second monotherapy trial [79].

**6.2. Surgical Management.** Patients with medically refractory TLE should be evaluated expediently for surgical management, given the poor prognosis with additional medication trials. Hippocampal sclerosis and dual pathology (hippocampal sclerosis and other lesion) were associated with only 11% and 3% seizure freedom at last followup in medically treated cases, respectively [80, 81]. Early surgical intervention is also warranted, as long-term AED use carries risks such as osteopenia and osteoporosis, menstrual irregularities, sexual dysfunction, reduced fertility, cardiovascular illness, and drug-drug interactions. Furthermore, children undergoing temporal lobectomy for intractable epilepsy show improvement in visual memory and attentional functions [82] and quality of life, with complication rates less than 5% [83]. However, successful surgery for epilepsy is dependent upon correctly identifying the ictal-onset zone. Therefore, careful presurgical evaluation is necessary.

### 6.2.1. Presurgical Evaluations

**Prolonged Video EEG.** Ictal scalp EEG monitoring is essential for determining region of seizure onset, especially differentiating mesial versus neocortical onset. This is important for seizure localization as well as having prognostic implications. Patients with mesial TLE may have higher seizure-free outcomes with surgery compared to patients with neocortical temporal and extratemporal lobe epilepsies, particularly if a single MRI lesion is present [84].

Although patients with TLE can have seizures without scalp-recorded ictal EEG patterns, due to insufficient source area (<10 cm<sup>2</sup>) and lack of synchrony to be detected as ictal activation, this is uncommon [85]. There are several EEG differences that can be identified between mesial- and neocortical-onset temporal seizures.

Distinguishing EEG features of lateral neocortical-onset temporal lobe seizures include a transitional sharp wave [86], as well as irregular  $\leq 5$  Hz, or repetitive epileptiform activities at ictal onset [87]. Using simultaneously scalp and intracranial recordings among patients with TLE, intermittent rhythmic delta slowing was highly correlated with the irritative and seizure-onset zones in patients with neocortical temporal epilepsy but poorly correlated with the irritative seizure-onset zone in patients with mesial TLE. The presence of intermittent rhythmic delta slowing among patients with mesial TLE likely represents epileptogenic propagation involving the temporal neocortex [88].

**Imaging Modalities.** Neuroimaging is also important for presurgical evaluation, as patients with lesional TLE, such as hippocampal sclerosis or foreign tissue lesions (tumor, vascular anomaly), have a higher probability of seizure freedom after resection than those with normal MRI [89]. Postsurgical seizure-free outcome is seen in 70% to 90% patients with mesial TLE with hippocampal sclerosis compared to lowered seizure-free outcome of 60% in patients with nonlesional TLE [84].

MRI of the brain with seizure protocol includes images oriented in the oblique coronal plane, perpendicular to the long axis of the hippocampal structures [90]. Hippocampal atrophy and T2 signal abnormality seen on fluid-attenuated inversion recovery sequences are suggestive of mesial temporal sclerosis (Figure 4(b)). However, T2 hyperintensity alone in the hippocampus should not be assumed to be the epileptogenic zone because up to 47.5% of healthy volunteers without epilepsy have unilateral or bilateral hippocampal T2 hyperintensity [91]. Quantitative volumetric studies can be helpful in assessing the hippocampal atrophy, particularly when there is a question of bilateral atrophy or hippocampal malrotation [92].

In addition to MRI, multimodality noninvasive imaging techniques are increasingly used to determine the presumed epileptogenic focus when the scalp EEG and MRI are nonlocalizing or normal. These include subtraction ictal SPECT coregistered to MRI (SISCOM), positron emission tomography (PET), magnetoencephalography (MEG), and magnetic resonance spectroscopy (MRS).

SISCOM is a noninvasive modality to determine the epileptogenic lesion. Intensity differences more than two standard deviations between interictal and ictal images are coregistered onto the individual patient's MRI [93]. This technique produces semiquantitative maps of cerebral perfusion differences between ictal and interictal states and places that information in the context of the patient's own anatomy. The ability of SISCOM to detect epileptogenic lesions is 88% as compared to 39% by ictal SPECT alone [94]. Bell et al. demonstrated that SISCOM abnormality localized to the resection site is predictive of seizure-free outcome among patients with MRI negative TLE [84].

PET is a measure of glucose metabolism using 18 fluorodeoxyglucose. During the interictal state, glucose hypometabolism or reduced glucose uptake is present in the epileptogenic zone. In patients with TLE and normal MRI, unilateral PET hypometabolism has a positive predictive value between 70 and 80% [95]. However, it provided no additional information for patients with localizing ictal scalp EEG findings and concordant MRI.

Among patients with mesial TLE, magnetoencephalogram (MEG) may provide additional localizing information in up to 50% to 60% of patients with nonlocalizing ictal scalp EEG [96, 97]. On proton magnetic resonance spectroscopy (MRS), decreased N-acetyl aspartate over creatine ratios is seen ipsilateral to spikes in patients with TLE with or without an MRI-evident lesion [98–100]. Similarly, in children with intractable TLE, decreased N-acetyl aspartate over choline plus creatine ratio is correctly lateralized to the side of seizure focus in 55% of cases [101].

*Testings for Language and Verbal Memory Lateralization.* Determination of the dominant hemisphere involved in language and verbal memory is important for presurgical counseling regarding the potential surgical risks. This is typically done through a combination of neuropsychological assessment, intracarotid sodium amobarbital testing, and functional MRI. Neuropsychological assessment prior to pediatric epilepsy surgery includes age-appropriate, standardized tests to evaluate multiple domains: intelligence, language, memory, attention, problem-solving/executive function, visuospatial and perceptual analysis and reasoning, academic skills, motor and sensory function, behavior, personality, emotional status, and adaptive functioning [102]. Such testing identifies areas of existing dysfunction, assists in determining language lateralization, and provides guidance in weighing the risks and benefits of surgery.

While Camfield et al. did not find a specific pattern of impairment in children [103], other studies have noted a similar pattern of memory deficits to what is seen in adults. In 22 right-handed children with intractable TLE, verbal memory dysfunction was worst among children with left foci compared to those with right foci and controls, whereas nonverbal dysfunction was most prominent among children with right foci [102].

In a large study from Germany, pediatric TLE was shown to have long-lasting impact on verbal learning and memory. Compared to controls, children and teens with epilepsy failed to build up an adequate learning and memory performance

in their early years, hit their learning peak at a younger age, and reached poor performance levels at a younger age [104]. Furthermore, atypical language lateralization is seen among 12% of epilepsy patients, particularly among those with congenital lesions or left hemispheric insult before the age of 6 years [51, 105].

Intracarotid sodium amobarbital testing (Wada test) is used to determine language lateralization and to screen for verbal memory dominance. Among children who underwent temporal lobectomy, better verbal memory performance after injection ipsilateral to the side of surgery than after contralateral injection (Wada memory asymmetries) predicted preserved postoperative verbal memory capacity [106]. The difficulty of Wada testing in children is cooperation. However, Szabo and Wyllie found that using pretest teaching, emotional preparation, and simplified test items, up to 96% of children, including those with borderline intelligence and moderate mental retardation, could complete at least one injection [107]. Those at greater risk of poor cooperation included children with full-scale IQ <80, age <10 years, and seizures arising from the dominant left hemisphere.

Functional MRI (fMRI) is a noninvasive option to determine language lateralization as well as identify patients at higher risk of verbal memory decline following surgery [108, 109]. In children, the preoperative neuropsychologic testing may identify those who can successfully comply and participate in the functional mapping procedures. If neither Wada nor fMRI is feasible, language lateralization and verbal memory capacity may be determined by neuropsychologic testing.

*6.2.2. Surgical Techniques.* Once the presurgical evaluation is completed, surgical options are discussed. Classically, resection has been offered. However, less invasive, nonresective surgical techniques are potential treatment options, but need further study.

*Resective Surgery.* There are two resective surgical options for mesial TLE. The first is standard anterior temporal resection or "anterior temporal lobectomy." The resection line extends 4 to 5 cm from the temporal pole in the nondominant hemisphere and 3.5 cm to 4 cm in the dominant hemisphere. Standard anterior temporal lobectomy is preferred when seizure onset occurs in the lateral temporal or neocortical regions. The second option is selective amygdalohippocampectomy, which is selective removal of the mesial temporal structures. One of the primary goals of selective amygdalohippocampectomy is to preserve neuropsychological outcome, but the evidence for this is equivocal, especially in children. Seizure outcome following selective amygdalohippocampectomy is poorer in children than adults, with seizure-free outcome reported in only 33% of children versus 71% of adults, likely due to a greater frequency of pathology outside the hippocampus in younger patients [110]. Furthermore, rates of verbal memory deterioration after left-sided operations have been shown to be low [111].

Lastly, in patients with a presumed epileptogenic lesion in the lateral temporal region, lesionectomy with or without additional hippocampectomy may be performed.

To aid in determination of the optimal resective procedure, intraoperative electrocorticography (ECoG) has been used to localize the irritative zone and guide extent of surgical resection. ECoG is unlikely to influence surgical resection in standard anterior temporal lobectomy in patients with mesial TLE with mesial temporal sclerosis. Among consecutive patients with mesial TLE who underwent standard anterior temporal lobectomy, 72% were seizure-free despite pre-resection ECoG showing active interictal discharges outside the area of planned resection in 48% [112]. In tailored temporal lobectomies, intraoperative hippocampal ECoG may guide the posterior extent of hippocampal resection. In 140 consecutive patients undergoing this procedure, McKhann et al. showed that removal of all ECoG confirmed epileptogenic hippocampal tissue, but not the size of resection, correlated with seizure-free outcome [113].

Although ECoG may be important in children with dual pathology to ensure complete resection of regions of cortical dysplasia, the intraoperative setting is limited by sampling time. ECoG epileptiform activities are exclusively interictal spikes, as seizures are rarely recorded. Success of epilepsy surgery depends on the resection of the ictal onset zone rather than resection of more restrictive irritative zone suggested by interictal spiking [114].

Complications of dominant temporal lobectomy include language and memory impairments, with naming and fluency deficits seen in 50% [115]. Verbal memory impairment depends on whether resection was done in the dominant hemisphere as well as preoperative level of function—those with higher preoperative function are more likely to show decline. Transient diplopia due to trochlear nerve palsy can occur in 1.5% of cases. Significant contralateral visual field deficits (such as those greater than 90 degrees requiring suspension of driver's license) are seen in about 35% of patients undergoing anterior temporal lobectomy, but approximately 38% of these patients experience improvement within the first year after surgery [116].

Failure of surgical intervention is a disappointment and challenge for the epilepsy treatment team. Seizure recurrence typically occurs within the first year of surgery [117]. Evaluations for additional surgical resection should be considered. Rarely, the presumed postresection seizures are actually nonepileptic in nature. Video EEG recording and clinical semiology may identify a small percentage of patients with nonepileptic seizures.

*Nonresective Epilepsy Surgery.* Ablative surgery including radiofrequency and thermal ablation is currently under investigation. Seizure remission is delayed up to 9–12 months after stereotactic radiosurgery for mesial temporal lobe epilepsy, occurring around the time of vasogenic edema on MRI [118, 119]. The risks and benefits of this procedure compared to conventional surgery remain to be determined.

Intermittent stimulation of the vagus nerve using a vagal nerve stimulator is typically reserved for patients who are not amenable to or have failed to respond to resective surgery. Additional studies of the potential efficacy of deep brain stimulation or focal stimulation have been done in adults. Limited studies on deep brain stimulation of thalamic nu-

clei and hippocampi have demonstrated reduced seizure burden among adult patients [120, 121]. In the prospective, randomized, double-blind, parallel group stimulation of anterior nucleus of thalamus trial, sixty percent of the patient population had TLE. Subjects with seizure origin in one or both temporal regions had a median seizure reduction compared to baseline of 44.2% in the stimulated group versus a 21.8% reduction in subjects receiving control treatment [122]. For those patients with focal seizure onset that occurs in nonresectable cortex, a responsive neurostimulator, which uses seizure detection algorithms to trigger focal stimulation, is currently being studied in adults, but not yet in children [123].

## 7. Pathology

In many children with new-onset TLE, the etiology remains unknown despite careful neuroimaging. In a community-based cohort of 63 children with new-onset TLE, children fell into three etiological groups [7]. Group 1, which accounted for 16% of cases, had neuroimaging evidence of malformations or long-standing, nonprogressive tumors. Group 2, which accounted for 29% of the cohort, had hippocampal sclerosis or a history of a significant antecedent event, such as focal or prolonged febrile seizure or intracranial infection. Finally, the third group, which accounted for the majority (54%) of cases, had normal neuroimaging and no significant past history. This group was termed *cryptogenic*.

In surgical series, there are two features that distinguish TLE in children from that of adults. Firstly, the prevalence of hippocampal sclerosis is significantly lower [124]. While this is the sole pathological feature found in two-thirds of surgically treated adult cases, in pediatric series, tumors and malformations of cortical development are more common. Secondly, in children, if hippocampal sclerosis is present, it is frequently associated with extrahippocampal pathology such as cortical dysplasia or low-grade tumors. Such dual pathology has been reported between 31 and 79% of all cases of mesial temporal sclerosis in children [15, 124–126]. Several possible mechanisms could explain this dual pathology. Firstly, factors resulting in cortical dysplasia may also interfere with the development of the hippocampus and its connections. Several authors have reported on the existence of amygdalohippocampal neuronal dysplasia in such children, using the term “dysgenetic mesial temporal sclerosis” [15, 127]. Alternatively, the extrahippocampal lesion could, in itself, predispose the hippocampal neurons to seizure-induced neuronal loss.

Several recent studies have reported on hippocampal malrotation (HIMAL) in a proportion of children with epilepsy [128, 129]. HIMAL results from failure of inversion of the hippocampus within the medial temporal lobe which occurs normally in fetal development and appears to be a rare finding in patients without seizures [130]. Lewis et al. reported a higher frequency of this finding in children with prolonged febrile seizures, indicating that it may play a role in temporal lobe epileptogenesis [129]. However, no study has focused exclusively on this finding in a cohort of children with TLE.

The association between prolonged febrile seizures, acute injury to the hippocampus with resultant hippocampal sclerosis, and intractable temporal lobe epilepsy remains controversial [131], and the frequency of this association is currently being investigated by the ongoing FEBSTAT study.

## 8. Outcomes

**8.1. Seizure Outcome.** Long-term seizure outcome in TLE is primarily affected by the underlying etiology. Harvey found that over half of children in his new-onset cohort were cryptogenic [7]. In a recently published population-based, long-term follow-up study of outcomes in nonidiopathic focal epilepsy of childhood, those with a cryptogenic etiology fared much more favorably than the symptomatic group, with lower rates of intractable epilepsy (7% versus 40%,  $P < 0.001$ ), higher rates of seizure freedom (81% versus 55%,  $P < 0.001$ ), and higher rates of medication freedom in those who were seizure-free at final followup (68% versus 46%,  $P = 0.01$ ) [131]. However, some of these cryptogenic cases likely had a form of familial TLE.

Children with neuroimaging abnormalities including low-grade tumors, cortical dysplasia, or mesial temporal sclerosis have a significantly higher likelihood of medical intractability and should be considered early for resective surgery. A recent paper summarized outcomes in children undergoing temporal lobectomy reporting seizure-free rates of 58–78% with mesial temporal sclerosis, and in 60–91% of neocortical temporal resections [132]. Children with dual pathology do not appear to have a poorer prognosis than those with mesial temporal sclerosis alone, providing both the hippocampus and the additional epileptogenic lesion are resected. Failure to resect the second lesion may explain part of the surgical failure rate following surgery for pediatric mesial temporal sclerosis, and as such, selective amygdalo-hippocampectomy is likely to be less successful in children [110]. Lack of an obvious imaging abnormality or presence of diffuse pathology is predictive of higher rates of recurrence [89].

Following surgery, the steepest decline in the proportion of patients who remain seizure-free is seen in the first postoperative year. However, several long-term studies have identified a risk of late relapse [133, 134]. Jarrar et al. reported that 40% of subjects who were seizure-free at 5 years had recurrence of seizures at the 15-year-follow-up point [133].

**8.2. Cognition and Memory.** In adults with TLE, cognitive concerns are common, with left-sided foci being associated with deficits in verbal memory and right-sided foci with visual memory problems. However, when chronic TLE begins in childhood, the impact on cognition appears much more significant [135]. In a study which compared neuropsychological testing and quantitative MRI volumetrics in patients with childhood onset chronic TLE, adult onset chronic TLE, and healthy controls, Hermann et al. found the most significant neuropsychological abnormalities in the childhood onset group. Furthermore, in that group, cognitive compromise was widespread and not just limited to memory function, and MRI studies showed significant

reductions in volumetric measurements of total cerebrum tissue and total white-matter volumes, consistent with the generalized nature of the cognitive deficits. These findings suggested that early-onset temporal lobe seizures and their treatment and/or factors leading to their development have significant impact on brain regions distant from the region of primary epileptogenesis.

A recent review of neuropsychological outcomes after epilepsy surgery, predominantly based on adult studies, showed specific cognitive changes, such as risk to verbal memory with left-sided surgery but noted that cognitive improvements may also be seen in some patients [136]. Most studies in children suggest greater functional recovery following temporal lobectomy than is seen in adults [82, 137]. In a multicenter study of 82 children less than 17 years at time of surgery, children undergoing left temporal lobectomy overall demonstrated no significant loss in verbal intellectual functioning and significant improvements in nonverbal intellectual functioning. Those undergoing right temporal lobectomy had no overall change in intellectual functioning [138]. However, analysis of individual changes showed that significant changes were seen in verbal functioning in 19% of cases (10% declined, 9% improved), and in nonverbal functioning in 18% (2% declined, 16% improved). Predictors of significant decline included older age at the time of surgery and structural lesions other than mesial temporal sclerosis. In most other studies, factors predictive of postoperative decline in verbal memory include left-sided surgery and higher baseline verbal IQ [137, 139, 140].

Historically, many studies in children have been limited by a relatively short postoperative followup and/or low patient number. Skirrow et al. recently reported on long-term followup of 42 children undergoing temporal lobectomy for intractable epilepsy and compared them to non-surgical controls [141]. Children were followed for a mean of 9 postoperative years; 86% were seizure-free and 57% off antiepileptic medication. The mean full-scale IQ improved significantly in surgical patients but remained relatively unchanged in controls, with a gain of ten or more IQ points seen in 41% of surgical patients. However, this increase in IQ was only seen after a follow-up period of 6 years or longer and was associated with cessation of antiepileptic drugs and increased brain grey matter volume on MRI. Those with lower IQs showed the most significant improvement. This study highlights that surgery for intractable TLE in children results in favorable cognitive outcome, but that a prolonged period may be required for this recovery and subsequent development.

**8.3. Psychiatric Conditions.** Children with epilepsy are known to be at higher risk of comorbid psychiatric disorders [142–144], and those with intractable focal seizures may be most vulnerable. In a cohort of children with complex partial seizures, Ott et al. demonstrated psychopathology in 52%, and those with lower IQ were at higher risk [145].

McLellan et al. assessed the rate and nature of psychiatric disorders in a cohort of children undergoing temporal lobectomy and then reevaluated this cohort postoperatively. One or more psychiatric disorders were found in 72% of children

preoperatively, but also in an equivalent number postoperatively. Only 16% of children had resolution of their mental health problems after surgery; however, 12% without a preoperative psychiatric diagnosis developed mental health problems after temporal lobectomy [146]. The most common preoperative diagnoses were pervasive developmental delay (38%), ADHD (23%), oppositional defiant disorder (23%), and disruptive behavior disorder, not otherwise specified (42%). While pervasive developmental delay was more common with younger age at seizure onset and a right temporal focus, no other biological predictors were found for any other psychiatric conditions. Surprisingly, this study found no clear relationship between seizure freedom postoperatively and psychopathology. However, other studies have shown reduction in behavior and psychiatric problems following epilepsy surgery in children [147, 148], and further work focusing on children undergoing temporal lobectomy is needed.

Mizrahi et al. assessed whether a delay in surgery impacted psychosocial functioning in children with temporal lobe epilepsy [149]. Higher rates of psychosocial, behavioral, and educational difficulties in those undergoing later versus earlier surgery were found, suggesting that early surgery may ameliorate some of these difficulties.

## 9. Conclusion

Although TLE is less common in children than adults, it still comprises a significant portion of pediatric epilepsy. Seizures arising from the temporal lobe can be difficult to identify based on semiology alone, particularly in younger children. Up to the age of 6 years, the traditional semiologic hallmarks of TLE in adults (including auras, automatisms, posturing, and head version) are less likely to be observed. Correct diagnosis often necessitates routine or prolonged EEG recordings. Although the interictal EEG hallmarks of TLE (including temporal spike or sharp-wave discharges and TIRDA) are classically seen in older children, young children may present with generalized or multiregional epileptiform discharges, further complicating diagnosis. Once identified, additional workup is warranted to determine if childhood TLE is lesional (classically low-grade tumors, cortical dysplasia, or mesial temporal sclerosis) or nonlesional (including autosomal dominant lateral TLE, idiopathic partial epilepsy with auditory features, familial mesial TLE, and partial reading epilepsy). Care must be taken to differentiate TLE from other conditions in which there is significant activation of spike-wave discharges during sleep, including LKS, CSWS, and BCECTS.

While the majority of children with TLE will achieve seizure freedom with AEDs alone, a significant minority will prove medically intractable. This is especially true when seizures are symptomatic of an underlying lesion. For children with TLE who fail two or more AEDs because of lack of efficacy, expedited epilepsy surgery evaluations are warranted. In addition to prolonged video EEG and MRI, SISCOM, PET, and MEG can be successfully utilized in this population to identify appropriate surgical candidates. Given the greater likelihood of pathology outside the hippocampus

in younger patients (including low grade tumors and cortical dysplasia), standard temporal lobectomy (versus selective amygdalohippocampectomy) may portend better outcome. Such intervention can be associated with seizure-free rates as high as 58–91% and improved neuropsychological outcomes. Given the significant morbidity associated with uncontrolled childhood TLE, further research into the efficacy of other interventions (such as radiofrequency/thermal ablation, stimulation of the anterior nucleus of thalamus, and responsive neurostimulation) is warranted.

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## Review Article

# Selective Amygdalohippocampectomy

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Received 8 November 2010; Revised 22 February 2011; Accepted 25 March 2011

Academic Editor: Seyed M. Mirsattari

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Epilepsy surgery can be an effective epilepsy treatment for patients whose seizures do not respond to best medical therapy. For patients with temporal lobe epilepsy, selective amygdalohippocampectomy (SAH) has emerged as a viable alternative to standard anterior temporal lobectomy. This paper reviews the indications for SAH, the technical advances that have led to greater adoption of the procedure, the expectations for seizure control, and the risks of morbidity.

## 1. Introduction

Epilepsy is a common condition that affects nearly 1% of the world's population. The World Health Organization reports that neurological disease outranks HIV, cancer, and coronary artery disease in years of life lost to disability, and among neurological conditions, epilepsy ranks 4th [1]. While nearly 2/3 of patients with epilepsy achieve good control of seizures using antiepileptic medications, the remaining 1/3 have seizures that are resistant to medications and may be considered as candidates for epilepsy surgery. The benefit of epilepsy surgery in treatment-resistant epilepsy has been demonstrated in numerous case series as well as by a recent randomized clinical trial which demonstrated that surgery is clearly superior to best medical therapy in patients with temporal lobe epilepsy (TLE) [2].

Most people with TLE have seizures that originate from the mesial-basal temporal lobe structures, including the hippocampus, amygdala, and parahippocampal gyrus. The traditional surgical approach has been en bloc anterior temporal lobectomy (ATL). In this procedure, approximately 3–6 cm of anterior temporal neocortex is resected (depending on hemispheric language dominance), permitting access to resection of mesial structures. A modification popularized by the Yale group limits neocortical resection to 3.5 cm from the temporal pole and spares the superior temporal gyrus, obviating the need for language mapping in most cases [3, 4].

ATL offers advantages of good surgical exposure to allow complete resection of mesial structures, relatively low morbidity, and permits pathological examination of en bloc specimens. This procedure is still commonly employed today.

The central epileptogenic role of mesial temporal structures in TLE has been demonstrated in animal models of TLE and in pathological, electrophysiological, and structural and functional imaging studies. Thus, more targeted mesial temporal resections that spared temporal neocortex (selective amygdalohippocampectomy) were envisioned as possible means of providing equivalent seizure control with fewer neuropsychological sequelae (Figure 1).

## 2. Historical Background

Paulo Niemeyer reported selective resection of mesial temporal structures for intractable epilepsy in 1958 [5]. In a letter to his colleague Henri Gastaut, he related "because the focus of this epilepsy is usually in the nucleus amygdalae, in Ammon's horn, or in the hippocampus of gyrus, I resected these 3 structures via a transventricular approach, almost without touching the temporal cortex" [6]. The fascinating history of his pioneering work in neurosurgery in Brazil is related in a recent historical article by Cavalcanti et al. [6]. It is notable that the procedure was developed well in advance of the advent of image-guided neuronavigation systems. Subsequently Wieser and Yasargil popularized a transylvian

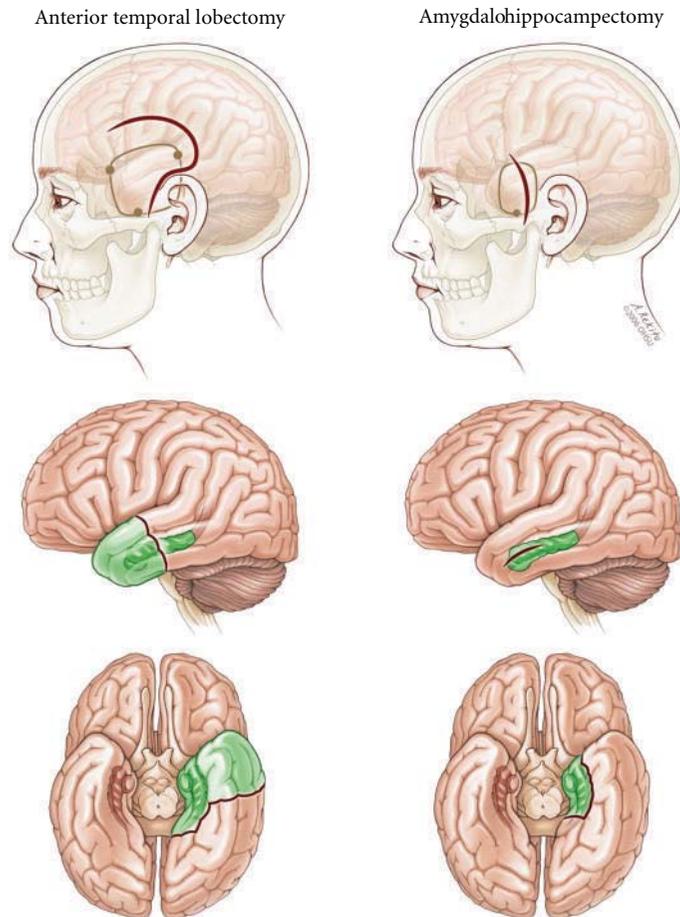


FIGURE 1: Comparison of anterior temporal lobectomy and selective amygdalohippocampectomy.

approach to SAH and reported outcomes of large numbers of patients who underwent this procedure [7, 8]. Other approaches including subtemporal [9] and variants of the transcortical approach have been described [10, 11]. Use of SAH became more widespread in the 1990s in tandem with increased utilization of intraoperative neuronavigation systems.

### 3. Indications

Selective amygdalohippocampectomy is employed in cases of medically refractory temporal lobe epilepsy of mesial temporal origin. There is no universally agreed upon definition of medically refractory or treatment-resistant epilepsy. Many authorities use a working definition of failure of at least two trials of antiepileptic drug monotherapy and one combination therapy when used at therapeutic levels over 1-2 years; however, a variety of definitions have been employed [12, 13]. In practice, many patients have failed much more extensive medication trials over much more extended time periods.

Most commonly, suitable candidates are selected based on convergent lines of evidence implicating unilateral mesial temporal structures as the epileptogenic region [14]. Central to this decision is a compatible ictal semiology and

neurological history. Video-EEG monitoring should confirm ictal semiology and stereotyped ictal onset on scalp EEG consistent with mesial temporal origin. Interictal EEG may show concordant unilateral or bilateral (usually ipsilateral predominant) epileptiform discharges. MRI often demonstrates an abnormality in the mesial temporal structures: most commonly hippocampal atrophy with or without mesial temporal signal change on T2-weighted or FLAIR sequences. Patients with exclusively mesial temporal foreign tissue lesions (e.g., low grade tumor) or neurodevelopmental abnormalities may also be good candidates for this procedure.

For patients in whom these lines of evidence fail to converge or for whom some data points are lacking (e.g., absence of MRI lesion, poorly localized ictal onsets on EEG), additional studies may be required, including PET, MEG, or Ictal SPECT. Particularly in nonlesional cases, if standard evaluation supplemented by specialized imaging studies defines a unilateral temporal lobe onset, intracranial EEG monitoring may be required to distinguish mesial from temporal neocortical onset and determine whether selective amygdalohippocampectomy is appropriate. Experience has shown that surgical failure rates are higher if strict criteria for unilateral mesial temporal onset are not applied [15].

Occasional patients with well-defined mesial temporal onset seizures should be excluded from consideration for SAH. These include most patients with documented independent bitemporal onset seizures [15] and those at risk for severe global memory impairment as a result of surgery. Patients with dominant temporal lobe foci are at greatest risk for postoperative functional decline in verbal memory, especially patients with high preoperative verbal memory performance, normal hippocampal volume, and later onset of seizures in adulthood [16]. Patients with a similar pattern in the nondominant temporal lobe can also experience clinically important deficits, but these are usually less prominent than in dominant temporal lobe resections [16]. While not always contraindications for surgery, this is important information that must be weighed carefully in presurgical decision making. Finally, patients with severe bilateral hippocampal atrophy who fail to demonstrate support of memory function contralateral to the proposed surgical side on intracarotid amytal procedure (Wada test) may be at risk for disabling global memory impairment, although there are few documented cases [17–19]. Clearly patients with idiopathic (primary) generalized epilepsies, extratemporal focal epilepsy, and temporal neocortical foci or temporal lobe epilepsy not clearly localized to mesial temporal structures are not candidates for SAH. Patients with exclusively psychogenic nonepileptic seizures (PNES) are not candidates; those with concurrent PNES and mTLE must be assessed very carefully, but the presence of PNES should not exclude patients *a priori* [20].

#### 4. Surgical Procedure

Here we describe in detail the commonly employed transcortical approach to SAH via the middle temporal gyrus. This is the preferred procedure at our center; however, alternative approaches including transsylvian and subtemporal methods are also commonly employed and will also be briefly discussed.

The procedure is accomplished with the assistance of an image-based frameless intraoperative guidance system (Figure 2). An MRI with placement of fiducial markers is performed just prior to surgery. The procedure is performed under routine general anesthesia with endotracheal intubation.

In the operating room, the patient is positioned supine with the head held in position in 3-pin fixation, rotated 90 degrees to the opposite side, and parallel to the floor.

Following registration of scalp fiducials, the planned entry point is marked on the scalp and the scalp is prepared by infiltration with lidocaine, bupivacaine, and epinephrine. After scalp and temporalis fascia incision and retraction, the neuronavigation system is used to locate the temporal craniotomy. Craniotomy is performed and dura opened and flapped inferiorly. The neuronavigation system is used to identify the location of the cortical incision in the middle temporal gyrus that is 2.5–3.0 cm behind the tip of the temporal lobe and in an area free of cortical vessels (Figures 2 and 3). The corticectomy is generally 2–2.5 cm in length. Guided by neuronavigation, dissection is performed toward the

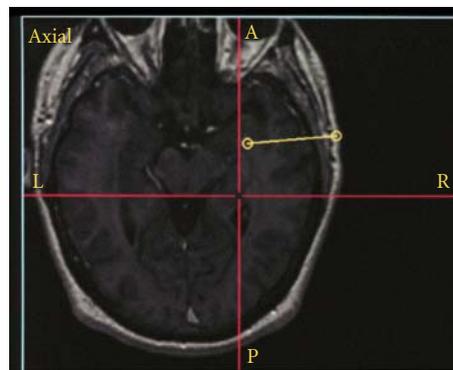


FIGURE 2: Intraoperative neuronavigation showing the entry point (lateral open circle), trajectory (yellow line), and target (medial open circle).

temporal horn until the temporal horn is entered (Figure 3). Two self-retaining brain retractors are placed to provide an optimal view of the intraventricular anatomy, and key anatomical structures are identified. The parahippocampal gyrus is resected beginning with subpial resection of the uncus and then advancing medially and posteriorly, with frequent confirmation of location using neuronavigation and care to preserve the mesial pial border. With resection of the anterior uncus, the incisura is visualized, and superiorly the internal carotid artery and third nerve can be seen through the pia. The choroidal fissure is identified. Care must be taken to insure that the dissection is not carried superior to the choroidal fissure. The hippocampus is then mobilized laterally and resected beginning anteriorly, with care to preserve the anterior choroidal artery, and carried posteriorly to the level of the tectal plate. Once the hippocampal resection is completed, the cerebral peduncle and anterior choroidal artery are visualized through the pia. Neuronavigation is used to confirm the completeness of the resection, and careful hemostasis is obtained.

In stepwise fashion the dura is closed, bone flap plated, temporalis muscle reapproximated, and scalp closed in layers to the skin. A postoperative neurological exam and head CT are performed, and care is taken to continue antiepileptic medications. Following overnight observation in a neurological intensive care unit, the patient completes a typically 3–4-day postoperative hospital stay before discharge to home.

Several alternatives to this middle temporal gyrus transcortical approach have been used. A minor variation with approach via the superior temporal sulcus was employed at the Montreal Neurological Institute [10].

Wieser and Yasargil [8] popularized a transsylvian approach and reported a large number of patients treated with this approach. The transsylvian approach avoids injury to the temporal neocortex and underlying white matter that is traversed in the transcortical approach and allows en bloc resections of the mesial temporal structures. However, it is generally regarded as being more technically difficult, allows limited surgical exposure, results in transection of the temporal stem, and poses a greater potential risk of

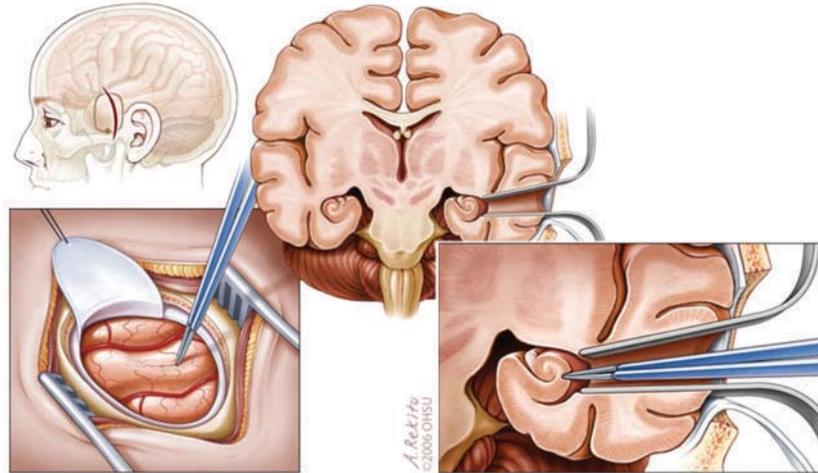


FIGURE 3: Transcortical amygdalohippocampectomy: position of craniotomy, position of cortical incision, surgical trajectory.

vascular injury or vasospasm [21], though this has rarely been reported in large surgical series [22].

A subtemporal approach has also been advocated [9, 23]. This largely avoids injury to Meyer's loop and resultant visual field defects that can occur with other approaches. There have been reports of fewer neuropsychological sequelae, but data are limited [24, 25]. This strategy carries disadvantages of potentially requiring excessive retraction of the temporal lobe, possible injury to the vein of Labbe, and may require removal of the zygomatic process.

## 5. Seizure Outcome

The ability of SAH to render patients seizure-free has been reported extensively in case series [15, 26–28], nonrandomized comparator trials with ATL [29–36], and comparator studies with historical controls [37].

Many centers exclusively employ one technique (ATL or SAH), making comparisons difficult. The existing nonrandomized comparator trials have a variety of methodological concerns, including comparison of noncontemporary groups as one procedure (ATL) was abandoned in favor of another (SAH), substantial risk of selection bias since patients were not randomized to procedure, and different neurosurgeons performing each procedure, or procedures being performed at different centers.

Overall, few differences in seizure-free outcomes based on choice of surgical procedure (ATL, SAH) have been demonstrated. Arruda and coworkers provided one of the earliest comparator trials of ATL and SAH [30]. They reported 74 patients, 37 of whom underwent each procedure. The groups were not randomized; however, different neurosurgeons preferred each procedure and selection of patients did not appear to be biased by clinical features. Both groups had equivalent seizure-free rates, and they concluded that the choice of procedure did not determine outcome; seizure freedom was better predicted by preoperative imaging findings and underlying pathology. More recent larger series have largely supported this conclusion. Clusmann et al.

reported 321 patients with TLE who underwent surgery, including ATL and SAH, and concluded that seizure outcome mainly correlated with diagnosis and clinical factors rather than resection type, and reaffirmed the strong correlation of MRI findings and underlying pathology with outcome [32]. Paglioli et al. compared a large non-contemporaneous group of 80 patients who underwent ATL and 81 who were treated with SAH with a mean followup of 5.8 years [34]. There were no significant group differences in outcome, except that fewer patients undergoing SAH were left with isolated auras. An early study by Mackenzie and coworkers was the exception: this study showed poorer outcomes following SAH [31]. Closer examination of patient selection reveals probable substantial selection bias. Patients with concordant findings on noninvasive evaluations underwent ATL, while SAH was performed only in a subset of more complex cases that underwent intracranial monitoring and that were more likely to have normal MRI findings.

Abosch and coworkers reported factors that might be predictive of failure to control seizures with SAH [15]. Many of the signs predictive of higher risk of surgical failure following SAH (bitemporal EEG findings, normal hippocampal volumes, use of intracranial monitoring) are not unique to this procedure and also predict lower success rates following ATL. In fact, those who underwent a second resection to extend the initial selective procedure largely continued to fare poorly [15].

There is little evidence to suggest that different approaches to SAH result in different seizure-free outcomes [38].

There are some small reports suggesting that seizure-free outcomes following SAH are less robust in children compared with adults [39, 40].

## 6. Neuropsychological Outcome

Neuropsychological outcome following SAH has been extensively reported in the literature. Often, the approach has been to report change scores before and after SAH [16, 41–43]. In some cases, attempts were made to compare to

cognitive outcomes following the “gold standard” procedure: ATL [19, 29, 32–34, 36, 44, 45]. Most of these direct comparator trials share similar methodological concerns with the seizure outcome comparator trials discussed above (noncontemporary cohorts, risk of selection bias, etc.). Further complexity is introduced by the nonuniform choice of cognitive assessments. Some studies focused on measures specifically targeted at anticipated deficits (e.g., verbal memory tests), others used extensive batteries of tests that run the risk of type I error, while others used general measures that may be insensitive to changes caused by surgery (e.g., IQ scores). It is important to keep in mind that an absence of demonstrated superior cognitive outcomes with the more selective procedure does not mean that it does not produce cognitive sparing; an alternative explanation is that the cognitive tests may be too insensitive to detect differences. Recent work has identified some previously unrecognized language areas in anterior temporal neocortex that could be at risk with a standard ATL procedure [46, 47], though the extent of functional sparing following SAH has been debated [48].

Many studies reported superiority of SAH compared with ATL in some aspects of postoperative cognitive performance [7, 8, 32, 49–51], but some showed substantially mixed findings or lack of superiority of more limited resection [36, 44, 52, 53]. Most of these studies still recognize the potential for meaningful cognitive declines following the more selective procedure, although there are exceptions [50, 54].

Some of the largest and most careful studies of cognitive outcome following SAH have come from the group in Bonn, Germany. Gleissner reported first 3-month and then 1-year findings in 140 patients who underwent SAH [16, 42]. They noted that the more selective procedure can have important cognitive consequences: at the 3-month time point, nearly half of the left SAH patients showed substantial loss of verbal memory; functional declines were less common with right-sided operations. Of the 115 who were studied at one year, there was no substantial recovery of verbal memory from the earlier time point. Preoperative performance was the primary predictor of postoperative performance at 1 year. Paglioli and coworkers’ study of 80 patients who underwent ATL and 81 submitted to SAH (nonrandomized, noncontemporaneous) similarly found that patients who underwent either procedure were at risk of verbal memory decline if surgery was carried out in the dominant temporal lobe; however, a greater proportion of left SAH patients had improved verbal memory after surgery compared with the left ATL procedure [34]. The large study of Clusmann reported better outcome following SAH for attention, verbal memory, and a composite of total neuropsychological performance [32]. Tanriverdi and coworkers compared a large number of SAH ( $n = 133$ ) and ATL ( $n = 123$ ) patients, found mixed cognitive results, and concluded that, although both surgeries are effective, they both have the potential to cause cognitive deficits [36].

Although accumulated evidence reviewed above suggests a potential cognitive benefit of the more selective procedure (SAH), it also provides ample evidence that the more

selective approach does not obviate the need for careful preoperative cognitive assessment, particularly with respect to risk of verbal memory worsening following dominant temporal lobe SAH. An important conclusion from a large series reporting neuropsychological outcomes following SAH was “Our data clearly show that this does not mean no or only very mild memory declines after SAH” [42]. Much as with ATL, the risk to verbal memory probably depends largely on the functional adequacy of the resected tissue, the cognitive reserve (perhaps related in part to age and duration of epilepsy), and the success in obtaining seizure freedom.

There have been some attempts to discern differential cognitive outcomes with different SAH surgical approaches [24, 25, 27, 38]. In theory, transcortical SAH can disrupt and disconnect fiber tracts, as demonstrated on diffusion tensor imaging by studying the path of a “virtual SAH” [55]. However, in most reports, methodological concerns and small numbers of patients limit the conclusions that can be drawn. The report of Lutz et al. is an exception [38]. This is a relatively large ( $N = 140$ ) randomized prospective trial of transylvian versus transcortical SAH in a uniform population of patients with presumed mesial temporal sclerosis. Few differences were found in the proportions of patients in each group with neuropsychological improvement or worsening on postoperative neuropsychological tests, and left-sided surgeries resulted in worsening of verbal memory regardless of approach. The exception was word fluency, which improved in the transcortical but not transylvian group.

## 7. Surgical Complications

The visual field deficits seen following ATL can also be seen with SAH, depending on the surgical approach, though they may be less severe following the more selective procedure [56, 57].

Potential complications include the following:

- (i) hemorrhage,
- (ii) infarction (commonly of deep penetrating vessels leading to lacunar stroke),
- (iii) infection,
- (iv) incomplete resection,
- (v) variable contralateral homonymous superior quadrant visual field defect from injury to Meyer’s loop (usually asymptomatic),
- (vi) memory impairment,
- (vii) transient dysnomia,
- (viii) mood changes.

Strict adherence to time out procedures, careful patient positioning, and careful visual identification of landmarks and repeated reconfirmation of stereotactic findings can minimize intraoperative complications. Detailed knowledge of the mesial temporal anatomy is critical, and such understanding will avoid the potential perils of overreliance on imagingbased neuronavigation systems. Attention to careful

patient selection and preoperative testing can minimize risk to memory and risk of mood disturbances and can maximize efficacy by excluding inappropriate patients.

## 8. Conclusions

Selective amygdalohippocampectomy has emerged as a viable alternative to standard anterior temporal lobectomy in patients with refractory TLE of mesial temporal origin. Success rates are highest if strict criteria are employed to determine suitable candidates. Progress in surgical technology including image-guided stereotactic surgery has made SAH more accessible and effective. In carefully selected candidates, seizure-free outcomes following SAH are comparable to ATL. While attention needs to be paid to risk of neuropsychological morbidity, particularly with respect to verbal memory, most studies suggest that there is benefit to sparing temporal neocortex in the surgical treatment of mTLE.

## Acknowledgment

The authors would like to thank Andy Rekito for permission to use the illustrations included in this paper.

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