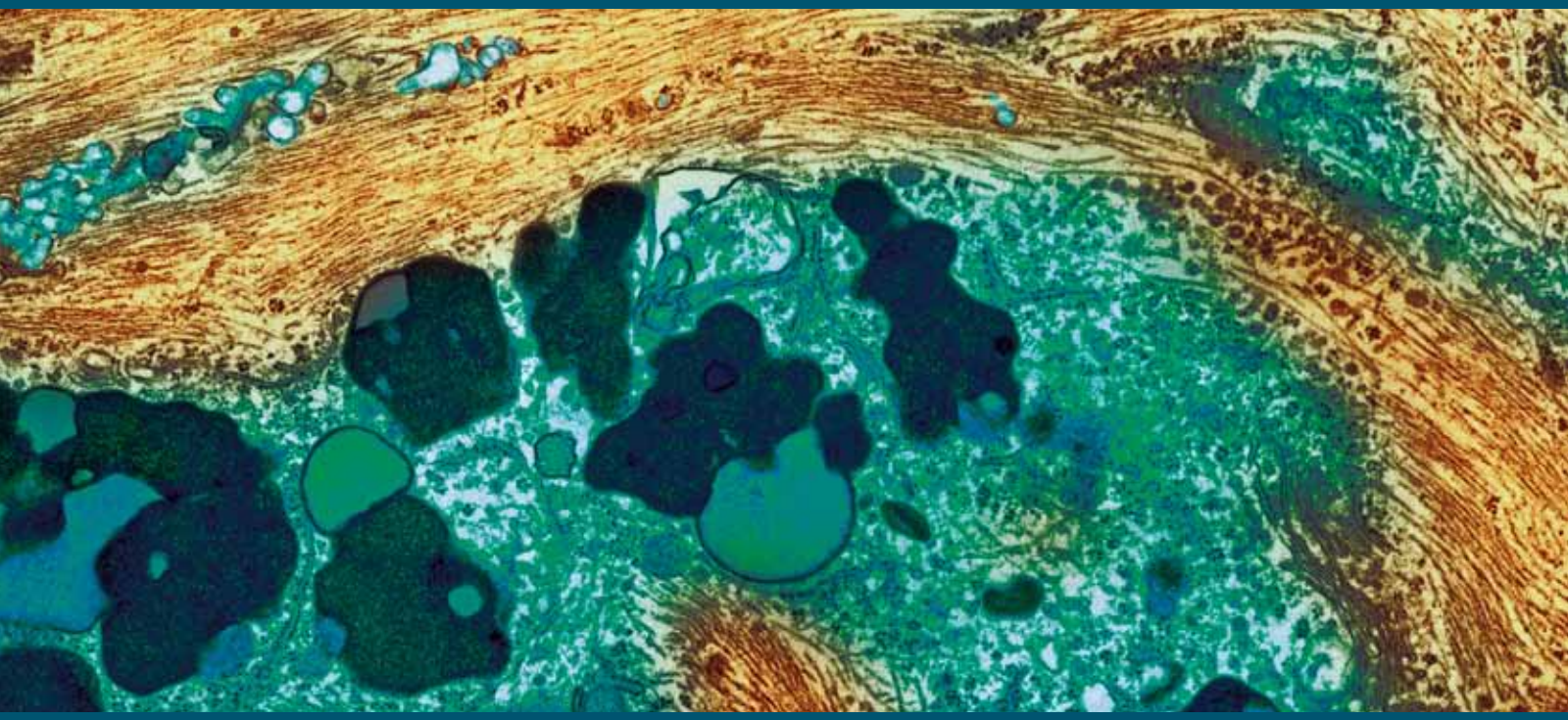
International Journal of Alzheimer's Disease

Clinical Neurophysiology in Alzheimer's Disease

Guest Editors: Florinda Ferreri, Sara Määttä, Fabrizio Vecchio, Giuseppe Curcio, and Fabio Ferrarelli



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Editorial Board

Contents

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Editorial

Clinical Neurophysiology in Alzheimer's Disease

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The pathophysiological mechanisms underlying normal aging and neurodegenerative disorders such as Alzheimer's disease (AD) have yet to be fully established. Early recognition of mild cognitive impairment (MCI) and AD requests the identification of biomarkers capable of distinguishing individuals with prodromes from healthy aging adults. Physiological brain aging is characterized by a loss of synaptic contacts and neuronal apoptosis even though neural redundancy as well as functional and structural plastic remodelling of brain networking promotes maintenance of brain activity in healthy elderly for everyday life. It is, then, important to implement techniques that are able to measure changes in normal aging brain and to discriminate them from neurodegenerative processes. As oscillatory electromagnetic brain activity is a hallmark of neuronal network function in various brain regions, an integrated approach utilizing modern neurophysiological techniques, including electroencephalography (EEG), event-related potentials (ERPs), and transcranial magnetic stimulation (TMS), together with biological markers and structural and functional imaging are promising for large-scale, affordable, and noninvasive evaluation of at-risk populations both at a group- and probably also at single-subject level.

This special issue contains a series of cutting-edge articles that provides innovative information and deal with the broad issue of the role of neurophysiology for the assessment of normal aging and dementia. Of necessity, these articles focus on selected topics but the mixture of novel contributions as well as review papers on EEG, TMS and ERP provide an overview and an insight into current areas of debate.

The first review of this special issue by G. Rodriguez et al., addresses an overview on the usefulness to study brain functional networks in the attempt to find noninvasive biomarkers of dementia; the second one, by R. Lizio et al., focuses on the role of modern EEG and on the possibility of combining its use together with biological and neuropsychological markers and structural and functional imaging for a low-cost, noninvasive, and widely available assessment of groups of individuals at-risk. Following these reviews, new EEG data are presented in the papers written by J. Dauwels et al. and F. Vecchio and C. Babiloni, dealing with the slowing and loss of complexity of EEG in AD patients and with the usefulness of EEG direction information flow in both AD and MCI patients, respectively. The subsequent three papers address EEG methodological issues, focusing on aspects helpful to better diagnose the AD: L.R. Trambaiolli et al. discuss in depth the possibility that EEG montage can influence AD diagnosis, F.B. Vialatte et al. provide suggestions on procedures to make EEG more specific in diagnosis, and K. van der Hiele et al. discuss the potential usefulness of electromyography in supporting the diagnosis of the disease. Then two review papers by F. Vecchio and S. Määttä and by A. Guerra et al., focus, respectively on the possibility to use auditory ERPs as well as TMS in complementing AD diagnosis, staging, and followup. The tenth study, by P. Julkunen et al., combines transcranial

magnetic stimulation and electroencephalography (TMS-EEG) to assess the severity of AD. Finally, two case reports are presented, in which neurophysiology plays a central role in supporting the diagnosis of dementia with particular attention to corticobasal loss of functionality (F. Mastrolilli et al.) and possible cooccurrence of nonconvulsive seizures and dementia (C. Campana et al.). As a corollary, the last contribution by L. Valeriani reports some considerations on the actual need in the management of AD patients in emergency departments.

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Review Article

Brain Functional Network in Alzheimer's Disease: Diagnostic Markers for Diagnosis and Monitoring

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Alzheimer's disease (AD) is the most common type of dementia that is clinically characterized by the presence of memory impairment and later by impairment in other cognitive domains. The clinical diagnosis is based on interviews with the patient and his/her relatives and on neuropsychological assessment, which are also used to monitor cognitive decline over time. Several biomarkers have been proposed for detecting AD in its earliest stages, that is, in the predementia stage. In an attempt to find noninvasive biomarkers, researchers have investigated the feasibility of neuroimaging tools, such as MR, SPECT, and FDG-PET imaging, as well as neurophysiological measurements using EEG. In this paper, we investigate the brain functional networks in AD, focusing on main neurophysiological techniques, integrating with most relevant functional brain imaging findings.

1. Introduction

Amnesic mild cognitive impairment (MCI) is characterized by memory impairment, either associated or not with mild deficit in other cognitive domains whereas the function of daily living is essentially preserved [1–3]. Annual conversion rate from normality to dementia of Alzheimer's type (Alzheimer's disease, AD) ranges between 0.2% and 4% [3, 4] whereas that from MCI to AD is between 6% and 25% [3, 5]. It is an open issue with important clinical implications whether or not MCI is essentially a prodromic stage of AD [3].

Although clinical manifestations of cognitive dysfunction and impairments of activities of daily living are the current standard measures for the diagnosis of AD, biomarkers are receiving increasing attention in research centers as possible early diagnostic surrogate measures of the ongoing pathology [6]. Not surprisingly, there is already a growing literature of biomarkers associated with the transition of MCI to AD [7–14].

Connectivity plays a critical role in mediating cognitive function. The breakdown of connectivity, both in the functional and structural system domain, plays a major role in the onset of AD symptoms. Thus, a failure of the regions of a network to interact at a high level of coordination may underpin the cognitive disorders which are present in AD. The failure of network function may be due to interaction failure among the regions of a network, which is denoted as the disconnection hypothesis [15]. The breakdown is thought to be due to chronically progressive AD neuropathology with underlying molecular mechanisms leading downstream to neuronal and synaptic dysfunction and ultimately to neuronal loss. Such AD-characteristic structural and functional changes are hypothesized to reflect, at least partially, the progressive impairment of fiber tract connectivity and integrity [16–18], suggesting that disconnection in AD is evident at both the functional and structural level.

Advances in electroencephalographic (EEG) signal analysis permit relatively precise localization of brain neural sources and the ability to track their hierarchical connectivity in sustaining a given function. This information can be integrated with structural and functional imaging provided by fluorodeoxyglucose (FDG) positron emission tomography (PET), perfusion single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI). Such integrated measures can index patterns of

neural activation responsible for sensory perception, attention, memory, movement, and higher mental operations including language and thought, since electromagnetic signals change in parallel over time and task, and can be impaired directly during such activity [19].

Actually, in the new guidelines for the AD diagnosis [20], EEG is not mentioned as a diagnostic measurement, instead of giving greater emphasis on MRI, cerebrospinal fluid (CSF), PET, and genetic findings.

The associations between brain pathology and indices of functional and structural connectivity may help our understanding of the role of connectivity in brain function [15].

The aim of this review is to investigate the brain functional network in AD focusing on main neurophysiological techniques and integrating the results with functional brain imaging findings. We will mainly review studies using EEG data to investigate functional networks; moreover, some very recent studies utilizing PET and SPECT to investigate functional brain imaging of AD-related pathology are reported.

2. Functional Network

2.1. EEG in Normal Aging. Studies in normal elderly individuals have consistently showed that healthy ageing is not associated with substantial EEG changes, which instead are caused by pathological conditions. Usually, the EEG signal is elaborated (quantitative EEG-qEEG) performing a fast Fourier transform (FFT) in order to estimate the power density of selected EEG frequency band, providing a power spectrum and high-density spatial EEG mapping of each frequency band.

A tendency toward a slower alpha rhythm has been reported in the elderly subjects, but it is poorly significant in comparison to normal adults. In fact, the normal alpha frequency is higher than 8 Hz also in the elderly. A qEEG study of age-related changes during cognitive tasks revealed no conclusive differences between the young and the elderly [21]. Therefore, it should be taken in mind that an abnormal EEG in aged people should prompt further investigation to disclose brain pathology, since normal aging *per se* is not associated with significant EEG alterations.

To make this point clear, it is noteworthy that slow waves over the temporal areas (mainly of the left hemisphere) are occasionally seen in the EEG of normal elderly subjects. The main features of these "nonpathological" slow waves are that they do not disrupt background activity, they are not associated with a substantial asymmetry of the alpha rhythm, their morphology is usually rounded, and their voltage is usually greater than 60–70 μV. Moreover, they are attenuated by mental activity and eye opening, and their prevalence is increased by drowsiness and hyperventilation. Finally, they occur sporadically as single waves or in pairs, not in longer rhythmic trains.

2.2. The Role of EEG in AD. Although EEG is the only clinical diagnostic instrument directly reflecting cortical neuronal functioning, the genesis of surface EEG rhythms is still the object of current investigation and partly not understood. The biological complexity of the brain modular function and the physical "sum" effect of different brain electrical fields on surface EEG recordings make the understanding of EEG components a very difficult task.

In general, EEG changes are well related to cognitive dysfunction in AD. Moreover, cognitive impairment is associated with a reduction or loss of EEG reactivity in AD [22]. Normal alpha was shown to be suppressed during eye opening in AD patients with significantly higher WAIS performance IQ scores whereas in AD patients with irregular alpha it does not or only weakly change during eye opening [23].

The most frequent findings are the power reduction of beta activity and alpha rhythm, the power increase of slow activities in the theta bands in milder dementias, and of delta activities in more severe dementia. Both intrahemispheric and interhemispheric coherence of fast and alpha EEG activities is reduced in neurodegenerative diseases causing dementia, thus suggesting a reduction of neural connections. On the contrary, coherence in delta and theta bands have been reported to be increased in AD, but this data is not agreed upon by all researchers [24]. The alpha (or background activity) also suffers from the slowing-down of its frequency, often till its peak falls below the 8–8.5 Hz. This phenomenon can happen together with a true increase of the theta power.

According to the "transition" hypothesis that considers MCI as a "reservoir" of patients possibly developing dementia, mainly of the AD type, EEG studies have tried to highlight early changes. Considered altogether, it is difficult to identify MCI patients from normal controls, but emerging data is consistent with the hypothesis that those who will convert to dementia already show similar EEG changes as early AD patients [7, 8, 13, 25]. Moreover qEEG features could predict longitudinal cognitive decline in normal elderly with subjective complaints, with an overall predictive accuracy of 90% [26].

It should be taken in mind that EEG measures electrical field variations, and a number of clinical conditions can disturb the normal electrical field of the brain. For instance, electrolyte changes may alter the appearance and time variation of the brain-generated electrical fields, and medications can slow the posterior dominant rhythm. Moreover, in assessing the frequency of the alpha rhythm, alerting manoeuvres are essential in order to ensure that the patient is not drowsy. Hence, a large number of conditions cause the EEG to appear abnormal. In EEG practice, the clinician has to rely to a large extent on the clinical history and the neurological examination findings to make a clinically meaningful conclusion.

In summary, a shift-to-the-left of background activity and the increase of theta power are the earliest and more robust features of AD. When the disease progresses to its moderate stage, theta activities increase further and delta activities appear. In the most severe stages, delta and theta activities increase again while the background activity cannot be longer recognized. These increasing EEG changes according to severity of AD have been highlighted by a study based

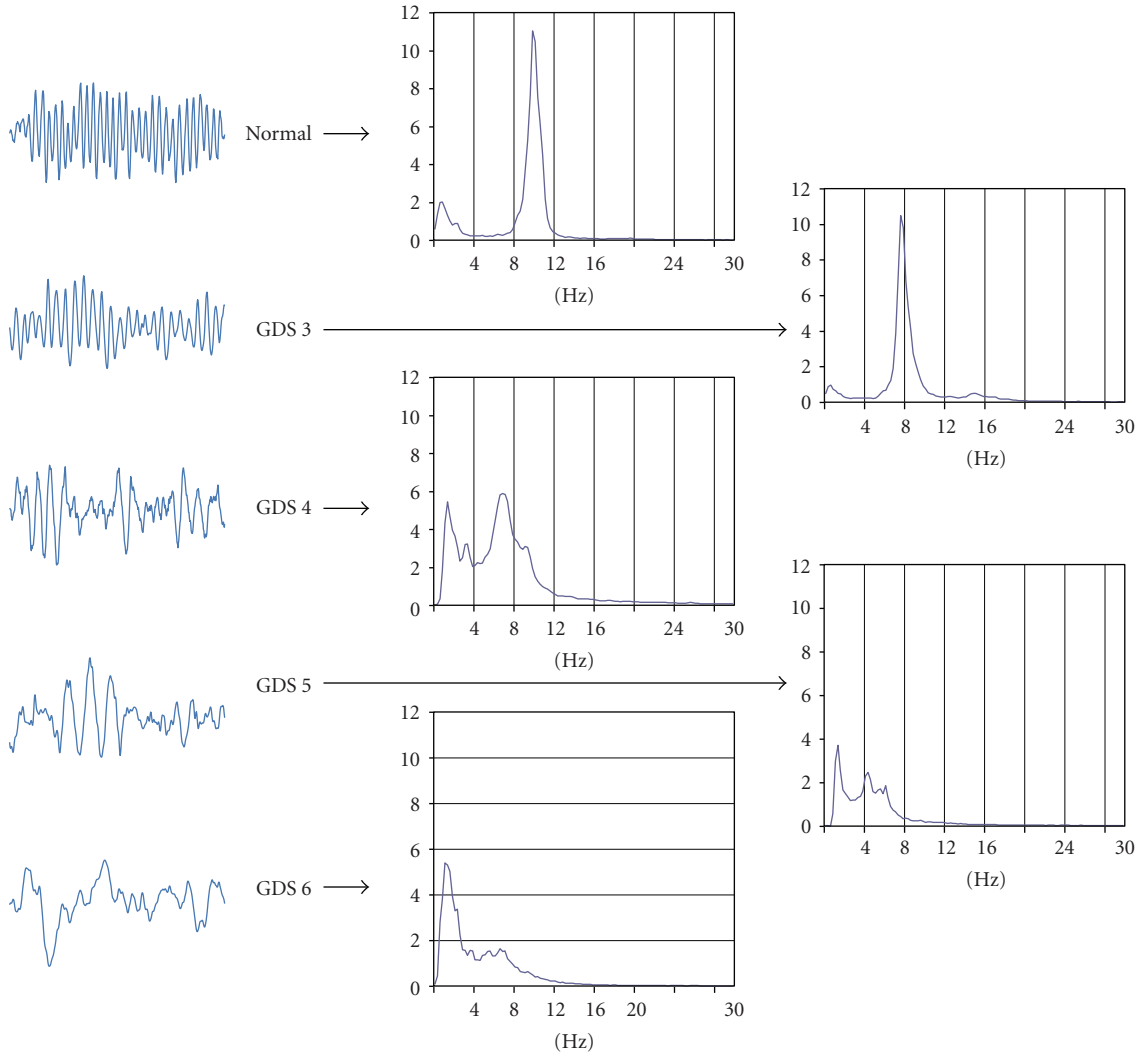

Figure 1: Sample of visual EEG and EEG spectrum on 4 clinical classes of severity (Global Deterioration Scale: GDS, from 3 to 6; for more details see text). EEG frequency bands (X-axis) and percent value of each band (Y-axis) are shown.

on 4 clinical classes of severity (GDS, from 3 to 6, Figures 1 and 2) [27].

2.3. Pathophysiology of EEG Changes in AD. With this basis, the understanding of pathophysiology of EEG changes in AD is even more complex and just some general concepts can be commented. Scalp alpha rhythms (8–13 Hz) mainly result from sequences of inhibitory (IPSP) and excitatory (EPSP) postsynaptic potentials at the dendrites of cortical pyramidal neurons. These potentials depend mainly on the influence of near and distant cortical modules [28], as well as on the interactions of excitatory corticothalamocortical relay fibres and inhibitory thalamic reticular fibres [29, 30]. Cholinergic and glutamatergic synapses are especially involved in the genesis of these potentials. In Alzheimer's disease (AD), characterized by an early cholinergic (and possibly glutamatergic) deficit, this may produce a slowing-down of alpha rhythm and a reduction up to disappearance of alpha rhythm in the severe stages.

Theta rhythms are usually not appreciated in normal awakening EEG. However, a theta power increase is observed over the frontal and temporal areas during learning and memory tasks. The theta rhythms that are recorded during these tasks are thought to be produced by the activation of septal-hippocampal system. Hippocampus has a cholinergic innervation originating from basal forebrain, the medial septum, and the vertical limb of the diagonal band of Broca. Populations of GABAergic and glutamatergic neurons have also been described in several basal forebrain structures. The synchronized depolarization of hippocampal neurons produces field potentials that have a main frequency of 3–12 Hz and are usually known as hippocampal theta rhythm [31]. A cholinergic-glutamatergic hypothesis of AD, in which most symptoms may be explained by cholinergic-glutamatergic deficits, has been advanced. Neuronal injury/loss may include an excitotoxic component that possibly contributes to the early cholinergic deficit. This excitotoxic component may occur, at least in part, at the septal level where somas

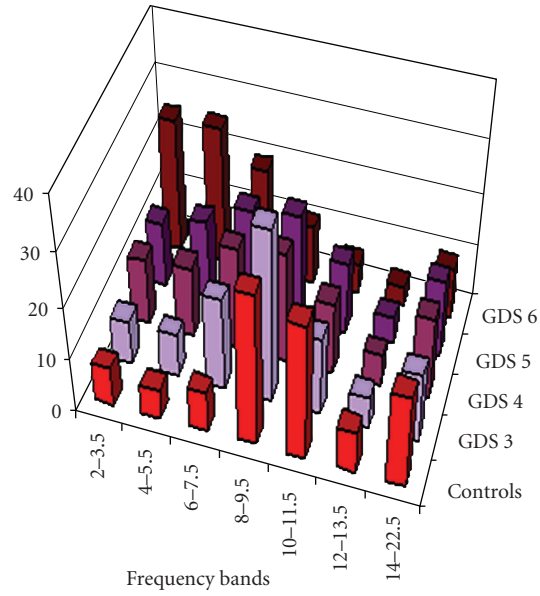

Figure 2: Histogram showing the relationship between 7 EEG frequency bands (2–3.5; 4–5.5; 6–7.5; 8–9.5; 10–11.5; 12–13.5;14–22.5 Hz) and disease's severity (normal controls and 4 clinical classes of severity; GDS 3 to 6).

of cholinergic neurons are found. This insult may modify septal networks and contribute to the abnormal information processing observed in AD brain, including its hyperexcitability states. According to this theory, the increased theta production in AD would derive from hyperexcitability of the septal-hippocampal system [32].

By means of observations in head injury patients, it has been suggested that delays in corticocortical fiber propagation may play a global role in determining human EEG frequencies, increasing the amount of delta activity [33]. Increased T2 relaxation times in cortical gray matter and white matter were correlated with a shift in relative EEG power to lower frequencies in the delta range (delta activity: 1–4 Hz) and reduced cognitive performance. Generally, these data are consistent with the idea that head injury somehow damages the ability of brains to form local cell assemblies within the global synaptic action field environment.

The increment of delta oscillations in mild cognitive impairment (MCI) and AD subjects might be related to loss of hippocampal and posterior cortical neurons, which are impinged by cholinergic inputs. Indeed, it has been demonstrated that early degeneration in mesial temporal cortex of AD subjects can affect functional connectivity between hippocampal formation and temporoparietal cortex [34]. Furthermore, a bilateral reduction of gray matter volume in the hippocampal formation and entorhinal cortex of AD subjects was correlated with an increment of delta rhythms in posterior cortex [9, 35].

3. Functional Brain Imaging

Historically, morphological imaging became easily a reliable diagnostic procedure for several brain disease, like neoplastic or cerebrovascular injuries, and at least for degenerative disease. This did not happen for functional neuroimaging, either metabolic or perfusional. This has actually slowed down these biomarkers introduction into dementia diagnostic criteria.

Recently, Dubois et al. proposed to revise the NINCDS-ADRDA criteria for the diagnosis of AD [20]. A specific pattern on functional neuroimaging with FDG-PET has been proposed as one of the supportive features in the diagnosis of probable AD, specifically in terms of reduced glucose metabolism in bilateral temporal parietal regions. In fact, a reduction of glucose metabolism as seen on PET in bilateral temporal parietal regions and in the posterior cingulate is the most commonly described diagnostic criterion for AD [36].

The newly proposed diagnostic criteria for AD entails a two-step diagnostic process, first identifying dementia syndrome (lack of episodic memory and other cognitive impairment) and then applying criteria based on the AD phenotype (presence of plaque and neurofibrillary tangles) [20]. As a matter of fact, this does not allow diagnosis in life. Furthermore, the pathogenetic role of amyloid deposition in AD patients is still unclear, highlighting the necessity of another diagnostic path [37–40]. In summary, the authors propose that the term "Alzheimer's disease" should refer only to the in vivo clinicobiological expression of the disease. Obviously, prospective studies with postmortem verification are needed to validate this new proposal. Actually, metabolic changes (as identified by FDG-PET) associated with neocortical dysfunction are detectable before atrophy appears [41]. Moreover, metabolism reductions exceeded volume losses in MCI [42], and in presymptomatic early-onset familial AD [43]. Actually, a pattern of parietotemporal metabolic reductions in MCI and AD, and frontal metabolic reductions later in the disease, has been established through the last decades of research [44–46] and has recently been confirmed in ADNI PET data [47]. The usefulness of FDG-PET could be highlighted also in detecting prodromal AD showing metabolic reductions in the anterior cingulate, posterior cingulate, and temporal, parietal, and medial temporal cortices [48–50].

Finally, several compounds have been developed for the imaging of amyloid for PET and SPECT. The rapid development of different compounds suitable for the visualising of amyloid during the past 10 years has led to the first promising in vivo studies of the amyloid ligands PIB (N-methyl-2-(4L′-methyl aminophenyl)-6-hydroxybenzothiazole) [51] and FDDNP (2-(1-[6-[(2-[18F]fluoroethyl](methyl)amino]-2-naphthyl]ethylidene)malononitrile) [52]; the latter compound also seems to label neurofibrillary tangles in patients with AD. Furthermore, both compounds have shown a pattern of increased radioligand retention in patients with AD compared with control individuals that is consistent with AD pathology [52–54]. Accumulation of amyloid, however, has also been reported in cognitively intact older people [37–40]. In a recent paper, Oh et al. using PET imaging with the PIB compound, structural MRI, and cognitive measures identify two brain networks in which the degree of gray matter volume fluctuates in a similar manner: a frontal network and a posterior network [39]. The authors suggested that β-amyloid deposition in older people without dementia

may influence a wide structural network, although it is not clear whether people with higher β-amyloid deposition will progress to AD.

Because SPECT is more widely available and cheaper than PET, it has received much attention as an alternative to PET. However, at present, the technique is not included in the criteria proposed by Dubois et al. [20] as the diagnostic accuracy estimates for this modality generally fall below the requisite 80% levels specified by the Reagan Biomarker Working Group [55].

4. Neurophysiological Evaluation of AD

In a clinical context, some firm points can be made concerning EEG in the evaluation of AD. In a more strict sense, the main applications of EEG should be as a different diagnostic tool between dementia and other conditions characterized by peculiar EEG pattern such as Creutzfeldt-Jakob disease (CJD), toxic-metabolic encephalopathy, or in case of pseudodepressive dementia [56]. In a broader sense, EEG can be useful to stage the severity of dementia on a pathophysiological basis, and, in AD, gives useful information for prognostic purposes [57]. Actually, all patients with moderate to severe AD could exhibit abnormal EEGs. When a substantial part of the dominant rhythm falls within the range of theta band physicians should be encouraged to perform qEEG. This, in order to identify the so-called transition frequency between dominant and theta activity, as suggested by Klimesh [58]. Moreover, qEEG is a highly sensitive method to evaluate the biological effect of drugs [59, 60].

Cortical sources of scalp EEG rhythms have been successfully evaluated in AD patients by single dipole sources deeply located into a spherical brain model [61]. Single dipole sources of alpha or beta rhythms are located more anteriorly as a function of AD severity. Such "anteriorization" of the dipole source is observed in AD patients not only with respect to normal subjects but also with respect to subjects with MCI [8, 61]. Notably, the location of the dipole sources correlates with the reduction of rCBF in anteroposterior and laterolateral brain axes [62]. By applying the LORETA technique, which elaborates solutions to compute the cortical sources of EEG activities, several multicenter studies have been performed in recent years in AD as well as in MCI, gaining substantial information [7–9, 63].

Even if not usually used in clinical practice, other neurophysiological measurements could be performed in the evaluation of AD. Event-related potentials (ERP) may reflect cognitive decline in the longitudinal followup of MCI [64] and AD patients [65], and ERP and MRI data fusion could improve diagnostic accuracy of early AD [66]. Moreover, transcranial magnetic stimulation (TMS), especially combined with EEG, may provide useful information about the degree and progression of AD [67–69].

However, it is obviously important to combine multiple biomarkers in order to obtain complementary information to be used in clinical AD diagnosis practice. This kind of investigation has been recently performed [41, 70–72] confirming that each biomarker (including EEG, PET, SPECT, MRI, apolipoprotein E risk gene (ApoE4), cerebrospinal fluid (CSF), and neuropsychological tests) does carry complementary information, and the simple combination of classifiers trained on these different modalities can improve the diagnostic performance. Indeed, ApoE2 has been suggested as having a protective effect and delaying the age of onset of AD [73, 74].

qEEG has been analysed together with other measures of brain function. For instance, qEEG was analysed together with regional cerebral blood flow (rCBF) quantitative measurements in order to investigate the correlation between EEG activities and hypoperfusion and to assess the diagnostic accuracy of the two methods used alone or in combination. In a study on 42 AD patients and 18 healthy controls [75], rCBF and qEEG were correlated with one another, suggesting that these measurements used together are reasonably accurate in differentiating AD from healthy aging. Another qEEG-SPECT (semiquantitative Tc-99 HMPAO technique) correlative study on 42 AD patients underlined that bilateral hippocampal rCBF was the perfusional index best correlated with the MMSE as well as being significantly correlated to qEEG [76] (Figures 3, 4, and 5).

A very interesting application of qEEG measures tried to evaluate their prognostic meaning in AD. In a preliminary study on 31 AD patients, right delta relative power predicted both the loss of activities of daily living (ADL) and death whereas right theta relative power predicted the onset of incontinence [77]. A confirmation came from an extended group of 72 patients. Because patients were in different stages of the disease, the statistical analysis was performed in the entire group as well as in the subgroup of 41 patients with mild AD (scoring 3 or 4 on the GDS). In the whole group, the loss of ADL was predicted by delta relative power in either side, incontinence was predicted by alpha relative power in the right side, a borderline statistical significance was reached for death ($P < .05$). In the subgroup of mildly demented patients, the loss of ADL was predicted by left delta relative power, incontinence by both delta and alpha relative powers in the right side, and death was not significantly predicted ($P = .08$) [78].

Using both conventional visual analysis and qEEG, other authors found that AD patients with an abnormal EEG at an early stage had a different pattern of cognitive decline than those (matched for severity of dementia) with a normal EEG. The patients with a deteriorating EEG during the first year of followup subsequently showed a greater decline of praxic functions, a tendency to Parkinsonism and a higher risk of institutionalisation than patients with a stable EEG during the 1st year [79]. In another study, more marked EEG abnormalities were found in patients with delusions and hallucinations who also showed a more rapid cognitive decline [80]. The same authors also found that an abnormal EEG and psychosis were independent predictors of disease progression [81].

As discussed in a recent paper [8], most of the EEG studies in AD patients have reported a prominent decrease of coherence at the alpha band. The reduction of alpha coherence in AD patients has been also found to be associated with ApoE genetics risk of dementia; this alpha power reduction

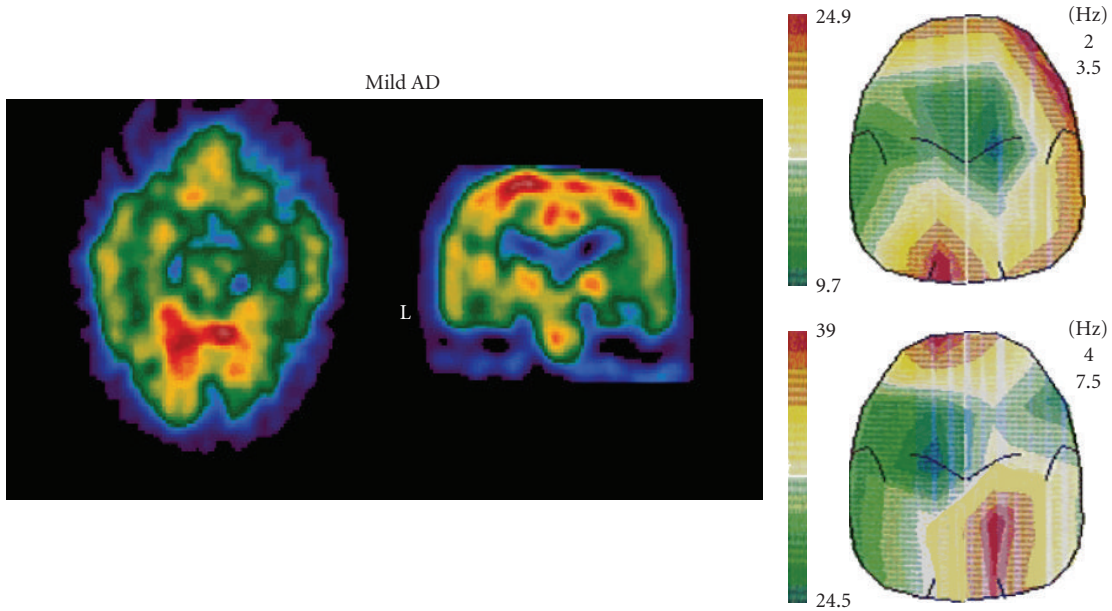

Figure 3: Sample of SPECT neuroimaging (Tc-99 HMPAO) and EEG brain mapping in a mild AD patient. Topographic scalp distribution of the EEG power on the 2.0 to 3.5 Hz frequency band (top right) and 4.0 to 7.5 Hz frequency band (bottom right) is shown. For more details, see text.

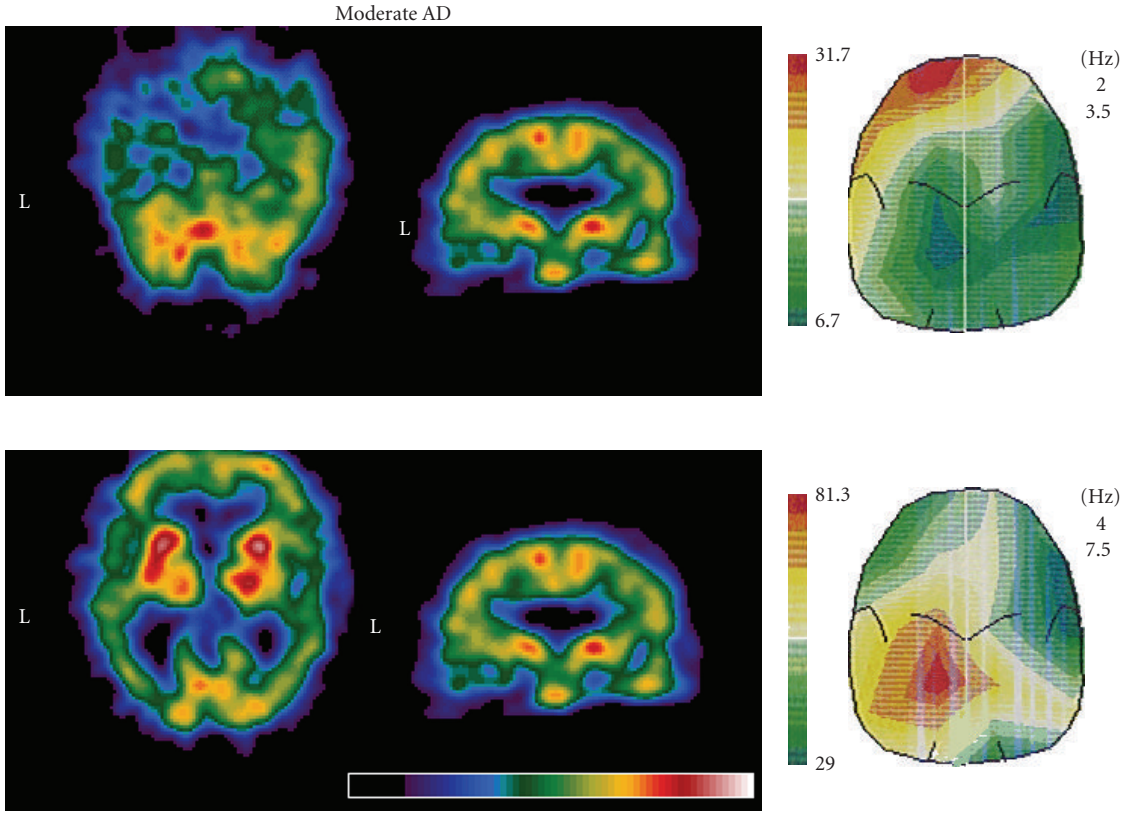

Figure 4: Sample of SPECT neuroimaging (Tc-99 HMPAO) and EEG brain mapping in a moderate AD patient. Topographic scalp distribution of the EEG power on the 2.0 to 3.5 Hz frequency band (top right) and 4.0 to 7.5 Hz frequency band (bottom right) is shown. For more details, see text.

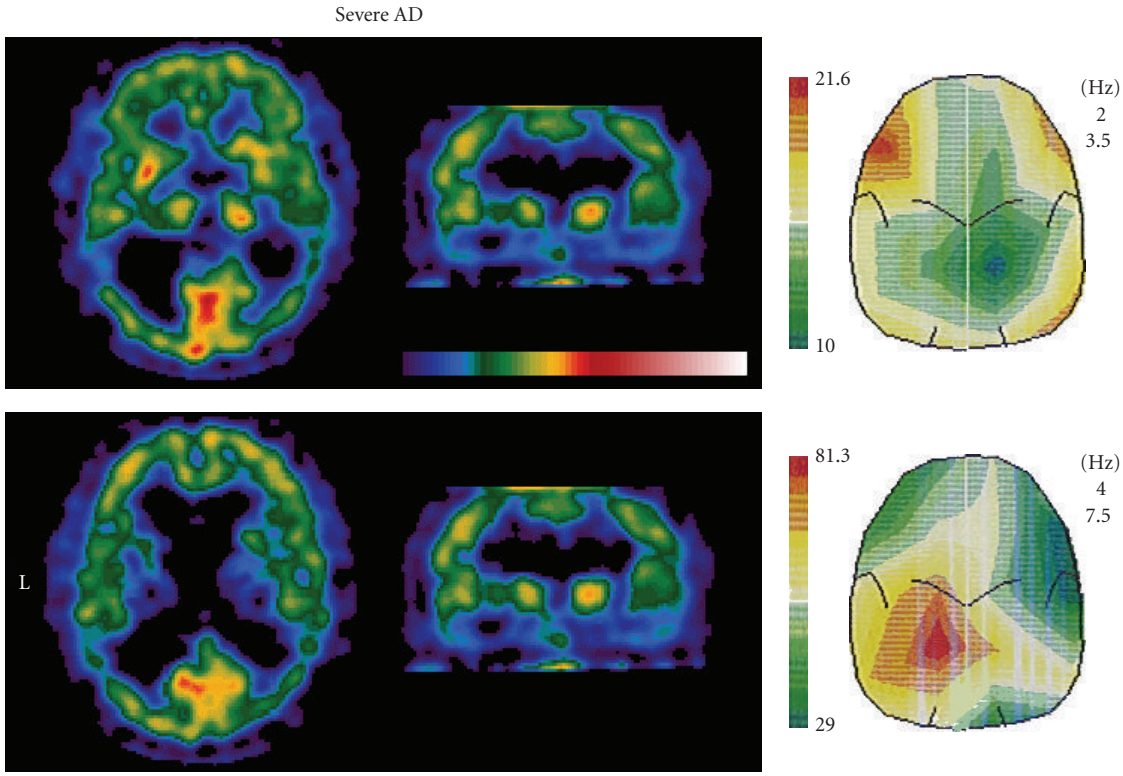

Figure 5: Sample of SPECT neuroimaging (Tc-99 HMPAO) and EEG brain mapping in a severe AD patient. Topographic scalp distribution of the EEG power on the 2.0 to 3.5 Hz frequency band (top right) and 4.0 to 7.5 Hz frequency band (bottom right) is shown. For more details, see text.

is supposed to be mediated by cholinergic deficit [82]. Instead, coherence at the delta and theta bands has been less straightforward. Some studies have shown a decrement of slow EEG coherence in AD patients [83] whereas others have reported its increase [84]. Wada et al. [85] examined intrahemispheric coherence at rest and during photic stimulation in 10 AD patients. In the resting EEG, patients with AD had significantly lower coherence than gender- and age-matched healthy control subjects in the alpha-1, alpha-2, and beta-1 frequency bands. EEG analysis during photic stimulation demonstrated that the patients had significantly lower coherence, irrespective of the stimulus frequency. The changes in coherence from the resting state to the stimulus condition showed significant group differences in the region of the brain primarily involved in visual functioning. These findings suggest that patients with AD may have an impairment of functional connectivity in both nonstimulus and stimulus conditions. This suggests a failure of normal stimulation-related brain activation in AD. In another study, alpha coherence was decreased significantly in temporo-parieto-occipital areas in the majority of patients while significant delta coherence increase was found in a few patients between frontal and posterior regions. This was expressed to a greater extent in patients with a more severe cognitive impairment [84]. The authors speculated that their findings could reflect two different pathophysiological changes: (i) the alpha coherence decrease could be related to alterations in corticocortical connections whereas (ii) the delta coherence increase suggests lack of influence of subcortical cholinergic structures on cortical electrical activity.

Finally, the EEG correlates of biological markers have been investigated in AD. Jelic et al. [86] found a positive correlation between levels of tau protein in the cerebrospinal fluid (CSF) and delta/alpha ratio. In a subgroup with high CSF tau levels, a strong relationship between EEG alpha/theta and alpha/delta power ratios was found. No such correlation was found in healthy controls and mildly cognitively impaired individuals with elevated CSF tau levels. ApoE 4 allele is a risk factor for late-onset AD and is proposed to have an impact on cholinergic function in AD.

The qEEG of 31 patients with AD was recorded at the early stage of the disease and after a 3-year followup. Patients with AD were divided into several subgroups according to the number of ApoE4 alleles, with a similar clinical severity and duration of dementia. The AD patients carrying the ApoE4 alleles had more pronounced slow-wave activity than AD patients without the ApoE4 alleles, although the disease progression rate did not change. These differences in EEG may suggest differences in the degree of the cholinergic deficit in these subgroups [87].

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Review Article

Electroencephalographic Rhythms in Alzheimer's Disease

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Physiological brain aging is characterized by synapses loss and neurodegeneration that slowly lead to an age-related decline of cognition. Neural/synaptic redundancy and plastic remodelling of brain networking, also due to mental and physical training, promotes maintenance of brain activity in healthy elderly subjects for everyday life and good social behaviour and intellectual capabilities. However, age is the major risk factor for most common neurodegenerative disorders that impact on cognition, like Alzheimer's disease (AD). Brain electromagnetic activity is a feature of neuronal network function in various brain regions. Modern neurophysiological techniques, such as electroencephalography (EEG) and event-related potentials (ERPs), are useful tools in the investigation of brain cognitive function in normal and pathological aging with an excellent time resolution. These techniques can index normal and abnormal brain aging analysis of corticocortical connectivity and neuronal synchronization of rhythmic oscillations at various frequencies. The present review suggests that discrimination between physiological and pathological brain aging clearly emerges at the group level, with suggested applications also at the level of single individual. The possibility of combining the use of EEG together with biological/neuropsychological markers and structural/functional imaging is promising for a low-cost, non-invasive, and widely available assessment of groups of individuals at-risk.

1. Introduction

Since its discovery and introduction, the electroencephalogram (EEG) was viewed with a great enthusiasm as the only methodology allowing a direct, online view of the "brain at work" [1]. The enormous complexity of the EEG signal should not surprise us since, the EEG is a direct correlate of brain function, and the brain is a complex system. So far, the EEG has been the most utilized signal to clinically monitor brain function. It offers appreciable promise as a means to characterize significant deviations from the "natural" aging found in Alzheimer and other dementias [2]. Since the 1970s, first with the introduction of structural imaging technologies such as computer-assisted tomography (CAT) and magnetic resonance imaging (MRI), and then with the development of regional metabolic-perfusion methods such as positron emission tomography (PET), single photon emission-computed tomography (SPECT), and the ability to map oxygen consumption and regional blood flow in specific neural locations with functional magnetic resonance imaging (fMRI), EEG has been supplanted in basic and clinical studies. These new techniques produce noninvasive views of in vivo brain anatomy with considerable resolution that contributed to their clinical and, therefore, economic utility. However, these functional brain imaging methods, despite their high spatial resolution for anatomical details, are relatively limited in their temporal resolution when measuring functional brain activation (seconds to minutes). Thus, these more recent neuroimaging techniques cannot discriminate the activation of different relays within a distributed network either in

series or in parallel [3]. Over the years, several improvements have been introduced to EEG measures in part, because neuroelectric signals can track information processing with millisecond precision. Therefore, even if the EEG is affected by the problem of low spatial resolution when compared to other techniques (e.g., fMRI and PET), its high temporal resolution makes it possible to highlight the mechanism of temporal synchronization of the cortical pyramidal neurons. Compared to fMRI and PET, the advantage of using EEG is the possibility to evaluate the physiological mechanisms of cortical neural synchronization at the basis of the emerging brain feature: brain oscillations.

It should be noted that a high temporal resolution is crucial for the study of an emerging property of brain activity, namely, the spontaneous and event-related oscillatory activity at different frequencies ranging at 2–4 Hz (delta), 4–8 Hz (theta), 8–13 Hz (alpha), 13–30 Hz (beta), and >30 Hz (gamma). Each of these frequencies conveys peculiar physiological information on brain functional state during sleep and wake periods.

Among the main purposes of modern neuroscientific research are the identification of patterns of neuronal activity underlying cognitive function and the finding of global functional indexes quick to be automatically computed towards clinical applications. It is, therefore, important to implement techniques that may measure natural brain aging and discriminate it from neurodegeneration [4, 5].

Recently, greater attention has been focused on the application of quantitative EEG (qEEG) and/or event-related potentials (ERPs) as suitable clinical markers of early stage of disease or its progression [6]. This is likely a result of recent improvements in the ease of the technology used and in the access to sufficient computing power and algorithms necessary for rapid processing of very complex raw datasets. Examples of recent technological advances include a reduction in the size (and portability) of EEG amplifiers and the development of high-density array nets that do not require skin abrasion to places with low impedance. It has been reported that a positive ERP peaking 600 ms after the zerotime of stimuli to be encoded (P600) was reduced in patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI), particularly in those MCI patients who subsequently converted to AD [7, 8]. Furthermore, a positive ERP peaking 300 ms after the zerotime of oddball stimuli (P300) was found reduced in patients with dementia [6]. Thus, there exist theoretical and empirical reasons for the application of ERPs as a measure of individual variation of cognitive function along pathological aging [9]. It has been shown that it is sensitive to Alzheimer's disease processes during its early stages [9]. However, recording of ERPs requires a peculiar setup between the stimulation device and EEG machine, about 40–60 minutes of time for the examination in the patient, and technicians able to carry out engaging experimental conditions. In this regard, recording of resting state EEG rhythms represents a procedure much easier and rapid that does not require stimulation devices.

The present paper outlines the impact of EEG techniques for the measurement of physiological and pathological brain aging and provides a comprehensive analysis of brain aging by the analysis of resting state EEG rhythms in elderly subjects with various degrees of cognitive decline. Its major goal is to highlight the emerging neurophysiological findings important to determine whether these techniques provide sufficient innovative and potentially useful information for the assessment of normal aging and dementia, both at the group- and at the single-subject levels.

Furthermore, it is to underline the practical utility of the EEG technique as global functional indexes quickly evaluable for automatic computation towards clinical applications.

2. Advanced EEG Techniques

Advanced EEG analysis techniques can illustrate changes in specific rhythms oscillating at various frequencies over time, provide quantitative measurements of individual rhythms, and reduce the effects of volume currents from far-field generators [10, 11]. Hence, EEG signals generated from extracerebral sources (e.g., electrocardiogram, electromyogram, electroretinogram, eye movement etc.) can be isolated from those produced by the brain, providing a direct measure of the recorded neuroelectric signals [11]. EEG coherence or synchronicity of rhythmic signals from separate electrodes, in different frequency bands, generated in different cortical areas, can also be measured.

The high-resolution EEG technique has markedly enhanced the spatial resolution of the conventional EEG from about 6–9 cm to 2-3 cm by the use of spatial enhancement methods such as Laplacian transformation with a regularized 3D spline function. This method reduces the low spatial EEG frequencies contributed by volume conduction and eliminates electrode reference influence [12–15]. Compared to other linear or nonlinear modelling analysis techniques of cortical sources of EEG-MEG, surface Laplacian estimation provides a rough representation of the neural currents without an explicit model of the generators (i.e., shape, number and location) by using a model of the head as a volume conductor [12, 13]. However, surface Laplacian methods cannot disentangle the activity of two spatially adjacent cortical zones such as primary somatosensory and motor areas that are contiguous across the central sulcus or deep cortical sources in secondary somatosensory and insular cortices. Surface Laplacian estimation is also unreliable when computed at the borders (i.e., temporo-parietal electrodes). Its maxima often overlie cortical sources of EEG potentials, since the influence of tangential relative to radial oriented generators is greater [12, 13, 16].

Spectral coherence analysis indexes the temporal synchronization of two EEG time series among electrodes in the frequency domain and permits characterization of linear functional corticocortical connectivity. EEG spectral coherence is a normalized measure of the coupling between two electroencephalographic signals at any given frequency [17, 18]. It is commonly interpreted as an index of functional coupling [19, 20], mutual information exchange [17], functional coordination [21], and integrity of cortical neural pathways [22]. Its basic theoretical assumption is that when the activity of two cortical areas is functionally coordinated,

the EEG rhythms of these cortical areas show linear correlation and high spectral coherence. In general, decreased coherence reflects reduced linear functional connections and information transfer (i.e., functional uncoupling) among cortical areas or modulation of common areas by a third region. In contrast, coherence increase is interpreted as augmented linear functional connections and information transfer (i.e., functional coupling), which reflects the interaction of different cortical structures for a given task. It has been repeatedly demonstrated that perceptive, cognitive, and motor processes are associated with enhanced EEG spectral coherence [23–26], as a function of the extension and type of the neural networks engaged [27, 28]. Finally, the direction of the information flow within the EEG rhythms between pairs of electrodes can be estimated by a directed transfer function (DTF) [29–34].

There are different methods to solve the noninvasive localization of the neuronal generators responsible for measured EEG phenomena (i.e., the source reconstruction of the electromagnetic brain scalp signals). Low-resolution electromagnetic tomography algorithm (LORETA) software, which can be freely downloaded by Internet (http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm), has been successfully used in recent EEG studies on pathological brain aging [35–40]. LORETA computes 3D linear solutions (LORETA solutions) for the EEG inverse problem within a 3-shell spherical head model including scalp, skull, and brain compartments [41–43].

LORETA solutions consisted of voxel z-current density values able to predict EEG spectral power density at scalp electrodes. As it is a reference-free method of EEG analysis, one can obtain the same LORETA source distribution for EEG data referenced to any reference electrode including common average. Furthermore, it can be also used from data collected by low spatial sampling (e.g., 19 electrodes) when cortical sources are estimated from resting EEG rhythms [44–47]. A normalization of the data was obtained by normalizing the LORETA current density at each voxel with the power density averaged across all frequencies (0.5–45 Hz) and across all voxels of the brain volume. After the normalization, the solutions lost the original physical dimension and were represented by an arbitrary unit scale. This procedure reduced intersubjects variability and was used in previous EEG studies [36–40].

3. Resting State EEG Rhythms and Physiological Aging

Resting state cortical EEG rhythms typically change across physiological aging, with gradual modifications in profile and magnitude of the spectra power; in detail, it was observed a marked amplitude decrease of alpha (8–13 Hz) and a global "slowing" of the background EEG, which increases in power and spatial distribution in the slower delta (2–4 Hz) and theta (4–8 Hz) rhythms [48–51]. A recent study in a large sample of healthy subjects ($N = 215$, 18–85 years) confirmed an age-dependent power decrement of posterior low-frequency alpha (alpha 1; 8–10.5 Hz) and delta rhythms [52].

Aging effects on parieto-occipital alpha rhythms presumably reflect the activity of dominant oscillatory neural network in the resting awaken brain. This activity is modulated by thalamocortical and corticocortical interactions facilitating/inhibiting the transmission of sensorimotor information and the retrieval of semantic information from cortical storage [27, 53, 54].

In the condition of awaken rest, alpha 1 frequency would be mainly related to subject's global attentional readiness [54–58]. Noteworthy, there is consensus that alpha rhythms represent the dominant resting oscillations of the adult, awaken human brain [54–58] and have been linked to intelligent quotient, memory, and cognition [51]. Whereas high-frequency alpha rythms reflect the oscillation of specific neural systems for the elaboration of sensorimotor or semantic information [50, 55, 56]. Over the course of "natural" aging, the power decrease of the occipital alpha rhythms might be associated with changes in the cholinergic basal forebrain system function, which sustain the excitatory activity in the cholinergic brainstem pathway [59].

Neuroelectric output does not scale linearly with inputs received. Therefore, that assessment of nonlinear EEG interactions is important, as this method can provide information on the strength, direction, and topography of the interdependencies. Spatial organization of nonlinear interactions between different brain regions has been investigated to compare anterior-posterior intrahemispheric and left-right interhemispheric interactions across physiological aging. Differences were found in the rates of interdependencies between the left prefrontal and the right parietal regions between young and elderly, suggesting that the aging brain engages the right parietal region to assist the pre-frontal cortex [60].

4. Resting State EEG Rhythms and Dementia

Dementia is one of the most frequent chronic diseases of the elderly, and it is characterized by loss of intellectual and behavioral abilities that interfere with daily functioning. Dementia incidence tends to increase with age affecting over 30% of people after age 85 [61, 62]. The elderly are the fastest growing segment of the population. Consequently, social costs for managing dementia are expected to rise becoming an important social problem. Furthermore, dementia profoundly affects the caregivers and family dynamics and relationships. Alzheimer's disease is the most common cause of dementia in geriatric patients.

Important neuropathological features indicating Alzheimer's dementia (AD) include brain cortical and subcortical atrophy leading to ventricular enlargements primarily due to neuronal loss in the temporal and parietal structures. Among the primary markers of Alzheimer's disease, microscopic signs including neurofibrillary tangles (intracellular aggregates of tau protein filaments) and amyloid plaques (extracellular aggregates of amyloid beta-peptides) that are dispersed throughout the cerebral cortex and basal ganglia, particularly concentrated in the hippocampus, entorhinal cortex, and postcentral parietal neocortex [63]. Tangles are

mainly found in hippocampal and parahippocampal limbic structures, whereas amyloid plaques are largely diffuse throughout the cortex [64]. A neurophysiological hallmark of brain aging is a progressive impairment of use-dependent synaptic plasticity and of synaptic connectivity between neurons and its association with the degree of dementia [65]. However, in preclinical conditions, plastic compensatory remodelling appears to continue that maintains neural function so that the neuronal and synaptic death can occur in the absence of dementia symptoms for an unknown period of time that might take for years or decades.

When compared to the resting state EEG rhythms of healthy normal elderly (Nold) subjects, AD patients showed an amplitude increase of widespread delta and theta sources and an amplitude decrease of posterior alpha (8–13 Hz) and/or beta (13–30 Hz) sources [35, 47, 66–69]. The observation of these abnormalities of the EEG rhythms could allow a discrimination among different dementia diagnoses for instance, a marked decline of posterior slow-frequency alpha power shows peculiar features in mild AD subjects when compared to cerebrovascular dementia, frontotemporal dementia and normal elderly subjects with similar cognitive impairment. Furthermore, pathological increased amplitude of the theta sources characterized cerebrovascular dementia patients [47].

These EEG abnormalities have been associated with altered regional cerebral blood flow/metabolism and with impaired global cognitive function as evaluated by MMSE [68, 70–72].

Of note, early stages of AD (even preclinical) are typically associated with slowing down of resting occipital alpha rhythms, namely, a decrease of the individual alpha frequency (IAF) peak in power density [73]. The IAF peak, defined as the frequency associated with the strongest EEG power at the extended alpha range [51], should be always taken into account in EEG studies in AD subjects, since power changes in theta and alpha bands might be dependent phenomena. Furthermore, the conventional partition of EEG power into many conventional frequency bands allows the comparison of the results with those of most of the field studies but may prevent the separation of independent EEG rhythms or sources.

Despite the evidence of abnormal cortical rhythms in MCI and AD, EEG analysis alone is unable to allow a diagnosis of disease. Additional biological parameters are needed for this purpose. In this regard, several studies have shown a strict relationship between genetic risk factors such as Apolipoprotein E $\varepsilon 4$ genotype (Apo-E $\varepsilon 4$) and late-onset AD. Apo-E $\varepsilon 4$ has been found to affect EEG rhythms in AD patients, it is associated with abnormalities of resting state EEG rhythms in AD [74–76] with relatively specific EEG measures. Compared to AD patients with $\varepsilon 2$ and $\varepsilon 3$, AD patients with $\varepsilon 4$ showed higher theta and lower beta spectral power [75]. Furthermore, the AD ApoE $\varepsilon 4$ carriers patients were characterized by higher theta power and lower beta power at baseline, whereas they were characterized by higher delta power and lower alpha power at 3 years at followup [76]. Moreover, AD patients with ApoE $\varepsilon 4$ has been related to selective decrease in functional corticocortical connectivity, which was suggested by the reduction of right and left temporoparietal, right temporofrontal, and left occipitoparietal alpha EEG coherence [74]. Thus, genetic risk factors for AD is combined with relatively specific EEG measures.

EEG power per se does not capture one of the main features of AD, namely, the impairment of functional neural connectivity. It has been reported that AD patients present a reduced linear coupling of resting state EEG rhythms among cortical regions, as revealed by spectral EEG coherence [22, 74, 77–80], suggesting a linear temporal synchronicity of coupled EEG rhythms from simultaneously engaged neural sources. Such findings imply that functional coupling of cortical rhythms at certain frequency bands might be interesting features of AD and that abnormality of cortical EEG coherence may be a fine-grained marker of AD, which is supposed to reflect a disease of cerebral networks subserving global cognition. It could be speculated that this impaired pattern of EEG functional coupling is modulated by cholinergic systems and that a decrease of cortical EEG coherence is characterized by defective basal forebrain cholinergic inputs to cortex and hippocampus [81].

Most EEG studies of AD have reported a prominent decrease of alpha band coherence [22, 65, 74, 77–80, 82–85] This result also has been found to be associated with ApoE genetic risk, which is hypothesized to be mediated by cholinergic deficit [74]. However, delta and theta band coherence changes in AD are not homogeneous, as some studies demonstrate contradictory results with either a decrease or an increase of slow-band EEG coherence [22, 79, 82, 86]. These conflicting results might be due to the use of coherence markers from single electrode pairs rather than for the "total coherence" as obtained averaging the EEG spectral coherence across all combinations of electrode pairs. The latter may better take into account frequency band-by-frequency band the global impairment of brain networks and cognition along the AD process, which is supposed to be a disease affecting the functional integration within cerebral neural networks subserving cognition. In a recent study [87], the results show that the delta total coherence is higher in the AD than in the MCI and in the MCI than in the Nold group. Furthermore, the alpha1 total coherence is lower in the AD group than in the MCI and Nold groups. This evidence confirms that the functional coupling of resting EEG rhythms is progressively abnormal in amnesic MCI and AD subjects.

To improve the functional coupling evaluation, EEG and MEG data have been analyzed with procedures inspired by the theory of nonlinear dynamics, which provides a measure of signal dynamic coordination [88]. It is shown that AD patients generate a nonlinearly defined dimensional "complexity" of the EEG, which is a measure of signal dynamic coordination. The AD patients have significantly lower dimensional complexity of EEG than age-approximated non-demented controls. Thus it may be associated with deficient information processing in the brain injured by AD. Brain rhythms loose the usual modulation in complexity as observed by eyes-open versus eyes-close comparisons, as a reflection of neuronal death, deficiency in neurotransmission, and/or loss of connectivity in local neuronal networks [89, 90]. Nonlinear analysis has also been used to model

brain flexibility in information processing, defined as the capability to affect state of information processing from identical initial conditions. AD patients show a decrease in information processing flexibility, such that EEG complexity decrease in AD might be attributable to decreased nonlinear dynamics that are associated with cognitive decline. Among the techniques for nonlinear brain dynamics, synchronization likelihood combines sensitivity to linear and nonlinear functional coupling of EEG/MEG rhythms [88]. This measure has been shown to be significantly decreased at alpha and low beta bands when comparing AD to MCI and/or Nold subjects [23, 91–93].

In addition to the corticocortical uncoupling progression, a decrease of synaptic coupling is likely to contribute to reducing selective EEG coherence for faster rhythms, as observed in healthy humans by transient use of a cholinergic synaptic blocker like scopolamine [94]. Animal models suggest that acetylcholine loss produces a decrease of high-frequency EEG couplings and an increase of slow-frequency couplings [95]. Loss or a significant drop in EEG synchronization in faster rhythms has also been correlated with decreased MMSE scores in MCI and AD patients [88]. Linear and Nonlinear EEG analyses improve classification accuracy of AD compared to unaffected controls, and these methods correlate with disease severity [23, 88, 91].

Few studies have assessed EEG measures over the course of dementia progression. A significant increase of delta and theta power in conjunction with decrease of alpha and beta power over a period of 30 months from diagnosis have been found [96]. The length of the followup is of paramount importance and indicates the reason for a lack of findings over a 12-month period [97]. The major question in this context is "Which is the physiological mechanism at the basis of abnormal resting brain rhythms in MCI and AD?" Abnormality of resting EEG rhythms may originate from impairment in the cholinergic neural projections from basal forebrain, which is a pivotal aspect of AD [98]. Resting EEG alpha power is decreased from experimental damage to this cholinergic pathway [99]. Furthermore, the cholinergic basal forebrain has been found to be responsive to the treatment with cholinesterase inhibitors more for AD than other dementias [100]. Conversely, brainstem cholinergic innervations of the thalamus are relatively spared in AD patients [98]. Long-term (1 year) treatments of acetylcholinesterase inhibitors (AChEI) demonstrate less temporal and occipital alpha reduction for responders compared to nonresponders and a combined effect on delta and low alpha [37, 101]. Hence, increasing cholinergic tone was related to restoring temporal and occipital alpha rhythms in responders. Brain cholinergic systems also appear to improve primarily cerebral blood flow with a functional impact on attentional and memory functions [102].

5. Resting State EEG Rhythms and Mild Cognitive Impairment

Assessing preclinical dementia is of keen interest as a clinical research issue, since MCI often precedes frank dementing illness. As the selective cognitive impairments characteristic of MCI are primarily memory-related and not severe enough to exceed standard clinical criteria for AD, their prodromal qualities do not greatly impair daily functioning and can be identified by refined clinical and neuropsychological evaluation. Consistent MCI symptoms 3–5 years following their identification either remain stable or decrease in 30%–50% of the cases, whereas the remaining cases progress toward a frank AD condition or, less frequently, to other dementias. The MCI condition has often been considered a precursor of AD despite the fact that not all the MCI patients develop the Alzheimer disease. Epidemiological and clinical followup studies confirm that MCI reflects a transition state towards mild AD and prompts the idea that early identification of MCI patients can facilitate rehabilitative or pharmacological interventions to slow down the disease progression [103–105]. Figure 1 illustrates MCI effects for low-frequency alpha (8–10.5 Hz) activity from parietal, occipital, and limbic areas that demonstrate an intermediate magnitude in MCI compared to mild AD and normal elderly [38]. Increase of slow EEG power coupled with a decrease in alpha activity is linked to cognitive performance decline in MCI compared to Nold. More important, the spectral magnitude of these sources is correlated negatively with MMSE scores across subjects of the three groups, suggesting that EEG evidence of alpha power decrease in MCI compared to normal subjects is related to behavioral cognition [66, 84, 106–109]. The relative spectral magnitude decrease of posterior low-frequency alpha sources in MCI may be related to an initial selective impairment of the cholinergic basal forebrain, which could induce a sustained increase of the excitatory activity in the cholinergic brainstem pathway [59, 94, 95]. TMS studies indicate that the cortex of AD patients is hyperexcitable and that such hyperexcitability even may offer clues for the differential diagnosis from other dementias in which the cholinergic deficit is not predominant.

As a consequence, the increased excitability of thalamocortical connections would desynchronize the resting alpha rhythms and enhance the cortical excitability.

Hence, changes of low-frequency alpha power in MCI and mild AD suggest a progressive impairment of the thalamocortical and corticocortical systems that govern visual attention. This hypothesis is consistent with clinical findings of increasing deficits of visuospatial abilities in MCI and mild AD [110]. Similarly, limbic sources imply a progressive impairment of thalamocortical and corticocortical systems regulating attention tone for memory functions.

Decreases in corticothalamic modulation and increase of slow EEG rhythms correlated to progressive cortical hypoperfusion have been found in AD [72, 111]. Abnormal delta and alpha sources in the posterior brain regions could, therefore, index the progressive decline of cognitive visuospatial functions across MCI and mild AD thereby supporting a transition between these conditions [103–105]. An intriguing aspect includes the peculiar magnitude increase of the parieto-occipital high-frequency alpha sources (alpha 2, 10.5–13 Hz) in MCI compared to mild AD and normal elderly [38]. Furthermore, prospective studies have demonstrated that increased delta/theta activity,

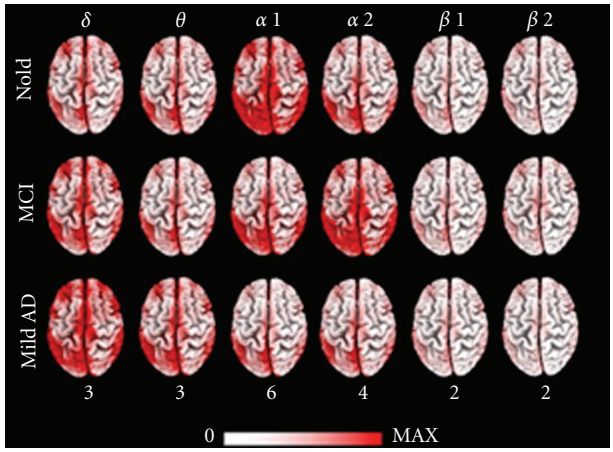

Figure 1: Grand average of low-resolution brain electromagnetic source tomography (LORETA) solutions (i.e., normalized relative current density at the cortical voxels) modeling the distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1 (13–20 Hz), and beta 2 (20–30 Hz) bands in normal elderly (Nold), mild cognitive impairment (MCI) and mild Alzheimer's disease (AD) groups. The left side of the maps (top view) corresponds to the left hemisphere. Legend: LORETA, low-resolution brain electromagnetic tomography. Color scale: all power estimates were scaled based on the averaged maximum value (i.e., alpha 1 power value of occipital region in Nold). The maximal value of power is reported under each column.

decreased alpha and beta, and slowed mean frequency may be predictors of progression from MCI to dementia [66, 84]. These findings imply that neuroelectric indices could be developed for the preclinical assessment of dementia, as their acquisition are inexpensive, easily implemented, entirely non-invasive, and very well suited for large-scale screening and followup of at-risk populations. The hypothesis that presence of ApoE $\varepsilon 4$ affects sources of resting EEG rhythms in MCI and AD was assessed in 89 MCI with 34.8%$\varepsilon 4$ incidence and 103 AD with 50.4%$\varepsilon 4$ incidence [112]. Alpha 1 and 2 sources in occipital, temporal, and limbic areas were of lower amplitude in subjects carrying the ApoE $\varepsilon 4$ allele. For AD homozygous for ApoE $\varepsilon 4$ allele, abnormal temporo-parietal and occipitoparietal EEG or MEG rhythms were found [74, 88]. However, in addition to ApoE $\varepsilon 4$ allele, another important genetic risk factor for late-onset AD is haplotype B of CST3 (the gene coding for cystatin C—a neurotrophic protein), which was investigated to establish eventual links with cortical rhythmicity [113]. EEG measures were obtained from 84 MCI with 42% B haplotype and 65 AD with 40% B haplotype. Slow alpha (from parietal, occipital, and temporal areas) and fast alpha (from occipital areas) power were statistically lower in CST3 B carriers. A trend was observed for occipital delta power sources as stronger in CST3 B carriers than in noncarriers for both MCI and AD patients.

Association between the presence and amount of hippocampus atrophy in AD and MCI subjects and changes in sources of posterior slow rhythms have been observed by EEG and whole-head MEG [114–116]. Less known is the relationships between impairment of white matter and slow rhythms across the continuum from MCI to AD. This issue has been addressed with EEG assessments in MCI ($N = 34$) and AD ($N = 65$) cases [36]. Delta activity was related to the amount of cortical atrophy revealed by MRI voxel-to-voxel volumetry of lobar brain volume (white and gray matter) such that as delta power increased, brain volume decreased. Thus, changes in brain structure and function could be found for MCI and AD patients.

As life expectancy and elderly populations in Western countries are increasing, the incidence of MCI that may predict AD or vascular dementia is rising. Cognitive impairment associated with MCI or AD is associated with decreased power and coherence in the alpha/beta band, at least at the group level. This observation suggests the occurrence of a functional disconnection among cortical areas, since both power and coherence in the delta and theta bands increase with cortical deafferentiation from subcortical structures [117]. However, the extent to which features of neuroelectric activity can be used to predict the conversion from MCI to AD in single subjects is as yet unclear. In a seminal EEG study, a multiple logistic regression of theta power (3.5–7.5 Hz), mean frequency, and interhemispheric coherence has been able to to predict decline from MCI to AD at long term for with an overall predictive accuracy of about 90% [118]. Furthermore, spectral EEG coherence or other EEG features have shown to contribute to the discrimination of Nold from mild AD with 89%–45% of success, from MCI to AD with 92%–78% of success, and the conversion of MCI subjects to AD with 87%–60% of success [66, 79, 84, 119–124]. These findings are encouraging for future development of this prognostic and perhaps diagnostic approach [125].

Rossini et al. [106] investigated whether combined analysis of EEG power and coherence provide early and reliable discrimination of MCI subjects who will convert to AD after a relatively brief followup. Cortical connectivity using spectral coherence measures and LORETA was evaluated to characterize EEG sources at baseline in 69 MCI cases that were reassessed clinically after about 14 months. At followup, 45 subjects were classified as stable MCI (MCI Stable), whereas the remaining 24 had converted to AD (MCI Converted). Results showed that at baseline, frontoparietal midline coherence as well as delta (temporal), theta (parietal, occipital, and temporal), and low-frequency alpha (central, parietal, occipital, temporal, and limbic) sources were stronger in MCI converted than MCI stable subjects. Cox regression modeling showed low midline coherence, and weak temporal source was associated with 10% annual rate AD conversion, while this rate increased up to 40% and 60% when strong temporal delta source and high midline gamma coherence were observed, respectively. This outcome indicates that quantitative EEG is able to predict with a good approximation MCI progression to AD in the short run.

6. Conclusions

The present paper highlights the use of modern EEG techniques that report assessment of physiological and pathological brain aging. Application of these techniques allows

the quantification of the power and functional coupling of resting state EEG rhythms at scalp electrodes and mathematical cortical sources. The results reviewed in the present paper suggest that these quantitative indexes of resting state EEG rhythms might reflect neurodegenerative processes along preclinical and clinical stages of AD. Moreover, risk factors including genetic causes correlate with neurophysiological findings to reinforce their causative role in diagnosis and prognosis of pathologic brain aging. Unfortunately, this remarkable literature suffers from the partial lack of integration of various EEG techniques such as analysis of power density and functional coupling (i.e., spectral coherence, and directed transfer function) within a unique frame of goal-directed test for evaluation of physiological brain aging and discrimination from abnormal scenarios heralding neurodegeneration. In the near future, systematic evaluation of AD and other dementing disorders relative to normal aging using refined and integrated EEG techniques will help to coalesce these methodologies and improve diagnostic utility. If this approach can provide clinically useful information at the individual level, such methods should prompt design of an instrument widely available for large-scale population-based screening studies. Future studies should find which are qEEG markers for early diagnosis, prognosis, and monitoring of Alzheimer disease and explore the clinical utility of this methodological approach. The global structural and functional indexes are quick to be automatically computed towards clinical applications.

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Research Article

Slowing and Loss of Complexity in Alzheimer's EEG: Two Sides of the Same Coin?

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Medical studies have shown that EEG of Alzheimer's disease (AD) patients is "slower" (i.e., contains more low-frequency power) and is less complex compared to age-matched healthy subjects. The relation between those two phenomena has not yet been studied, and they are often silently assumed to be independent. In this paper, it is shown that both phenomena are strongly related. Strong correlation between slowing and loss of complexity is observed in two independent EEG datasets: (1) EEG of predementia patients (a.k.a. Mild Cognitive Impairment; MCI) and control subjects; (2) EEG of mild AD patients and control subjects. The two data sets are from different patients, different hospitals and obtained through different recording systems. The paper also investigates the potential of EEG slowing and loss of EEG complexity as indicators of AD onset. In particular, relative power and complexity measures are used as features to classify the MCI and MiAD patients versus age-matched control subjects. When combined with two synchrony measures (Granger causality and stochastic event synchrony), classification rates of 83% (MCI) and 98% (MiAD) are obtained. By including the compression ratios as features, slightly better classification rates are obtained than with relative power and synchrony measures alone.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia; it is the sixth leading cause of death in the United States. More than 10% of Americans over age 65 suffer from AD, and it is predicted that the prevalence of AD will triple within next 50 years [1–3]. Currently, no known medicine exists for curing AD, but a number of medications are believed to delay the symptoms and the causes of the disease.

The progression of AD can be categorized into three different stages: mild, moderate, and severe AD; there is also a stage known as Mild Cognitive Impairment (MCI) or predementia, that characterizes a population of elderly subjects who are not compromised in their daily living, but have a subclinical and isolated cognitive deficit and are potentially at risk of developing Alzheimer's disease [4–6]. Around 6% to 25% of people affected by MCI progress to AD. MCI may develop into mild AD and next moderate AD; in those stages, cognitive deficits become more severe, and the patients become more dependent on caregivers. In the final stage known as severe AD, the personality of patients may change dramatically, and patients are entirely dependent on caregivers [7].

Table 1: Overview of statistical measures: relative power, Lempel-Ziv complexity, and lossless compression ratio.

Measure	Description	References
Relative power	Power within specific EEG frequency band normalized by total power	[12]
	Frequency bands: 0.5–4 Hz (delta), 4–8 Hz (theta), 8–10 Hz (alpha 1), 10–12 Hz (alpha 2), 12–30 Hz (beta)	
Lempel-Ziv complexity	Number of different patterns present in an EEG signal (complexity measure)	[13]
Lossless compression ratio	Reduction of the size of EEG data after lossless compression (regularity measure)	[14, 15]
	Compression algorithms considered here: 1D SPIHT, 2D SPIHT, and 2D SPIHT followed by arithmetic coding	

Diagnosing MCI and Mild Alzheimer's disease is hard, because most symptoms are often dismissed as normal consequences of aging. To diagnose MCI or mild AD, extensive testing is required, to eliminate all possible alternative causes. Tests include psychological evaluations such as Mini-Mental State Examination (MMSE), blood tests, spinal fluid, neurological examination, and imaging techniques [8, 9].

Several research groups have investigated the potential of electroencephalograms (EEGs) for diagnosing AD in recent years. Since EEG recording systems are nowadays relatively inexpensive and mobile, EEG may potentially be used in the future as a tool to screen a large population for the risk of AD, before proceeding to any expensive imaging or invasive procedures. To date, however, EEG does not have sufficiently high specificity and sensitivity to assume the role of reliable and reproducible method of screening AD.

In recent years, several studies have shown that AD has at least three major effects on EEG (see [10, 11] for an in-depth review): slowing, reduced complexity, and loss of synchrony. However, these effects tend to vary across patients, which makes diagnosis of AD a difficult task. Many recent studies are devoted to improving the sensitivity of EEG for diagnosing AD. We refer to [11] for a detailed review on various EEG statistics that have been used in this context.

In this paper, we investigate the relation between slowing and reduced complexity in AD EEG. Those two phenomena are often silently assumed to be independent. However, since low-frequency signals are more regular than signals with high-frequency components, one would expect that slowing and reduced complexity in AD EEG are strongly related to each other. Nevertheless no study so far has analyzed the relation between both phenomena on a statistical basis though.

In order to investigate the slowing effect in AD EEG, we compute relative power in the standard EEG frequency bands (see Table 1). When relative power is larger than usual in low-frequency bands (delta and/or theta), it is said that the EEG is "slower" and that "EEG slowing" occurs. We quantify the irregularity of EEG by a standard measure, that is, Lempel-Ziv complexity (see Table 1). We also apply several lossless compression algorithms to the EEG, and we use the resulting compression ratios (reduction in data size after compression) as regularity measures (see Table 1). Regular signals are more compressible than irregular signals, and therefore, they result in larger compression ratios; as a consequence, compression ratios are a measure of the regularity of signals.

We consider two EEG datasets: (1) EEG of predementia patients (a.k.a. Mild Cognitive Impairment; MCI) and control subjects; (2) EEG of mild AD patients and control subjects. The two datasets are from different patients, different hospitals and obtained through different recording systems.

We will show that the theta band (θ) relative power is significantly larger in both groups of patients compared to age-matched control subjects and that the lossless compression ratios are significantly larger in MiAD patients than in the age-matched control subjects; however, no significant perturbation of Lempel-Ziv complexity and the lossless compression ratios is observed for the MCI patients. Interestingly, our numerical analysis will reveal strong correlation between theta relative power on the one hand and Lempel-Ziv complexity and the lossless compression ratios on the other hand; in other words, the effects of slowing and loss of complexity in AD EEG seem to be significantly coupled, at least in the two EEG datasets at hand.

The paper is structured as follows. In Section 2 we explain how relative power of EEG may be computed. In Section 3, we describe the Lempel-Ziv complexity measure and the lossless compression schemes used in this study. In Section 4 we discuss the two EEG datasets, and in Section 5 we present our results. We provide concluding remarks and topics of future research in Section 6.

Readers who are not interested in the technical and mathematical details of our data analysis may skip Sections 2 and 3 and may directly proceed to Section 4.

2. Relative Power of EEG

The spectrum of EEG is helpful in describing and understanding brain activity. The EEG spectrum is commonly divided in specific frequency bands: 0.5–4 Hz (delta), 4–8 Hz (theta), 8–10 Hz (alpha 1), 10–12 Hz (alpha 2), 12–30 Hz (beta), and 30–100 Hz (gamma) [12]. Neurological diseases, including MCI and AD, often affect the EEG spectrum. Many studies have shown that MCI and AD cause EEG signals to "slow down" (see [11] and references therein), corresponding to an increase of power in low-frequency bands (delta and theta band, 0.5–8 Hz) and a decrease of power in higher-frequency bands (alpha and beta, 8–30 Hz).

The EEG spectrum can be computed by means of the Discrete Fourier Transform (DFT) of the EEG [11]. The DFT

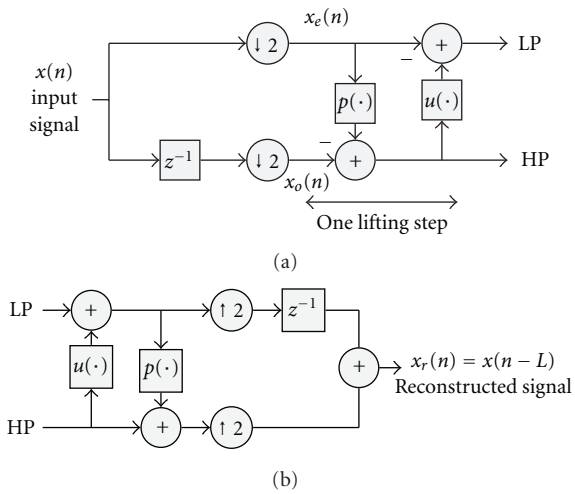


Figure 1: Wavelet transform realization via lifting scheme (a) Forward transformation. (b) Inverse transformation. The boxes labeled by z^{-1} stand for delays (over one sample). The boxes ↓ 2 and ↑ 2 represent downsampling and upsampling by a factor of two, respectively; in the latter a zero is inserted after every sample, whereas in the former, every second sample is removed. The lifting scheme repeats two primitive steps: prediction p and update u.

$X(f_n)$ of the sequence x is usually computed at multiples f_n of $f_T = 1/T$, where T refers to the length of the signal. For computational convenience, the length of the sequence x is often extended to the nearest power of two by zero padding. As in [11], let us consider an example with $T = 20$ s and the sampling frequency 200 Hz, then DFT is computed at 0 Hz, 0.05 Hz, 0.1 Hz,...,200 Hz. The Nyquist theorem states that only one half the spectrum is of interest, while the other half is the mirror image of the first half; hence for the above example, it is enough to retain the DFT values at 0 Hz, 0.05 Hz, 0.1 Hz,...,100 Hz. The DFT values $X(f_n)$ are complex, and we are mostly interested in their absolute magnitude $|X(f)|$. The relative power of a frequency band is computed by summing $|X(f_n)|$ over the frequencies f_n in that band and next by dividing the resulting intraband sum by the sum of $|X(f)|$ over all DFT frequencies f_n.

3. Complexity Measures

A variety of complexity measures have been used to quantify EEG complexity, stemming from several areas ranging from statistical physics to information theory. We refer to [11] for more information. Earlier studies have reported that the EEG of MCI and AD patients seems to be more regular (i.e., less complex) than in age-matched control subjects. It is conjectured that due to MCI/AD-induced loss of neurons and perturbed anatomical and/or functional coupling, fewer neurons interact with each other, and the neural activity patterns and dynamics become simpler and more predictable.

As mentioned earlier, we quantify EEG complexity by a standard measure, that is, Lempel-Ziv complexity. In addition, we use lossless compression ratios as regularity measures. In the following, we describe Lempel-Ziv complexity, and next we elaborate on lossless compression and its use as measure for regularity.

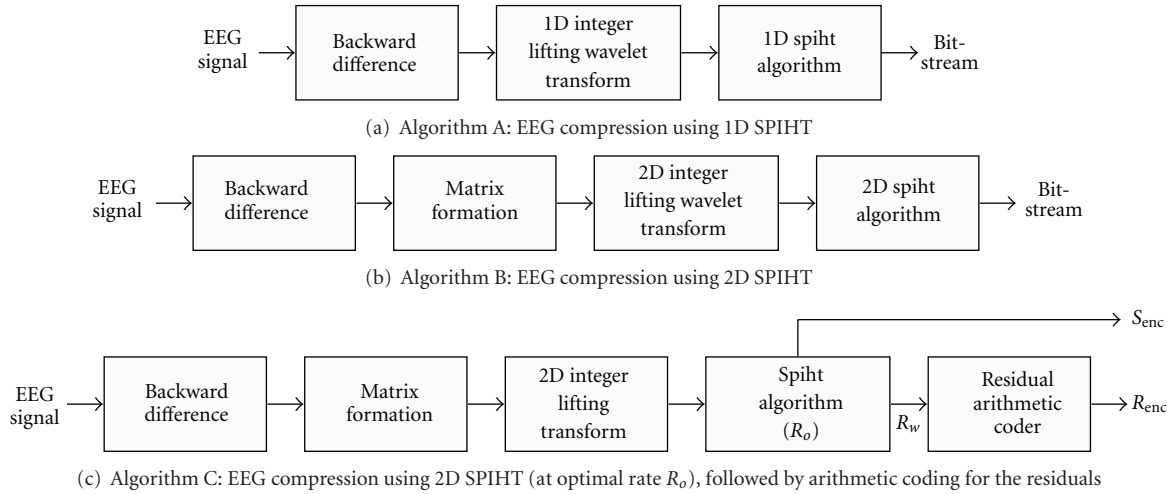
3.1. Lempel-Ziv (LZ) Complexity. The Lempel-Ziv complexity measure (LZ complexity) computes the number of different patterns present in a sequence of symbols [13]; if the number of different patterns is large, the sequence is complex and hence difficult to compress. LZ complexity is obtained by dividing the number of different patterns by the maximum complexity of a sequence of length N. For more details we refer to [16].

To compute LZ complexity, the time series is first reduced to a symbol list. For the sake of simplicity, we convert the EEG signals into binary sequences $s = s(1), s(2), \ldots, s(N)$, where $s(i) = 0$ if $x(i) < T_d$ and $s(i) = 1$ otherwise; that approach was also followed in [16]. The threshold T_d is chosen as the median of x, since the latter is robust to outliers.

3.2. Lossless Compression Algorithms. In this section, we briefly explain the lossless compression algorithms applied in this study (see Figure 2); we will consider three different algorithms, which were all proposed in [14, 15]. The aim of compression is to reduce the size of a given data source (e.g., EEG data). In lossless compression (e.g., ZIP compression algorithm), no information in the original data source is lost after compression, in contrast to lossy compression, where the original can only approximately be constructed after compression (e.g., JPEG compression algorithm for images).

Biomedical signals such as EEG often have a *decaying* spectrum: the energy is mostly concentrated at low frequencies, and it decays with increasing frequency. Therefore, the spectral components are close to zero at high frequencies; the same holds for coefficients in the time-frequency representation corresponding to high frequencies. To exploit this phenomenon, compression algorithms often subject the given data source to a transform (e.g., time-frequency transform), which results in an alternative representation of the data. The three algorithms used in this study all map the signals into another domain, that is, time-frequency domain; the sparseness of the time-frequency representation is then exploited to form a compact code. We now briefly outline the compression process (see Figure 2). First the EEG signal is *preprocessed*, that is, the DC component (average value of EEG signal) is removed by applying backward difference; the resulting zero-mean signal is then arranged as a 1D vector (see Figure 2(a); Algorithm A) or 2D matrix (see Figures 2(b) and 2(c); Algorithms B and C). The resulting structure is then decomposed into different frequency bands via *integer lifting wavelet transform*, which maps the signals to integers on several time scales; at last, a *set partitioning* coding scheme converts the (integer) wavelet coefficients into a compact representation. In the following sections we describe those different steps in more detail, and then we elaborate on the differences between the three algorithms (Algorithms A, B, and C).

3.2.1. Backward Difference. First the EEG signal x is *preprocessed*, that is, the DC component (average value of EEG



(a) Algorithm A: EEG compression using 1D SPIHT

(b) Algorithm B: EEG compression using 2D SPIHT

(c) Algorithm C: EEG compression using 2D SPIHT (at optimal rate R_o), followed by arithmetic coding for the residuals

Figure 2: Lossless EEG compression algorithms apply wavelet transforms followed by Set Partitioning in Hierarchical Trees (SPIHT).

signal) is removed; this is performed via *backward difference* operation

$$\tilde{x}(n) = x(n) - x(n-1), \tag{1}$$

where $\tilde{x}(n)$ is the signal obtained by applying the backward difference. Next the EEG is arranged as a vector of size N (1D compression) or as a matrix of size $N \times N$ (2D compression); the latter matrix is filled starting at the top left-hand side, from left to right on the odd rows, and from right to left on the even rows. In matrices, each entry has 8 nearest neighbors (except for entries in the first/last row/column), compared to two nearest neighbors in vectors (except for first and last entries). In the present application, neighboring entries are adjacent EEG samples, which are highly correlated [14]. By leveraging on the additional nearest neighbors (8 instead of 2), 2D compression often yields better compression ratios than 1D compression [14].

3.2.2. Lifting Wavelet Transform. A wavelet transform decomposes a given signal into different frequency bands; it allows to represent the signal in multiple resolutions (coarse to fine) [17]. Wavelets are usually realized by a set of filters, operating in parallel ("filter banks"). An alternative method of realizing wavelets is a *lifting scheme* [18], which consists of a cascade of simple filters; it may be viewed as the factorization of a filter bank into elementary filters. One such simple filter is depicted in Figures 1(a) and 1(b)). The former shows the forward lifting transformation; the signal x is first split into *odd* and *even* phases x_o and x_e, respectively, containing the odd and even samples, respectively, of input signal x. The odd and even phases contain adjacent samples; in natural signals such as EEG, adjacent samples are highly correlated. Therefore, the odd phase may be predicted from the even phase (and vice versa). By subtracting the prediction $\hat{x}_o = p(x_e)$ from the odd phase, we are left with a high-frequency residue signal (HF) of the odd phase. The latter is used in another lifting step, to predict the even phase x_e ("update" u); the resulting prediction is subtracted from the

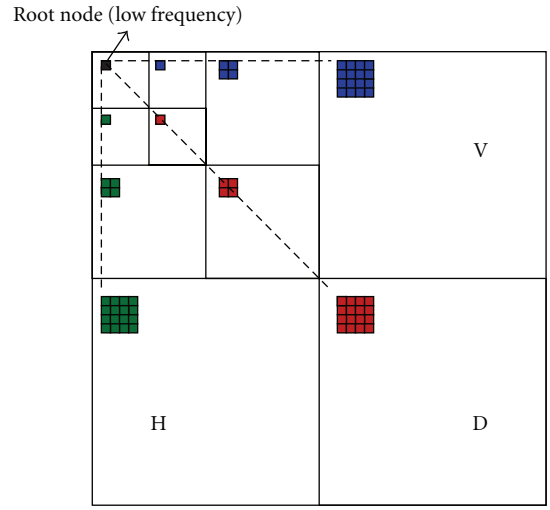


Figure 3: Wavelet decomposition of the 2D matrix and associated tree-based set originating from the low-frequency band. The root node (black) branches towards horizontal, vertical, and diagonal higher-frequency bands (H, V, D).

even phase x_e, which leaves the low-frequency component (LF) of the even phase x_e; this also ensures the complete frequency separation between an LF and HF component. The forward transform of Figure 1(a) is easily invertible by reversing the steps and flipping the signs (see Figure 1(b)). We implement the prediction p and update u by means of the widely used biorthogonal 5/3 filter [19], as we did in our previous study on EEG compression [15].

In a lifting scheme, the pair of lifting steps, that is, prediction p and update u, is repeated several times, leading to multiscale representation of the input signal x ("wavelet"); the nature and number of lifting steps p and u depend on the type of wavelets [18]. Integer wavelet transforms can easily be realized by systematic rounding and truncation of the intermediate results, that is, output of p and u [20].

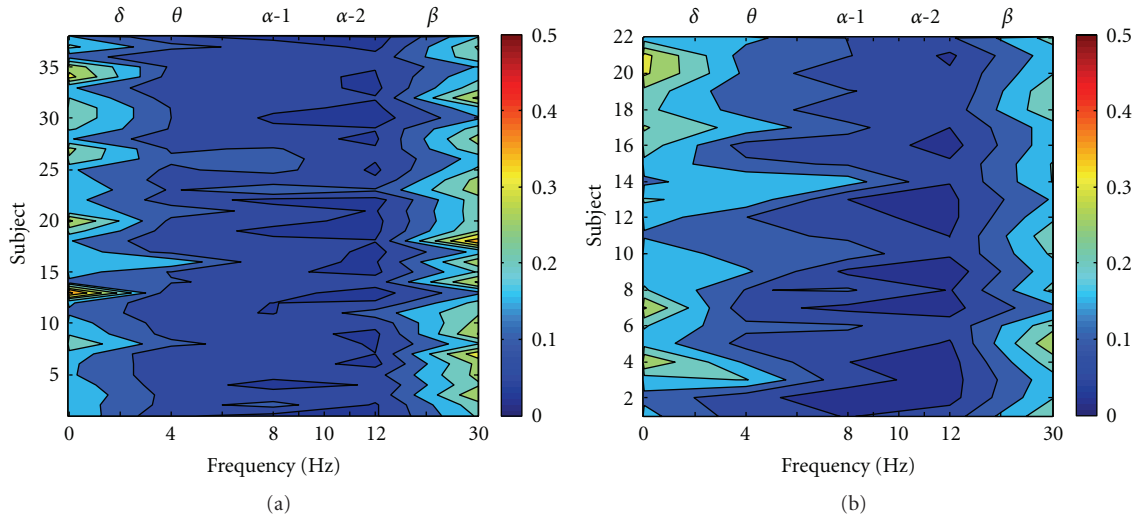


Figure 4: Relative power distribution in various frequency bands for all the datasets. (a) Control group. (b) Mild cognitive impaired subjects.

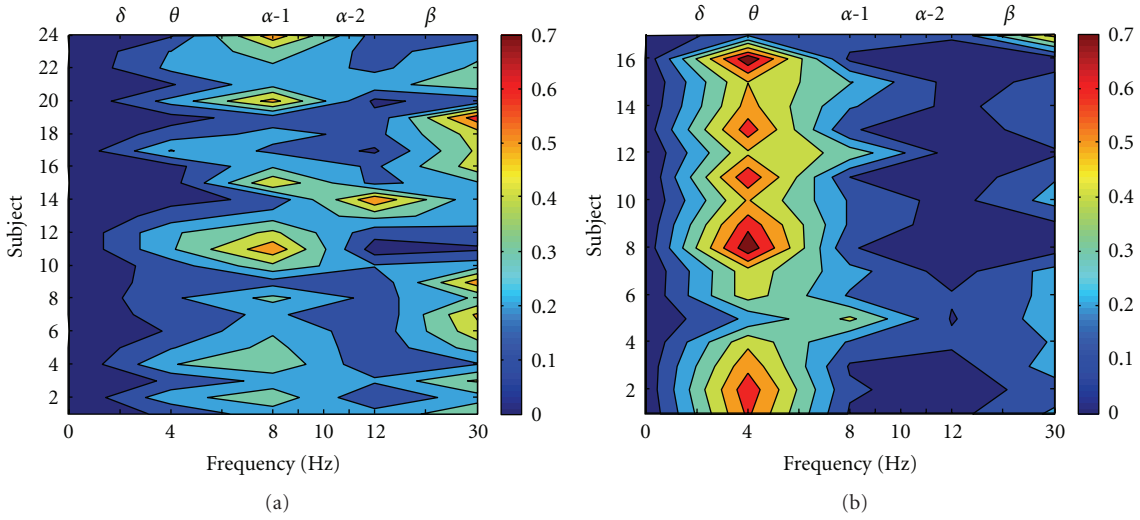
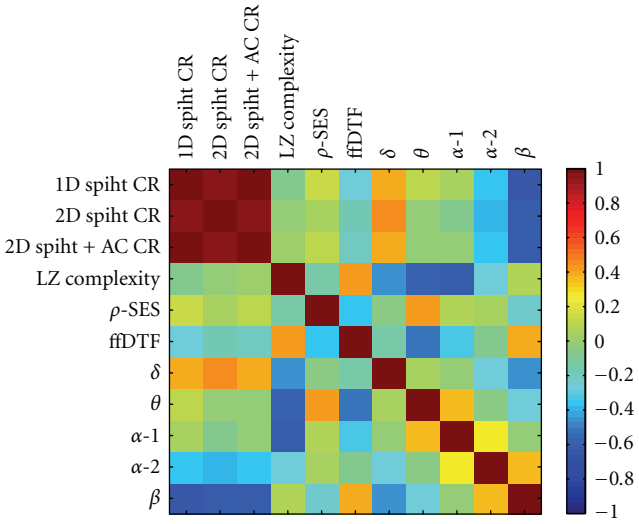


Figure 5: Relative power distribution in various frequency bands for all the datasets. (a) Control group. (b) Mild Alzheimer's disease subjects.

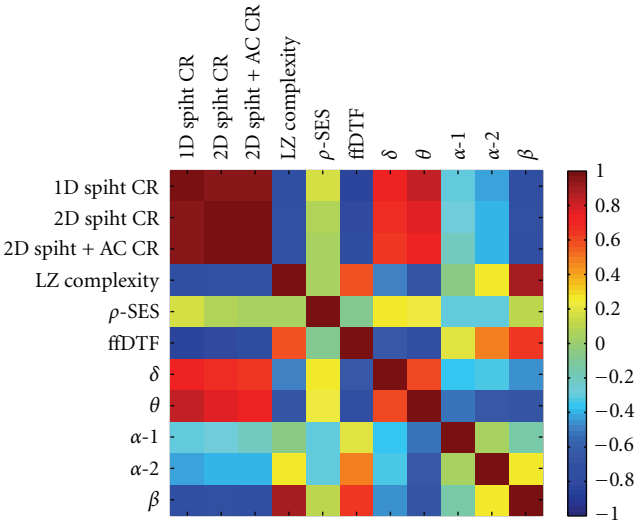
The lifting wavelet transform provides a sparse, multiresolution representation, that is well suited for effective compression (e.g., by means of SPIHT, to be explained in next section); *integer* lifting in particular enables convenient and simple implementations of lossless compression.

3.2.3. Set Partitioning in Hierarchical Trees Algorithm (SPIHT). As the last step in the process, the wavelet-transformed signals are compressed. We use a widely known wavelet-based compression scheme, that is, *Set Partitioning in Hierarchical Trees* (SPIHT) [21]. The underlying idea is *set partitioning*: sets of samples are recursively split, guided by a series of threshold tests. This approach is particularly well suited for wavelet-transformed data, as wavelet coefficients are naturally clustered. In SPIHT the sample sets are non-overlapping, and they are organized by means of a tree each set is rooted in a subset of low-frequency coefficients, and branches successively to subsets of high-frequency coefficients in the same orientation (see Figure 3). The search for coefficients associated with a particular threshold usually starts at the root node and proceeds successively towards the leaves of the tree, until all significant coefficients are listed. Such tree-based search, starting at coarse resolution at the root and ending with the finest resolution at the leaves, results in output signals of increasing quality and resolution.

The integer wavelet transform, in conjunction with SPIHT, yields a quality and resolution scalable bitstream: the quality and resolution of the signal improve as bitstream progresses. This is a very desirable property for real-time applications. Moreover, the output bitstream is embedded: the bitstream can be truncated at any point to approximately reconstruct the signal. When the bitstream is fully decoded, we obtain a lossless representation.

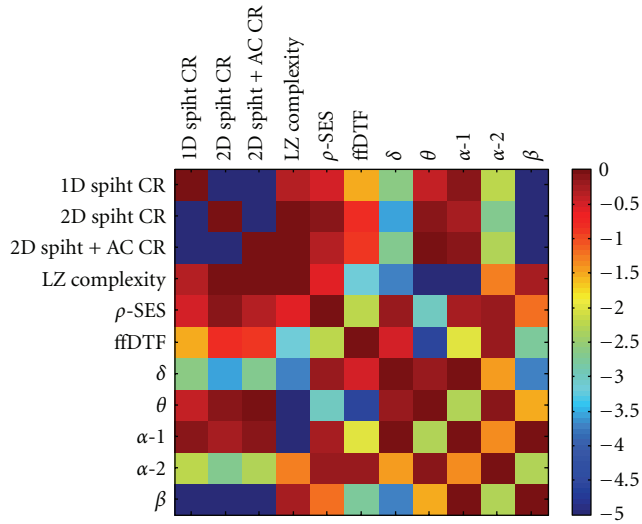


(a) MCI (Dataset 1)

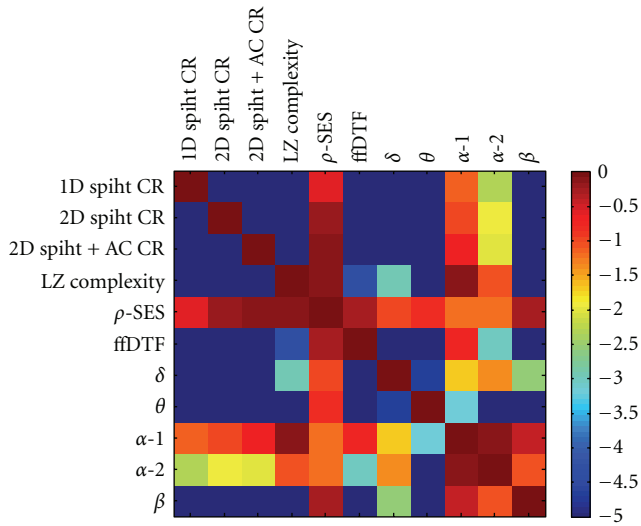


(b) Mild AD (Dataset 2)

Figure 6: Correlation between the lossless compression ratios, LZ complexity, relative power in different bands, Granger causality (ffDTF), and stochastic event synchrony (ρ); red and blue indicate strong correlation and anticorrelation, respectively.



(a) MCI (Dataset 1)



(b) Mild AD (Dataset 2)

Figure 7: Pearson correlation test between the lossless compression ratios, LZ complexity, relative power in different bands, Granger causality (ffDTF), and stochastic event synchrony (ρ). The (uncorrected) P values are shown on a logarithmic scale.

Though this coding scheme is specifically developed for images, it can be applied to all data sources with decaying spectrum [22].

3.2.4. Three SPIHT Compression Algorithms. The three compression algorithms are depicted in Figure 2: (1) 1D SPIHT compression, where the EEG is arranged as a vector (Figure 2(a)), (2) 2D SPIHT compression, where the EEG is arranged as a matrix (Figure 2(b)), and (3) 2D SPIHT compression (at optimal rate R_o), followed by arithmetic coding for the residuals (Figure 2(c)). In the 1D SPIHT compression scheme, backward differentiated EEG is subjected to integer wavelet transformation followed by SPIHT coding. The 2D SPIHT compression scheme arranges the EEG as a matrix instead of a vector. In the two-stage 2D SPIHT compression scheme, arithmetic coding is applied to the residuals of 2D SPIHT compression: first SPIHT encodes the wavelet coefficients till the source loses its memory and behaves as independent and identically distributed (corresponding to the optimal bit-rate R_o); next the residuals are encoded by means of single-context arithmetic coding.

4. EEG Datasets

4.1. Dataset 1: MCI versus Control. The first EEG data set has been analyzed in previous studies concerning early diagnosis of AD [23–27].

Ag/AgCl electrodes (disks of diameter 8 mm) were placed on 21 sites according to 10–20 international system, with the reference electrode on the right earlobe. EEG was recorded with Biotop 6R12 (NEC San-ei, Tokyo, Japan) at a sampling rate of 200 Hz, with analog bandpass filtering in the frequency range 0.5–250 Hz and online digital bandpass filtering between 4 and 30 Hz, using a third-order Butterworth filter. We used a common reference for the data analysis (right earlobe) and did not consider other reference schemes (e.g., average or bipolar references).

The subjects comprise two study groups. The first consists of 25 patients who had complained of memory problems. These subjects were diagnosed as suffering from mild cognitive impairment (MCI) when the EEG recordings were carried out. Later on, they all developed mild AD, which was verified through autopsy. The criteria for inclusion into the MCI group were a mini-mental state exam (MMSE) score = 24, though the average score in the MCI group was 26 (SD of 1.8). The other group is a control set consisting of 56 age-matched, healthy subjects who had no memory or other cognitive impairments. The average MMSE of this control group is 28.5 (SD of 1.6). The ages of the two groups are 71.9 ± 10.2 and 71.7 ± 8.3, respectively. Finally, it should be noted that the MMSE scores of the MCI subjects studied here are quite high compared to a number of other studies. For example, in [28] the inclusion criterion was MMSE = 20, with a mean value of 23.7, while in [29], the criterion was MMSE = 22 (the mean value was not provided); thus, the disparity in cognitive ability between the MCI and control subjects is comparatively small, making the classification task relatively difficult.

4.2. Dataset 2: Mild AD versus Control. The second EEG data set also has been analyzed in previous studies [30, 31]; these data were obtained using a strict protocol from Derriford Hospital, Plymouth, UK, and had been collected using normal hospital practices [31]. EEGs were recorded during a resting period with various states: awake, drowsy, alert, and resting states with eyes closed and open. All recording sessions and experiments proceeded after obtaining the informed consent of the subjects or the caregivers and were approved by local institutional ethics committees. EEG dataset is composed of 24 healthy control subjects (age: 69.4 ± 11.5 years old; 10 males) and 17 patients with mild AD (age: 77.6 ± 10.0 years old; 9 males). The patient group underwent full battery of cognitive tests (Mini-Mental State Examination, Rey Auditory Verbal Learning Test, Benton Visual Retention Test, and memory recall tests). The EEG time series were recorded using 19 electrodes positioned according to Maudsley system, similar to the 10–20 international system, at a sampling frequency of 128 Hz. EEGs were bandpass filtered with digital third-order Butterworth filter (forward and reverse filtering) between 0.5 and 30 Hz.

4.3. Recording Conditions Common to Both Datasets. In both datasets, all recording sessions were conducted with the subjects in an awake but resting state with eyes closed, and the length of the EEG recording was about 5 minutes, for each subject. The EEG technicians prevented the subjects from falling asleep (vigilance control). After recording, the EEG data has been carefully inspected. Indeed, EEG recordings are prone to a variety of artifacts, for example, due to electronic smog, head movements, and muscular activity. For each patient, an EEG expert selected one segment of 20 s artifact-free EEG by visual inspection, blinded from the results of the present study. Only those subjects were retained in the analysis whose EEG recordings contained at least 20 s of artifact-free data. Based on this requirement, the number of subjects of EEG Dataset 1 was further reduced to 22 MCI patients and 38 control subjects; in EEG Dataset 2 no such reduction was required. From each subject in the two datasets, one artifact-free EEG segment of 20 s was analyzed.

5. Results and Discussion

We compute relative power, compression ratios, and LZ complexity for the EEG signals of all subjects. More specifically, we calculate those measures for all individual EEG channels, and then the measures are averaged over all channels; this results in average measures for all subjects. Our results are summarized in Tables 2 and 3 and Figures 6 and 7. In the analysis we also include two measures of EEG synchrony: stochastic event synchrony (ρ) [32, 33] and a Granger causality measure, that is, full frequency directed transfer function (ffDTF) [34]; in an earlier hat study we observed that those two measures indicated statistically significant differences between MCI/MiAD and age-matched control subjects, for the datasets described in Section 4 [26, 27, 30, 31]. Since the two datasets (MCI and MiAD) were obtained through different recording systems and at different hospitals, a direct comparison of the results obtained from MCI with those from mild AD is not straightforward.

In Table 2 we list statistics of the average measures, including the average computed across the entire subject groups and the standard deviation. We apply the Mann-Whitney test for the average measures between MCI and the reference subjects (Dataset 1) and MiAD and reference subjects (Dataset 2). The Mann-Whitney test allows us to investigate whether the statistics at hand (EEG measures) take different values between two subject populations. Low P values indicate large difference in the medians of the two populations. The resulting P values are listed in Table 2. Since we conduct multiple statistical tests simultaneously, we need to apply statistical postcorrection. We adopt Bonferroni postcorrection [35] and multiply the P values by the number of tests (11). In Table 2 we indicate which EEG measures remain statistically significant after postcorrection.

Theta relative power is significantly larger in MCI patients compared to reference subjects, whereas beta power is significantly smaller. In the MiAD patients the perturbations on EEG relative power are stronger: delta and theta relative power is significantly larger than in the reference subjects, whereas alpha and beta power is significantly smaller. In other words, slowing occurs in both the MCI and MiAD patients, which is in agreement with earlier studies

(see [11] for a review). The slowing effect can also readily be seen from the (normalized) EEG spectra, shown in Figures 4 and 5 for Datasets 1 and 2, respectively. The effect of slowing in the MiAD subjects is very clear from Figure 5: power is obviously more concentrated in theta band in MiAD patients than in the age-matched control subjects. For the MCI patients (see Figure 4), no such clear effect can be observed from the spectra; this is no surprise, since MCI is a less severe disease state than MiAD. However, one may notice a slight increase (decrease) in theta (beta) relative power in MCI patients. In both the MCI patients and control subjects, power is concentrated in low-frequency bands (delta and theta band) and in high-frequency band (beta band); high-frequency power (beta band) is much smaller in the MiAD patients. In summary, as in earlier studies (see [11] for a review), we observe slowing in MCI and MiAD EEG.

No significant effect on the complexity and regularity measures can be observed in MCI patients. On the other hand, the regularity measures and complexity measures are significantly larger and smaller, respectively, for MiAD patients than for control subject; in other words, the EEG signals of MiAD patients are significantly less complex than in healthy subjects. This observation is in agreement with several earlier studies (see [11] for a review).

We also try to classify patients versus control subjects by means of the most discriminative EEG measures ($P < .05$). We test those measures individually and jointly for their discriminative ability. Table 3 shows the resulting classification performance with linear and quadratic discriminant analysis and support vector machine, determined through leaving-one-out cross-validation [36]. Only the best performing combinations of EEG measures are listed. From Table 3 we can see that theta band relative power yields good performance when used separately and results in even better performance when combined with the most discriminative lossless compression ratio and synchrony measure. The other relative power measures are less discriminative, for both datasets (not shown here); this observation is in agreement with the P values listed in Table 3. The compression ratios and LZ complexity fail to discriminate MCI patients from control subjects (not shown here). However, those measures yield good classification performance for the MiAD patients. Interestingly, the lossless compression ratios result in better classification rates than LZ complexity; this may be explained as follows: LZ complexity is based on binary approximations of the continuous EEG signals, whereas the former are derived from accurate representations of the EEG, associated with lossless compression.

In order to gain more insight in the relationship between the different measures, we calculate the correlation between those measures (see Figure 6). The correlation coefficient among each pair of measures is calculated as follows:

$$r_{ij} = \frac{1}{N_{\text{subject}}} \sum_{k=1}^{N_{\text{subject}}} \frac{m_i(k) - \overline{m_i}}{\sigma_i} \frac{m_j(k) - \overline{m_j}}{\sigma_j}, \qquad (2)$$

where $m_i(k)$ and $m_j(k)$ the average value of EEG measure i and j, respectively, for subject k, the sum is computed over all subjects, and $\overline{m_i}$, $\overline{m_j}$, σ_i, and σ_j are the mean and standard deviation of m_i and m_j, respectively. The resulting correlation coefficients are displayed in Figure 6, for Dataset 1 and Dataset 2 separately. We also conduct the Pearson correlation test, to verify whether the correlations or anticorrelations are statistically significant. The resulting P values are shown in Figure 7 (logarithmic scale). Since we have multiple simultaneous tests, statistical postcorrection is required. Again we adopt Bonferroni postcorrection [35] and multiply the P values by the number of tests (55).

As expected, the compression measures are significantly mutually correlated as all the schemes are based on the same principle; they are also significantly anticorrelated with LZ complexity in the MiAD dataset (Dataset 2).

Interestingly, the compression ratios are significantly correlated with low-frequency relative power (delta and theta; MiAD) and anticorrelated with high-frequency relative power (beta; both datasets). Likewise LZ complexity is strongly anticorrelated with low-frequency relative power (delta and theta; both datasets) and correlated with high-frequency relative power (beta; MiAD). Taken together, this observation strongly suggests that slowing and loss of

Table 2: Mean and standard deviation values of compression ratio, LZ complexity, relative power, and synchrony measures. Sensitivity of the measures in discriminating between MCI and mild AD is given in last column. Uncorrected P values from Mann-Whitney test, where * and ** indicate $P < .05$ and $P < .005$, respectively; † Indicates P values that remain significant after postcorrection (Bonferroni, $P < .05$).

MCI versus control			
Measure	Control	MCI	P value
1D SPIHT CR	1.34 ± 0.04	1.35 ± 0.03	.3077
2D SPIHT CR	1.36 ± 0.04	1.37 ± 0.03	.3778
2D SPIHT+AC	1.36 ± 0.04	1.37 ± 0.03	.4477
LZ complexity	0.65 ± 0.07	0.62 ± 0.09	.0830
ρ	0.25 ± 0.07	0.36 ± 0.10	**.00044****†
ffDTF	0.05 ± 0.003	0.051 ± 0.003	**.0012****†
delta	0.20 ± 0.06	0.21 ± 0.06	.2934
theta	0.08 ± 0.03	0.12 ± 0.04	**.0001****†
alpha-1	0.07 ± 0.03	0.08 ± 0.03	.1698
alpha-2	0.05 ± 0.02	0.05 ± 0.02	.9939
beta	0.24 ± 0.05	0.21 ± 0.03	**.0116***
Mild AD versus control			
Measure	Control	Mild AD	P value
1D SPIHT CR	1.09 ± 0.01	1.12 ± 0.04	$\mathbf{3.45 \times 10^{-5}}^{**\dagger}$
2D SPIHT CR	1.11 ± 0.02	1.15 ± 0.04	$\mathbf{6.09 \times 10^{-5}}^{**\dagger}$
2D SPIHT+AC	1.07 ± 0.02	1.11 ± 0.04	$\mathbf{4.86 \times 10^{-5}}^{**\dagger}$
LZ complexity	0.63 ± 0.06	0.55 ± 0.08	**.0024****†
ρ	0.46 ± 0.04	0.49 ± 0.03	**.0024****†
ffDTF	0.04 ± 0.004	0.037 ± 0.009	**.0001****†
delta	0.001 ± 0.004	0.017 ± 0.01	**.0029****†
theta	0.17 ± 0.08	0.54 ± 0.16	$\mathbf{8 \times 10^{-7}}^{**\dagger}$
alpha-1	0.32 ± 0.12	0.18 ± 0.10	**.0009****†
alpha-2	0.17 ± 0.11	0.06 ± 0.02	$\mathbf{3.41 \times 10^{-6}}^{**\dagger}$
beta	0.33 ± 0.14	0.18 ± 0.11	**.0006****†

Table 3: Classification rates for discriminant analysis (DA) of the lossless compression ratios, LZ complexity and relative power in theta band.

MCI versus control			
Measure	Linear DA	Quadratic DA	SVM
theta	76.67%	76.67%	76.67%
ffDTF	63.33%	71.67%	78.33%
ρ	75%	75%	76.67%
ffDTF + ρ	76.67%	**83.33**%	80.00%
Theta + ρ	78.33%	**83.33**%	80.00%
Mild AD versus control			
Measure	Linear DA	Quadratic DA	SVM
1D SPIHT CR	80.49%	80.49%	80.49%
2D SPIHT CR	82.93%	82.93%	**85.37**%
2D SPIHT+AC CR	75.61%	80.49%	82.93%
LZ complexity	68.29%	68.29%	68.29%
theta	**95.12**%	**95.12**%	**95.12**%
ffDTF	58.54%	78.05%	82.93%
ρ	56.10%	63.41%	63.41%
ffDTF + ρ	65.85%	70.73%	78.05%
theta + ffDTF	**95.12**%	**92.68**%	**95.12**%
theta + ffDTF + 1D SPIHT CR	**95.12**%	**92.68**%	**97.56**%

complexity in AD EEG are *not independent* phenomena but are strongly related; to the best of our knowledge, this observation has not been reported before in the literature.

Perhaps surprisingly, Granger causality (ffDTF) [34] is significantly correlated with LZ complexity and high-frequency relative power (MiAD) and significantly anticorrelated with lossless compression ratios (MiAD) and low-frequency relative power (both datasets). We believe that this observation has not been documented yet. We conjecture that the observed statistical (anti)correlation between ffDTF and the other measures is an artefact of the multivariate model underlying Granger causality (and ffDTF in particular). More specifically, Granger causality is derived from a multivariate autoregressive model (MVAR). The order of the latter needs to be kept low, since the coefficients of the MVAR need to be inferred from a short EEG segment; high-order MVARs contain many coefficients, which cannot be reliably inferred from the limited amount of data. Low-order MVARs have short memory and cannot capture low-frequency components in the EEG. Consequently Granger causality may underestimate the correlation among brain signals when the EEG contains strong low-frequency components.

Stochastic event synchrony (ρ) [32, 33] seems to be uncorrelated with the other measures (both datasets), and therefore, it may provide complementary information.

6. Conclusion

In this study, we investigated the use of relative power, LZ complexity, and lossless compression ratio as EEG markers for MCI and mild AD. Lossless compression ratio is shown to be discriminative for mild AD, whereas it is not discriminative for MCI. On the other hand, theta band relative power was observed to be statistically larger in MCI and mild AD patients than in control subjects. Maximum discrimination is obtained by combining the compression ratio, relative power, and synchrony measures (Granger causality and/or stochastic event synchrony).

We would like to reiterate, however, that the two datasets analyzed (MCI and MiAD) were obtained through different recording systems and at different hospitals; a direct comparison of the results obtained from MCI with those from mild AD is therefore difficult. On the other hand, since the datasets are independent, our observations are probably not dependent on particularities of the recording systems and/or procedures at the hospitals.

Interestingly, compression ratios were found to be significantly correlated to delta and theta band relative power, showing their strong correlation with relative power at low frequencies; also strong anti-correlation between compression ratios and beta relative power was observed. Therefore, slowing and loss of complexity in the EEG of MCI and MiAD patients may be strongly related phenomena.

More generally, this study also underlines the importance of analyzing MCI and AD EEG by means of a variety of statistical measures (relative power, complexity/regularity measures, synchrony measures), in order to detect potential correlations between various observed phenomena associated with MCI and AD.

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Research Article

Direction of Information Flow in Alzheimer's Disease and MCI Patients

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Is directionality of electroencephalographic (EEG) synchronization abnormal in amnesic mild cognitive impairment (MCI) and Alzheimer's disease (AD)? And, do cerebrovascular and AD lesions represent additive factors in the development of MCI as a putative preclinical stage of AD? Here we reported two studies that tested these hypotheses. EEG data were recorded in normal elderly (Nold), amnesic MCI, and mild AD subjects at rest condition (closed eyes). Direction of information flow within EEG electrode pairs was performed by directed transfer function (DTF) at δ (2–4 Hz), θ (4–8 Hz), $\alpha 1$ (8–10 Hz), $\alpha 2$ (10–12 Hz), $\beta 1$ (13–20 Hz), $\beta 2$ (20–30 Hz), and γ (30–40 Hz). Parieto-to-frontal direction was stronger in Nold than in MCI and/or AD subjects for α and β rhythms. In contrast, the directional flow within interhemispheric EEG functional coupling did not discriminate among the groups. More interestingly, this coupling was higher at θ, $\alpha 1$, $\alpha 2$, and $\beta 1$ in MCI with higher than in MCI with lower vascular load. These results suggest that directionality of parieto-to-frontal EEG synchronization is abnormal not only in AD but also in amnesic MCI, supporting the additive model according to which MCI state would result from the combination of cerebrovascular and neurodegenerative lesions.

1. Introduction

It has been shown that modifications of resting electroencephalographic (EEG) rhythms can be observed during pathological aging. When compared to healthy elderly (Nold) subjects, Alzheimer's disease (AD) patients have been characterized by high power of δ (0–4 Hz) and θ (4–7 Hz) rhythms, and low power of posterior α (8–12 Hz) and/or β (13–30 Hz) rhythms [1–7]. These EEG abnormalities have been associated with altered regional cerebral blood flow/metabolism and with impaired global cognitive function, as evaluated by mini mental state examination (MMSE; [5, 8–11]. Furthermore, posterior α rhythms have shown a power decrement even in subjects with amnesic mild cognitive impairment (MCI), a clinical state between elderly normal cognition and dementia, which is characterized by the objective evidence of memory deficit either isolated or combined with other cognitive impairment [3, 7, 12–15]. More recently, the hypothesis that the amplitude of EEG rhythms, which are affected by AD processes, is relatively preserved in amnesic MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load has been tested.

Despite the converging evidence of abnormal cortical EEG rhythms in MCI and AD, EEG power alone does not reliably predict conversion from MCI to dementia. A reasonable hypothesis is that the amplitude of EEG rhythms per se does not capture one of the main features of AD, namely the impairment of functional neural connectivity. In this vein, it has been reported that AD patients present an abnormal linear coupling of EEG rhythms between cortical regions, as revealed by spectral EEG coherence [16–22]. Such a coherence denotes linear temporal synchronicity of coupled EEG rhythms, as a reflection of neural sources whose firing is oscillating with a nearly identical timing and phase. It has been proposed that functional coupling

of cortical rhythms is related to brain processes involving the coupled sources and is modulated by cholinergic systems [23]; AD is characterized by a disruption of basal forebrain cholinergic inputs to cortex and hippocampus [24]. This is why a decrease of cortical EEG coherence might be a sensible and reliable marker of AD.

Both linear and nonlinear connectivity have an important limitation: they do not reflect the direction of the information flux within the functional coupling of brain rhythms at paired brain sites. One can overcome this limitation by the computation of the directed transfer function (DTF; [25]). DTF has been proven to be reliable for the modeling of directional information flux within linear EEG functional coupling, as an intrinsic feature of cerebral functional connectivity [26–28]. Concerning the functional role of intrinsic directional connectivity in cognition, a dominant parietal-to-frontal directional flux within EEG coupling has been reported in healthy awake subjects during visuospatial information processing [15, 29]. Across pathological aging, a reduction of parietal-to-frontal directional information flow within EEG functional coupling in both MCI and mild AD subjects compared to Nold subjects it has been shown, in line with the idea of a common pathophysiological background linking these conditions.

In the present study, we summarized the results of two previous studies [30, 31] testing the hypothesis that directionality of frontoparietal functional coupling of EEG rhythms are affected by AD processes but relatively preserved in amnesic MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load (as revealed by MRI). Resting EEG was recorded in Nold, Alzheimer, and amnesic MCI subjects, while the directionality of frontoparietal functional coupling of EEG rhythms was estimated by DTF.

2. Methods

2.1. Subjects. In the first multicentric EEG study, 73 AD patients, 69 amnesic MCI patients, and 64 Nold subjects were recruited. In the second study, 80 amnesic MCI subjects were enrolled. Furthermore, 40 cognitively normal elderly (Nold) subjects were recruited to form control group. These individual data sets were mostly overlapped in the two studies.

Local institutional ethics committees approved the studies. All experiments were performed with the informed and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Author's Institutional Review Board.

2.2. Diagnostic Criteria. Probable AD was diagnosed according to NINCDS-ADRDA [32] and DSM IV criteria. All recruited AD patients underwent general medical, neurological, and psychiatric assessments. Patients were also rated with a number of standardized diagnostic and severity instruments that included the Mini Mental State Examination (MMSE, [33]), the Clinical Dementia Rating Scale (CDR, [28]), the 15-item version of the Geriatric Depression Scale (GDS, [34]), the Hachinski Ischemic Scale (HIS, [35]), and the Instrumental Activities of Daily Living scale (IADL, [36]). Neuroimaging diagnostic procedures (CT or MRI) and complete laboratory analyses were carried out to exclude other causes of progressive or reversible dementias, in order to have a homogeneous AD patient sample. Exclusion criteria included, in particular, evidence of (i) frontotemporal dementia, (ii) vascular dementia based on clinical and radiological grounds, (iii) extrapyramidal syndromes, (iv) reversible dementias, and (v) fluctuations in cognitive performance and visual hallucinations (suggestive of a possible Lewy body dementia). Inclusion and exclusion criteria for amnesic MCI diagnosis aimed at selecting elderly persons with objective cognitive deficits, especially in the memory domain, who did not meet the criteria for dementia or AD [37, 38]. Inclusion criteria for amnesic MCI subjects were (i) objective memory impairment on neuropsychological evaluation, as defined by performances ≥ 1.5 standard deviation below the mean value of age- and education-matched controls for a test battery including Busckhe-Fuld and memory Rey tests, (ii) normal instrumental activities of daily living as documented by history and evidence of independent living as assessed by a formal questionnaire (IADL, see above), and (iii) a clinical dementia rating score of 0.5. Exclusion criteria for amnesic MCI were (i) MCI subjects without objective memory deficits, (ii) AD, as diagnosed by the procedures described above, (iii) evidence of concomitant dementia such as frontotemporal, vascular dementia, reversible dementias (including dementia of depression), fluctuations in cognitive performance, and/or features of mixed dementias, (iv) evidence of concomitant extrapyramidal symptoms, (v) clinical and indirect evidence of depression as revealed by GDS scores greater than 14, (vi) other psychiatric diseases, epilepsy, drug addiction, alcohol dependence, and use of psychoactive drugs or drugs interfering with brain cognitive functions including acetylcholinesterase inhibitors, and (vii) current or previous uncontrolled systemic diseases or traumatic brain injuries.

The Nold subjects were recruited mostly among nonconsanguineous patients' relatives. All Nold subjects underwent physical and neurological examinations as well as cognitive screening. Subjects affected by chronic systemic illnesses, subjects receiving psychoactive drugs, and subjects with a history of present or previous neurological or psychiatric disease were excluded. All Nold subjects had a geriatric depression scale score lower than 14 (no depression).

2.3. Magnetic Resonance Imaging. High-resolution sagittal T1-weighted volumetric magnetic resonance images (MRIs) were acquired in 80 MCI subjects of the second study using a 1.0 T Magnetom scanner (Siemens, Erlangen, Germany), with a gradient echo 3D technique: TR = 10 ms, TE = 4 ms, TI = 300 ms, flip angle = 10°, field of view = 250 mm, acquisition matrix 160×256, and a slice thickness of 1.3 mm.

In order to rate the subcortical vascular lesions (SVLs), a single operator visually assessed digital MRI images of MCI subjects [39]. Interrater reliability calculated with weighted k value was 0.67, indicative of moderate agreement (as indicated by the Wahlund scale). The SVLs were scored separately

for the right and left hemispheres with the following scores: 0 (no lesion), 1 (focal lesions), 2 (beginning confluence of lesions), or 3 (diffuse involvement of the entire region). The MRI data of an MCI subject could not be used for technical problems. Another MCI subject was not further considered due to an abnormal EEG spectrum. In total, 78 MCI subjects were considered for the DTF analysis.

2.4. Composition of the Experimental Groups of MCI Subjects. Based on the Wahlund scale score, the MCI subjects were subdivided in two subgroups: 36 with low degree of white-matter lesion (MCI V−, score of Wahlund scale <3) and 42 with higher degree of white-matter lesion (MCI V+, score of Wahlund scale ≥3). The two subgroups of MCI subjects were comparable for demographic and clinical features.

Table 1 summarizes the relevant demographic and clinical data of MCI, AD, and Nold of the first study (part a) and the MCI V−, MCI V+, and Nold of the second study (part b). Of note, age, education, gender, and IAF were used as covariates in all the statistical evaluations of the cortical sources of EEG rhythms to remove possible confounding effects.

Table 1: Mean values (± standard error) of the demographic and clinical characteristics of the investigated cohorts.

(a)

Study 1	AD	aMCI	Nold
Subject	73	69	64
MMSE	20.9 ± 0.5	26.6 ± 0.2	28.6 ± 0.2
Age	74.1 ± 1.0	74.1 ± 0.8	73.7 ± 0.9
Education	9.8 ± 0.6	9.8 ± 0.5	9.7 ± 0.6
IAF	8.6 ± 0.2	9.2 ± 0.2	9.2 ± 0.1
Female/Male	35F/39M	38F/31M	32F/32M

(b)

Study 2	MCI V−	MCI V+	Nold
Subject	36	42	40
MMSE	26.7 ± 0.3	26.0 ± 0.3	28.4 ± 0.2
Age	68.5 ± 1.3	72.6 ± 1.0	69.1 ± 1.1
Education	7.7 ± 0.7	7.1 ± 0.5	7.6 ± 0.5
IAF	9.4 ± 0.2	9.3 ± 0.2	9.4 ± 0.1
Female/Male	23F/13M	23F/19M	22F/18M

2.5. EEG Recordings. EEG data were recorded in resting subjects (eyes-closed) by specialized clinical units. All EEG recordings were performed (0.3–70 Hz bandpass) from 19 electrodes positioned according to the International 10–20 System (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). To monitor eye movements, the electrooculogram (0.3–70 Hz bandpass) was also collected. All data were digitized in continuous recording mode (5 min of EEG; up to 256 Hz sampling rate). In all subjects, EEG recordings were performed in the late morning. State of vigilance was controlled by visual inspection of EEG traces during recording session and subjects' drowsiness was avoided by verbal warnings. At the time of EEG recording, no patient received medications that could influence EEG rhythms such as benzodiazepines.

2.6. DTF Analysis: "Direction" of the Functional Connectivity Estimated by the Mvar Model. Before computing the DTF, the EEG data were preliminarily normalized by subtracting the mean value and dividing by the variance, according to standardized rules by Kaminski and Blinowska [25]. An important step of the DTF method was the computation of the so-called Mvar model [25–27]. EEG data at 9 electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) were simultaneously given as an input to the Mvar model towards the computation of the directional information flux among all the pair combinations of these electrodes. This model was used to estimate the "direction" of the information flow within the EEG rhythms between the frontal and parietal regions (F3-P3, Fz-Pz, F4-P4). In nonmathematical terms, coefficients of the Mvar model fitted to the data can be interpreted as causal influence of signal recorded from electrode A on signal recorded from electrode B, or information flow between electrodes A and B. A direction of information flow from A to B is stated when that case is statistically more probable than a directionality from B to A. This Mvar model has already been used successfully to estimate the "direction" of the corticocortical and corticomuscular information flow [40–42].

The mathematical core of the Mvar algorithm used in this work is based on the ARfit programs running on the platform Matlab 6.5. The model order was 7, as estimated by the Akaike criterion suggested in previous DTF studies; that order has been demonstrated to be valid for the evaluation of EEG rhythms at both low- and high-frequencies along wakefulness and sleep [25–27]. The goodness of fit was evaluated by visual inspection of the values of noise matrix V of the Mvar model.

The Mvar model is defined as

$$\sum_{j=0}^{p} A_j X_{t-j} = E_t, \tag{1}$$

where X_t is the L-dimensional vector representing the L-channel signal at time t; E_t is white noise; A_j is the $L * L$ matrix of the model coefficients, and p is the number of time points considered in the model. From the identified coefficients of the model A_j, spectral properties of the signals can be obtained by the following z-transformation of the above equation:

$$X(z) = H(z)E(z), \tag{2}$$

where $H(z)$ is a transfer function of the system

$$H(z) = \left(\sum_{j=0}^{p} A_j z^{-j} \right)^{-1}, \qquad z^{(-j)} = \exp(-2\pi i j f dt), \tag{3}$$

where f is frequency and dt is the time step.

Since the transfer function $H(f)$ is not a symmetric matrix, the information transmission from the jth to the ith channel is different from that from the ith to the jth channel. The DTF from the jth channel to the ith channel is defined as the square of the element of $H(f)$ divided by the squared sum of all elements of the relevant row,

$$\mathrm{DTF}_{ij}(f) = \frac{\left|H_{ij}\right|^2}{\sum_{m=1}^{L}\left|H_{im}(f)\right|^2}. \quad (4)$$

A substantial difference between $\mathrm{DTF}(f)_{ij}$ and $\mathrm{DTF}(f)_{ji}$ may suggest an asymmetric information flow from electrode i to electrode j. When $\mathrm{DTF}(f)_{ij}$ is greater in magnitude than $\mathrm{DTF}(f)_{ji}$, the "direction" of the information flow is from electrode j to electrode i. On the other hand, the "direction" of the information flow is from electrode i to electrode j, when $\mathrm{DTF}(f)_{ji}$ is greater in magnitude than $\mathrm{DTF}(f)_{ij}$. Of note, the normalization of the DTF depends on the denominator of the previous formula.

To simplify the visualization and statistical analysis of the DTF results, the anterior-posterior directional flow of information of EEG functional coupling was indexed as "parietal-to-frontal" minus "frontal-to-parietal" DTF values, namely anterior-to-posterior DTFdiff values. Positive anterior-to-posterior DTFdiff values indicated a prevalence of parietal-to-frontal over frontal-to-parietal direction of the information flux.

The fact that the DTF analysis was done on the difference between the two reciprocal DTF directions should require a careful interpretation of the results. A zero value of such a difference meant equivalence of the two opposite DTF directions within the period of EEG data acquisition; namely, that the DTF directions were equally strong or equally weak or both equal to zero in the EEG period taken into account. It should be emphasized that this equivalence is true for the whole EEG period, but not necessarily for subperiods. At this preliminary stage of the study, we preferred to evaluate the DTF values for the entire EEG period, since the DTF values for shorter periods are supposedly less reliable from the statistical point of view [6, 43].

2.7. Statistical Analysis of DTFdiff Values. Statistical comparisons were performed by repeated measure ANOVAs. The Mauchley test evaluated the sphericity assumption and correction of the degrees of freedom was carried out using the Greenhouse-Geisser procedure. Subjects' age, gender education, and IAF were used as covariates in the statistical design. The Duncan test was used for post hoc comparisons ($P < .05$).

Statistical analysis of the anterior-to-posterior DTFdiff values ("direction" of the information flow between frontal and parietal regions) was performed using a three-way ANOVA including the factors Group (AD, amnesic MCI, and Nold; independent variable), Band (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ), and Electrode pair (F3-P3, Fz-Pz, and F4-P4) for the first study, and Group (MCI V−, MCI V+, and Nold; independent variable), Band (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ), and Electrode pair (F3-P3, Fz-Pz, and F4-P4) for the second study. The working hypothesis was a statistical effect indicating a progressive reduction of anterior-to-posterior DTFdiff values across Nold, MCI V−, and MCI V+ subjects.

3. Results

The Nold subjects showed wide positive anterior-posterior DTFdiff values (parietal-to-frontal DTF values prevailing over frontal-to-parietal values), which were maximum in magnitude at $\alpha1$ for all electrode pairs of interest (F3-P3, Fz-Pz, F4-P4). Compared to Nold subjects, AD patients were characterized by a decrease of these DTFdiff values. MCI subjects presented a DTF trend similar to that of the AD, except for $\alpha1$, $\alpha2$, and $\beta1$ in which they showed intermediate values of anterior-to-posterior DTFdiff values, when compared to those of Nold and AD. In contrast to the anterior-to-posterior, inter-hemispheric DTFdiff values had similar magnitude values in the three groups, for all electrode pairs of interest (F3-F4, C3-C4, P3-P4).

Statistical ANOVA of the anterior-to-posterior DTFdiff values showed a two-way ANOVA interaction ($F(12,1218) = 3.49$; $P < .00001$) between the factors group (AD, amnesic MCI, Nold) and Band (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ). Duncan post hoc testing showed that the anterior-posterior DTFdiff values matched the patterns Nold > MCI > AD ($\beta1$: $P < .05$ to $P < .000001$), Nold > AD (θ: $P < .01$; $\alpha1$: $P < .000005$; $\alpha2$: $P < .000005$; $\beta2$: $P < .05$), and Nold > MCI (θ: $P < .01$; $\alpha1$: $P < .00001$; $\alpha2$: $P < .00001$). The upper part of Figure 1 shows the mean anterior-to-posterior DTFdiff values computed in the Nold, amnesic MCI, and AD subjects, for all frequency bands of interest (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ), obtained by averaging the anterior-to-posterior DTFdiff values of the three electrode pairs (F3-P3, Fz-Pz, F4-P4). These values represent the above-mentioned two-way ANOVA interaction.

Statistical ANOVA of the inter-hemispheric DTFdiff values showed no statistically significant effect including the factor group (AD, amnesic MCI, Nold). The bottom part of Figure 1 reports the mean inter-hemispheric DTFdiff values computed in the Nold, amnesic MCI, and AD subjects at all frequency bands of interest (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ), obtained by averaging the inter-hemispheric DTFdiff values of the three electrode pairs (F3-F4, C3-C4, P3-P4).

Compared to Nold subjects, MCI V− patients were characterized by a decrease of these DTFdiff values. MCI V+ subjects showed intermediate values of anterior-to-posterior DTFdiff values, when compared to those of Nold and MCI V−.

Statistical ANOVA of the anterior-to-posterior DTFdiff values showed a two-way ANOVA interaction ($F(12,690) = 3.65$; $P < .000001$) between the factors Group (MCI V−, MCI V+, Nold) and Band (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ). Duncan post hoc testing showed that the anterior-posterior DTFdiff values matched the patterns Nold > MCI V+ > MCI V− (θ: $P < .019$ to $P < .000002$; $\alpha1$: $P < .0016$ to $P < .000001$; $\alpha2$: $P < .0015$ to $P < .000001$; $\beta1$: $P < .015$ to $P < .000002$).

Figure 2 shows the mean anterior-to-posterior DTFdiff values computed in the Nold, MCI V+, and MCI V−

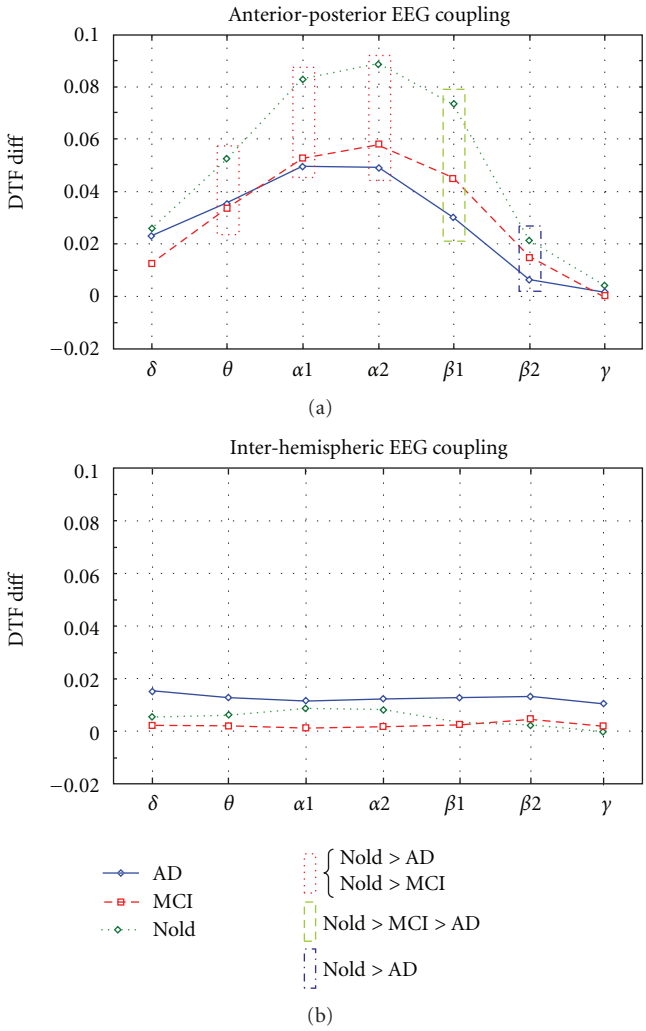

FIGURE 1: (a) Means of anterior-posterior DTFdiff values computed in the Nold, amnesic MCI, and AD for all frequency bands of interest (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ) averaging the anterior-posterior DTFdiff values of the three electrode pairs (F3-P3, Fz-Pz, F4-P4), in order to represent a two-way ANOVA interaction ($F(12,1218) = 3.49$; $P < .00001$) between the factors group (AD, amnesic MCI, Nold) and Frequency band (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ). (b) Means of inter-hemispheric DTFdiff values computed in the same subjects and frequency bands of interest. Means were obtained averaging the inter-hemispheric DTFdiff values of the electrode pairs (F3-F4, C3-C4, P3-P4).

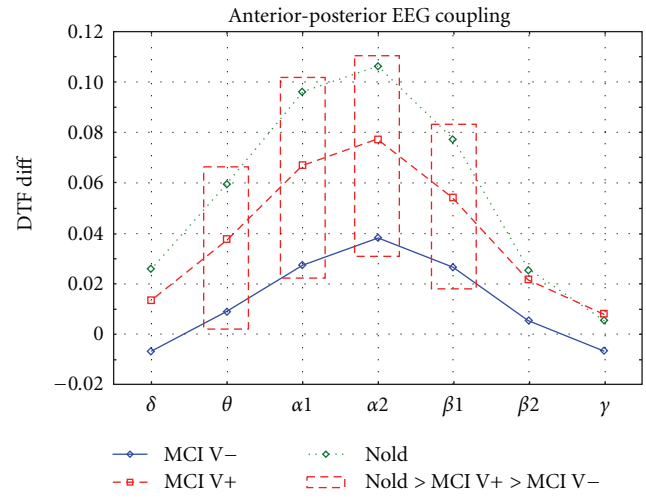

FIGURE 2: Means of anterior-posterior DTFdiff values computed in the Nold, MCI V−, and MCI V+ subjects for all frequency bands of interest (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ). These means were obtained averaging the anterior-posterior DTFdiff values of the three electrode pairs (F3-P3, Fz-Pz, F4-P4), in order to represent a two-way ANOVA interaction ($F(12,690) = 3.65$; $P < .000001$) between the factors group (MCI V−, MCI V+, Nold) and Frequency band.

subjects, for all frequency bands of interest (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ), obtained by averaging the anterior-to-posterior DTFdiff values of the three electrode pairs (F3-P3, Fz-Pz, F4-P4). These values represent the above-mentioned two-way ANOVA interaction.

4. Discussion

It has been shown previously that frontal-to-parietal direction of information flux within EEG functional coupling is an intrinsic feature of cerebral connectivity [6, 15, 29, 43, 44]. In the first study, we tested whether that direction of information flux is abnormal in pathological aging conditions such as amnesic MCI and AD, in line with the hypothesis that amnesic MCI is a preclinical stage of AD at the group level. Results showed that parietal-to-frontal direction of the information flux within EEG functional coupling was stronger in Nold than in amnesic MCI and/or AD subjects, principally at α and β rhythms. In contrast, the directional flow within inter-hemispheric EEG functional coupling did not discriminate among the three groups. These results suggest that directional information flux within EEG frontal-to-parietal coupling is quite sensitive to the preclinical stage of the AD at the group level. In the second study, we tested the hypothesis that dominant parietal-to-frontal EEG coupling, which is affected by AD processes as revealed in the first study, is relatively preserved in amnesic MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load. As main results, the dominant parietal-to-frontal EEG coupling at θ, α, and β rhythms was maximum in Nold, intermediate in MCI V+, and low in MCI V− subjects. These results are in line with the additive model of cognitive impairment, postulating that the cognitive impairment arises as the sum of neurodegenerative and cerebrovascular lesions. EEG might be especially sensitive to aging neurodegenerative processes and would be relatively spared in elderly subjects in whom the cognitive impairment is mainly explained by cerebrovascular lesions. The results of the present studies motivate future investigations aimed at evaluating the functional coupling of frontal and parietal sources of EEG activity as revealed by high-resolution techniques including linear or nonlinear inverse estimation and realistic modeling of the head as a volume conductor [5, 45].

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Research Article

Does EEG Montage Influence Alzheimer's Disease Electroclinic Diagnosis?

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There is not a specific Alzheimer's disease (AD) diagnostic test. AD diagnosis relies on clinical history, neuropsychological, and laboratory tests, neuroimaging and electroencephalography. Therefore, new approaches are necessary to enable earlier and more accurate diagnosis and to measure treatment results. Quantitative EEG (qEEG) can be used as a diagnostic tool in selected cases. The aim of this study was to answer if distinct electrode montages have different sensitivity when differentiating controls from AD patients. We analyzed EEG spectral peaks (delta, theta, alpha, beta, and gamma bands), and we compared references (Biauricular, Longitudinal bipolar, Crossed bipolar, Counterpart bipolar, and Cz reference). Support Vector Machines and Logistic Regression classifiers showed Counterpart bipolar montage as the most sensitive electrode combination. Our results suggest that Counterpart bipolar montage is the best choice to study EEG spectral peaks of controls versus AD.

1. Introduction

Alzheimer's disease (AD) diagnosis is based upon clinical history, neuropsychological and laboratory tests, neuroimaging, and electroencephalography (EEG). New approaches are necessary to earlier and more accurate diagnosis [1, 2] and to measure treatment results [3].

EEG visual analysis can be a helpful diagnostic test in AD [4, 5]. Background frequency displacement to delta and theta frequencies and the dropout of central alpha rhythm are common EEG findings in AD [6]. Accordingly, Sandmann et al. [7] observed a direct correlation between the degree of cognitive impairment and the power of low-frequency electrical activity in the EEG.

Since the first quantitative EEG (qEEG) studies by Lehmann [8] and Duffy et al. [9], spectral analysis (specA) and statistics have been applied to EEG. Moreover, specA has been considered from 71% to 81% sensitive to changes [10–13] in AD EEG background. Saletu et al. [14] found a localized temporal decrease of alpha and beta activities in AD and slow cerebral rhythms widespread distribution in vascular dementia (VaD) [10–13]. Pucci et al. [15] proposed that a decrease in alpha frequency to 6.0–8.0 Hz could be an AD marker.

Despite the knowledge grounded in this field during the last decades, there are lots of unanswered questions that hinder qEEG consolidation as an AD diagnostic tool. Our objective was to study if distinct electrode montages have different sensitivity when differentiating controls from AD patients.

2. Materials and Methods

2.1. Subjects. The dataset was composed of electroencephalograms (EEGs) recorded from two groups aged from 60 to 80 years: (S1) 12 normal subjects and (S2) 22 probable AD patients (NINCDS-ADRDA criteria) [16]. AD group

was classified as having mild to moderate symptoms (DSM-IV-TR) [17]. Both groups were submitted to the Brazilian version of the Mini-Mental State Examination (MMSE) [18, 19]. AD patients scored below 26 points. All probands did not have a history of diabetes mellitus, kidney disease, thyroid disease, alcoholism, liver disease, lung disease, or vitamin B12 deficiency to avoid other causes of cognitive impairment.

2.2. Data Acquisition and Processing. The EEGs were recorded with 12 bits resolution, band pass of 1–50 Hz, and sampling rate of 200 Hz. A *Braintech 3.0 (EMSA "Equipamentos Médicos")* was the recording hardware. Impedance was maintained below 10 K, and the electrodes were placed according to the International 10–20 System [5, 20]. The interconnected ear lobe electrodes reference (without resistor) is standard in our laboratory, despite the fact that there are controversies regarding which reference is the best [21, 22]. The EEGs were recorded during 20 minutes. Probands were awake and relaxed, with closed eyes. Two skilled neurophysiologists removed EEG artifacts (blinking, drowsiness, muscle movements, or equipment-related artifacts) from the recordings. Subsequently, from each EEG, 40 epochs of eight seconds were selected by visual inspection [23].

A 512-point Hamming Fast Fourier Transform (FFT) algorithm was used to process the epochs analysis. The windows were 2.5 seconds long with 90% of overlap between successive windows [23]. EEG signals were filtered using an infinite impulse response low-pass elliptic filter with a cutoff frequency at 50 Hz and a zero in the frequency of 60 Hz to eliminate the interference of the power grid (60 Hz).

2.3. Feature Extraction. Feature extraction is the method used to mining some characteristics of a particular signal epoch producing data that can represent events [23]. The spectral peak feature (or peak spectrum), chosen in this work, corresponds to the frequency where the EEG spectrum amplitude reaches its maximum value. The montages used were

(i) Biauricular reference (Bar): Fp1-A1, Fp2-A2, F7-A1, F8-A2, F3-A1, F4-A2, C3-A1, C-A2, T3-A1, T4-A2, P3-A1, P4-A2, O1-A1, O2-A2;

(ii) Longitudinal Bipolar (Lbp): Fp1-F3, F3-C3, C3-P3, P3-O1, O1-T5, T5-T3, T3-F7, F7-Fp1, Fp2-F4, F4-C4, C4-P4, P4-O2, O2-T6, T6-T4, T4-F9, F8-Fp2;

(iii) Crossed Bipolar (Bcr): Fp1-Fp2, F7-F3, F3-Fz, Fz-F4, F4-F8, T3-C3, C3-Cz, Cz-C4, C4-T4, T5-P3, P3-Pz, Pz-P4, P4-T6, O1-O2;

(iv) Counterpart bipolar (Bco): F7-F8, F3-F4, T3-T4, C3-C4, P3-P4, T5-T6, O1-O2;

(v) Cz reference (Czr): Fp1-Cz, Fp2-Cz, F3-Cz, F4-Cz, F7-Cz, F8-Cz, T3-Cz, T4-Cz, C3-Cz, C4-Cz, T5-Cz, T6-Cz, P3-Cz, P4-Cz, O1-Cz, O2-Cz.

Each of these electrode montages (Figure 1) had spectral peaks calculated for delta (from 0.1 to 4.0 Hz), theta (from 4.0 to 8.0 Hz), alpha (from 8.0 to 12.0 Hz), beta (from 12.0 to 30.0 Hz), and gamma (from 30.0 to 50.0 Hz) bands [24].

2.4. Classifiers. The EEG dataset was composed of 1360 epochs (40 epochs of 34 subjects). The analysis was based on the leave-one-subject-out process: 1320 epochs were used for training and 40 epochs from one subject for testing. It means that, each time, the classifier was trained with epochs from all individuals except the one going to be tested. This procedure was performed to test the classifiers discriminative capacity to work with data diverse from that presented in the training period. The leave-one-subject-out process was repeated for all 34 individuals (34 tests each montage).

2.4.1. Support Vector Machines (SVMs). SVMs constitute a supervised Machine Learning (ML) technique based on the Statistical Learning Theory [25]. In this method, a training dataset (containing known labeled data examples) is used to draw a hyperplane with maximum margin, based on the feature coordinates, which separates the two classes (in our case, Controls and AD). Subsequently, the coordinates of this hyperplane are used to test a dataset and the accuracy of the model [26]. When classes are not linearly separable, feature coordinates should be mapped to a higher dimension by a Kernel function. In this new space, the classes become linearly separable and the maximum margin hyperplane can then be found [26].

In this experiment, the Weka tool [27] with default values was used to the SVM induction. The regularization coefficient of SVM was maintained in $C = 1.0$, while the *Kernel* used was RBF [28]. The cache size was 250007, and the gamma value was 0.01.

2.4.2. Logistic Regression (LR). Logistic regression is part of a category of statistical models called generalized linear models. LR is a classification tool frequently used to help diagnosis [29]. In this method, the discriminant function analyses the sum of the scores of each feature and then delimitates the boundaries between the two groups [30]. Logistic regression calculates the predicted probability of different subgroups (in our analysis) falling into a category [30]. In LR induction, we also used Weka tool [27] with default values. In this case, the maximum interaction value was -1.0, and the ridge value in the log-likelihood was configured to 1.0.

3. Results and Discussion

Table 1 shows the results of both classifiers to each electrode montage. The columns represent, respectively, from left to right, accuracy, sensitivity (patients correctly diagnosed as AD), and specificity (controls correctly diagnosed as normals). The first line of each montage shows the percentage of epoch classification (mean and standard deviations).

The second line of Table 1 presents the per subject percentage. The leave-one-out analysis of each subject took into consideration the ratio between the number of epochs classified correctly and the total number of epochs. When this

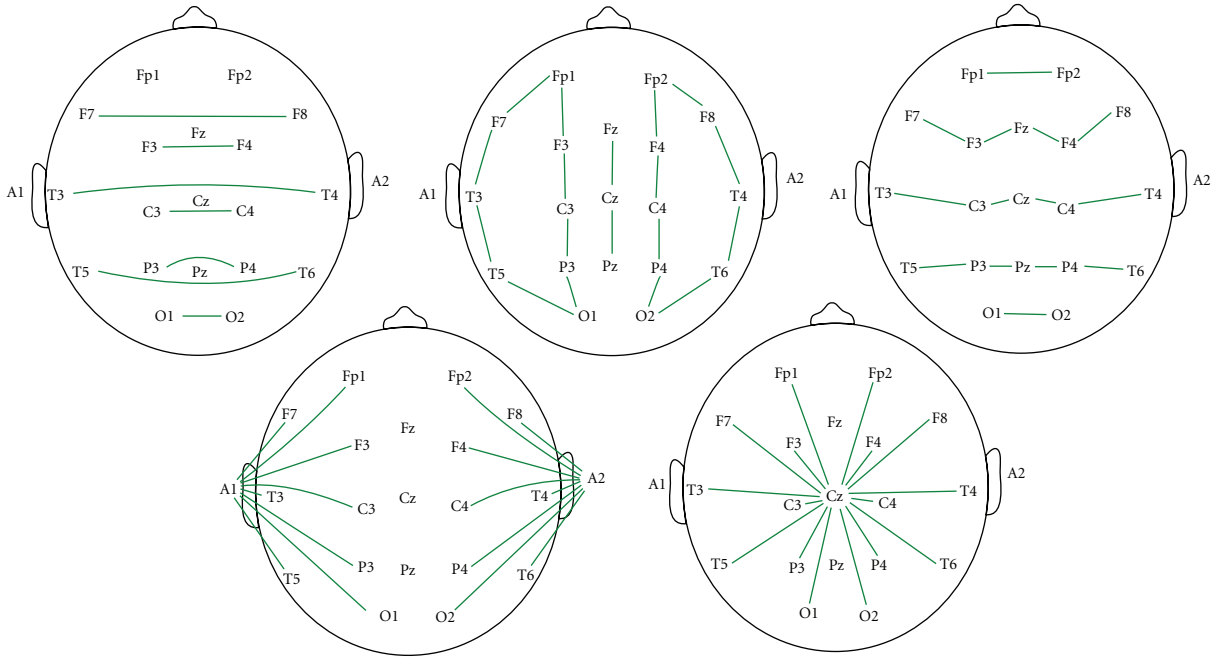

Figure 1: Spectral peaks montage maps. Lines correspond to subtractions used to calculate spectral peaks. From left to right, top to bottom: Counterpart Bipolar (Bco), Longitudinal Bipolar (Lbp), Crossed Bipolar (Bcr), Biauricular reference (Bar), and Cz reference (Czr).

Table 1: Accuracy, sensitivity, and specificity rates for each montage. Best results in bold and worst results in italic.

	Support Vector Machines			***Logistic Regression***		
	Accuracy (%)	*Sensitivity (%)*	*Specificity (%)*	*Accuracy (%)*	*Sensitivity (%)*	*Specificity (%)*
	Bipolar Counterpart			**Bipolar Counterpart**		
Epochs	**81,32 ± 28,00**	**89,43 ± 20,92**	**66,46 ± 33,84**	**82,13 ± 20,86**	**86,93 ± 17,49**	**73,33±24,32**
Patient	**85,29**	**90,91**	**75,00**	**91,18**	**95,45**	**83,33**
	Longitudinal Bipolar			**Longitudinal Bipolar**		
Epochs	72,72 ± 36,80	84,09 ± 27,52	51,88 ± 43,39	66,03 ± 35,76	*75,45 ± 31,42*	48,75 ± 38,04
Patient	79,41	**90,91**	58,33	*64,71*	*72,73*	50,00
	Crossed Bipolar			**Crossed Bipolar**		
Epochs	*69,19 ± 37,60*	*80,23 ± 32,40*	48,96 ± 39,32	*65,07 ± 36,09*	76,59 ± 33,23	*43,96 ± 32,36*
Patient	*64,71*	*81,82*	*41,67*	67,65	77,27	50,00
	Biauricular Reference			**Biauricular Reference**		
Epochs	70,07 ± 36,81	85,57 ± 23,12	*41,67 ± 41,03*	66,32 ± 32,50	76,14 ± 28,05	48,33 ± 33,50
Patient	76,47	95,45	*41,67*	67,65	81,82	*41,67*
	Cz Reference			**Cz Reference**		
Epochs	70,22 ± 37,70	81,36 ± 31,15	49,79 ± 41,33	71,62 ± 28,37	80,45 ± 24,64	55,42 ± 28,52
Patient	70,59	*81,82*	50,00	73,53	86,36	50,00

ratio was over 0.5, the subject classification was considered correct. After 34 tests, the rate of subject correct diagnosis was calculated. In Table 1, Bco is the montage with highest number of correct diagnosis and the lowest standard deviation to all classifiers. Bco also had high specificity (correct diagnosis of AD) and sensibility. These findings are relevant because they validate this qEEG technique as a diagnostic method. Therefore, it can help supporting clinical diagnosis.

It is important to note that high standard deviation (SD) is a methodological consequence of the leave-one-subject-out test. If an individual had bad epochs accuracy, the group mean was low and the SD high. Bco was the montage with

Table 2: Number of patients with epoch accuracy rates equal to 100%, exceeding or equal to 75%, less than or equal to 50%, and equal to 0% for each test. Best results in bold and worst results in italic.

	Support Vector Machines				Logistic Regression			
	= 100	*≥ 75*	*≤ 50*	*= 0*	*= 100*	*≥ 75*	*≤ 50*	*= 0*
Bipolar Counterpart	15	**26**	**5**	**0**	**12**	**25**	**3**	**0**
Longitudinal Bipolar	**16**	21	7	2	7	20	*12*	1
Crossed Bipolar	*13*	20	*12*	*3*	8	*18*	11	*2*
Biauricular Reference	14	*19*	8	2	8	*18*	11	**0**
Cz Reference	15	20	10	*3*	*4*	20	9	**0**

Table 3: Odds ratio to Bipolar Counterpart LR test. In bold the significant ones (>1).

	delta	theta	alpha	beta	gamma
F3-F4	0,371 ± 0,063	**2,496 ± 0,575**	0,969 ± 0,230	**1,188 ± 0,101**	0,913 ± 0,052
F7-F8	**128,806 ± 50,806**	**2,580 ± 0,958**	0,728 ± 0,221	**1,543 ± 0,126**	0,659 ± 0,045
C3-C4	0,693 ± 0,176	**3,667 ± 1,213**	0,734 ± 0,191	**2,229 ± 0,275**	0,975 ± 0,047
T3-T4	0,753 ± 0,182	0,177 ± 0,068	0,263 ± 0,059	0,836 ± 0,087	**1,118 ± 0,049**
T5-T6	0,277 ± 0,075	**1,011 ± 0,258**	0,104 ± 0,029	0,875 ± 0,080	0,649 ± 0,034
P3-P4	0,574 ± 0,107	0,511 ± 0,091	0,019 ± 0,008	0,962 ± 0,118	**1,888 ± 0,087**
O1-O2	**2,231 ± 0.364**	0,402 ± 0,126	0,767 ± 0,177	0,761 ± 0,072	0,792 ± 0,036

lower SD, consequently, indicating less variability in number of correct diagnosis.

Table 2 shows the results of the individual accuracy rate variability. The columns show, respectively, from left to right, epochs accuracy by each subject of 100%, ≥75%, ≤50%, and 0% (all epochs incorrectly classified by one subject).

SVMs tests presented Lbp as the montage with maximum epoch accuracy (16 subjects with 100% accuracy), followed by Bcp e Czr (15 cases each). Bco was the montage with higher number of cases with accuracy greater than or equal to 75%, less cases with accuracy less than or equal to 50%, and without cases of 0% correct classification.

The LR tests ratified Bco as having the highest number of 100% accuracy results, the highest number of cases with accuracy greater than or equal to 75%, less cases with accuracy less than 50%, and no cases of 0% correct classification (in this last case similar to Bar and Czr, both with zero cases).

This study suggested that Bco was the more trustworthy montage because of his higher rates of 100% epoch accuracy and absence of 0% cases to both classifiers. Consequently, other parameters could be tested based on LR. The odds ratio values (ODDR) could be analyzed from the ratio AD/controls (Table 3). It was possible to verify 11 features presenting ODDR > 1. Consequently, there is a possibility that these features can be associated with AD.

Among these ODDR features, the electrodes F3-F4, F7-F8, C3-C4, and T5-T6 presented values of ODDR > 1 to theta band; the electrodes F7-F8 and O1-O2 presented values of ODDR > 1 to delta band; F3-F4, F7-F8 and C3-C4 presented values of ODDR > 1 to beta band, and T3-T4 and P3-P4 presented values of ODDR > 1 to gamma band.

EEGs of mild DA have higher theta activity and low beta activity [31, 32], as seen in our cases (F3-F4, F7-F8, C3-C4, and T5-T6). Furthermore, these electrodes were directly associated with the inter-hemispheric differences found in our AD population [33]. Moderate to advanced cases of AD are associated with increasing of delta activity [32, 34–36], and this could explain the values found in F7-F8 and O1-O2. Thus, our findings are in accordance to data presented by others.

The analysis of the number of electrodes related to each montage demonstrates that the montages with higher number of signals were Lbp and Czr with 16 signals each, followed by Bar and Bcr with 14 signals. The montage with lowest number of signals was Bco (7 signals). We can say that Bco is also the more compact (less electrodes), consequently, less expensive in terms of processing time.

4. Conclusion

To sum, our results are in accordance with the literature that suggests that the spectral peak is an efficient tool in AD diagnosis [24, 37]. Our contribution is to answer the question that gave origin to the paper. Yes, the analysis indicates that the bipolar inter-hemispheric montage (Counterpart bipolar) is the best to evaluate AD patients with the help of automatic classifiers (DA versus N) [38, 39], when using EEG spectral peaks as features (predictors).

Although more tests are needed to confirm the generalization power of our classifiers, we propose that spectral peak calculation using different montages of electrodes have an influence on the classification results (differentiation) of normal subjects and patients with AD. Our future goal is to generalize the results obtained increasing the number of probands.

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Research Article

Improving the Specificity of EEG for Diagnosing Alzheimer's Disease

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Objective. EEG has great potential as a cost-effective screening tool for Alzheimer's disease (AD). However, the specificity of EEG is not yet sufficient to be used in clinical practice. In an earlier study, we presented preliminary results suggesting improved specificity of EEG to early stages of Alzheimer's disease. The key to this improvement is a new method for extracting sparse oscillatory events from EEG signals in the time-frequency domain. Here we provide a more detailed analysis, demonstrating improved EEG specificity for clinical screening of MCI (mild cognitive impairment) patients. *Methods*. EEG data was recorded of MCI patients and age-matched control subjects, in rest condition with eyes closed. EEG frequency bands of interest were θ (3.5–7.5 Hz), α_1 (7.5–9.5 Hz), α_2 (9.5–12.5 Hz), and β (12.5–25 Hz). The EEG signals were transformed in the time-frequency domain using complex Morlet wavelets; the resulting time-frequency maps are represented by sparse bump models. *Results*. Enhanced EEG power in the θ range is more easily detected through sparse bump modeling; this phenomenon explains the improved EEG specificity obtained in our previous studies. *Conclusions*. Sparse bump modeling yields informative features in EEG signal. These features increase the specificity of EEG for diagnosing AD.

1. Introduction

AD is the most common neurodegenerative disorder; one of its earliest signs is progressive memory loss. Since the number of individuals with AD is expected to increase considerably in the near future [1, 2] (see also Figure 1), reliable treatment and diagnosis of AD are critical. Many approaches to treatment are currently being investigated [3, 4]. A clinical diagnosis accuracy of approximately 85% of detection rate is commonly achieved, by a procedure of exclusion after structural or functional imaging tests—including quantitative electroencephalography (QEEG), laboratory, and psychometric tests [5].

QEEG recordings of subjects in resting condition and with eyes closed are conventionally used in daily clinical routine as a diagnostic tool for AD [6–8]. The main advantage of QEEG is its low cost and its mobility. Several studies have demonstrated that QEEG is useful for investigating Alzheimer's disease (AD) [7, 9–15]. Topographical EEG power changes are believed to reflect early signs of cortical atrophy and/or compensatory cortical reorganization during the early stages of the disease [16]. More specifically, it is commonly believed that AD induces enhanced mean power of slow rhythms (0.5–8 Hz) and loss of fast (8–30 Hz) rhythms [6, 9, 11, 17, 18]. In the EEG of healthy subjects, recorded in resting condition with closed eyes, alpha rhythms are usually mostly distributed in the occipital area; in AD patients, the alpha rhythms increasingly relocate towards anterior areas as the disease progresses [9, 19, 20].

More precisely, these effects have been shown to correlate with severity of AD expressed by mini mental state evaluation (MMSE, [15]) and, more recently, with clinical dementia rating scale (CDR, [13]).

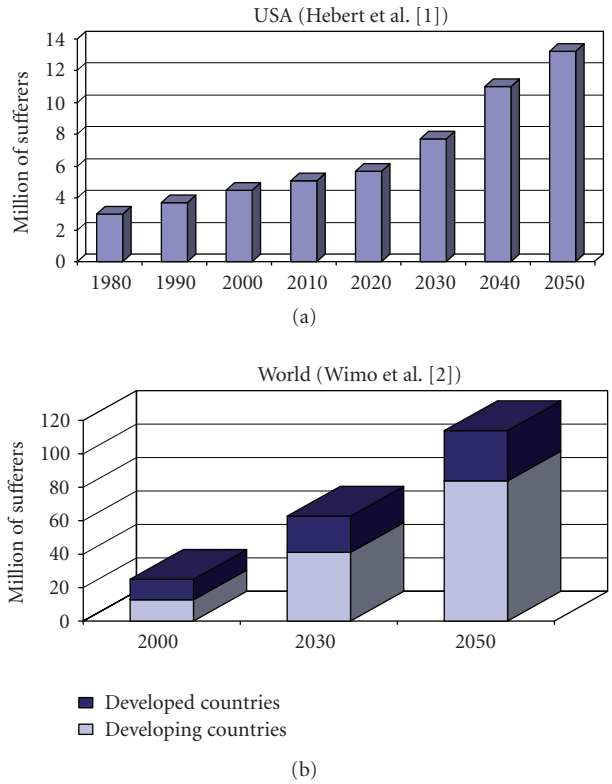

Figure 1: Projection of the prevalence of AD and dementia in the near future. Illustration based on demographic estimates of Hebert et al. [1] (projection of AD prevalence in USA) and Wimo et al. [2] (projection of AD prevalence worldwide).

Early stages of AD have been associated with an increase of theta activity and/or a decrease of alpha activity. In more severe stages of AD, an increase in both theta and delta activities has been observed, together with activity decrease in both alpha and beta frequency bands, in addition to a reduction in peak alpha frequency [5, 13].

Since EEG could be used as a cost-effective screening tool for early detection and diagnosis of the Mild Cognitive Impairment (MCI) stage (see Figure 2), it may change the objectives of treatment: if AD could be reliably diagnosed in an early stage, medical treatments would, instead of being palliative, become curative: they may be used to delay or, hopefully, even bring the disease progress to a halt. However, EEG is not yet considered as a reliable diagnostic tool, because of its lack of specificity [21].

Our long-term research objective is to develop signal processing methods that improve EEG specificity for diagnosing AD; we wish to discover EEG signal features that not only significantly differ in AD patients, but also allow us to reliably separate AD patients and control subjects. This approach is valuable for clinical purposes (as diagnostic tool for AD), and it also more fundamentally contributes to a better understanding of brain dynamics of MCI patients. In this paper, we focus on time-frequency representations of EEG signals, which will enable us to extract EEG features that improve the specificity of EEG for diagnosing AD.

2. Methods

Most often clinical EEG of AD patients is analyzed either in time domain or in the frequency domain (Fourier power analysis). However, those standard approaches entirely ignore the fact that EEG is mainly a nonstationary signal, that is, the statistics of brain rhythms evolve in time. Both signal domains, that is, time domain and frequency domain, may be exploited simultaneously: instead of studying either time or frequency separately, we extract time-frequency information (Figure 3). This is possible through time-frequency representations, such as windowed Fourier transforms, or the more recently proposed wavelet time-frequency representations (WTFRs). However, WTFRs describe signals by means of thousands of coefficients. The information is distributed over those many coefficients and as a result, the coefficients cannot be used directly as signal features; therefore, additional processing is required before discriminative analysis can be carried out. In our previous work [22], we extracted signal features from time-frequency maps by means of sparse bump models; those models consist of time-frequency patterns ("bumps") of high magnitude, lasting nearly 4 time periods centered at a specific frequency. Those patterns are likely to be representative of transient local synchronization of neuronal assemblies, conveying key information on higher-order cognitive and sensory processing. The bump modeling approach allows us to capture oscillatory events in EEG on a trial-by-trial basis, which in turn may be considered as reliable characteristic signatures in Local Field Potentials (LFP) and EEG signals [23, 24]. We hypothesize that those signatures contain significant EEG information about brain disorders such as AD.

Computations were performed using Matlab 7.0 (The MathWorks, Inc.). Statistical analysis was performed using Sigmastat 3.5 (Systat software, Inc.). Wavelet analysis and time-frequency sparsification were performed using the ButIf Toolbox [22, 24, 25].

2.1. Subjects. Patients who complained of only memory impairment were recruited from the outpatient memory clinics of the National Center Hospital for Mental, Nervous, and Muscular Disorders, and the National Center of Neurology and Psychiatry between 1998 and 2000. They underwent thorough neuropsychological testing that revealed quantified, objective evidence of memory impairment with no apparent loss in general cognitive, behavioral, or functional status. In the course of the clinical study, EEG was recorded in rest condition with closed eyes (under vigilance control), by 21 Ag/AgCl electrodes (disks of diameter 8 mm), arranged according to the 10–20 international system. The experiment was conducted with the understanding and the consent of the human subject. The responsible Ethical Committee has approved the experiments.

EEG was recorded with Biotop 6R12 (NEC San-ei, Tokyo, Japan) at a sampling rate of 200 Hz with analog bandpass filtering in the frequency range of 0.5–25 Hz; the signals were then digitally filtered with a high pass filter above 4 Hz by a third-order Butterworth filter. The subjects comprised two study groups; the first group consists of 25 subjects

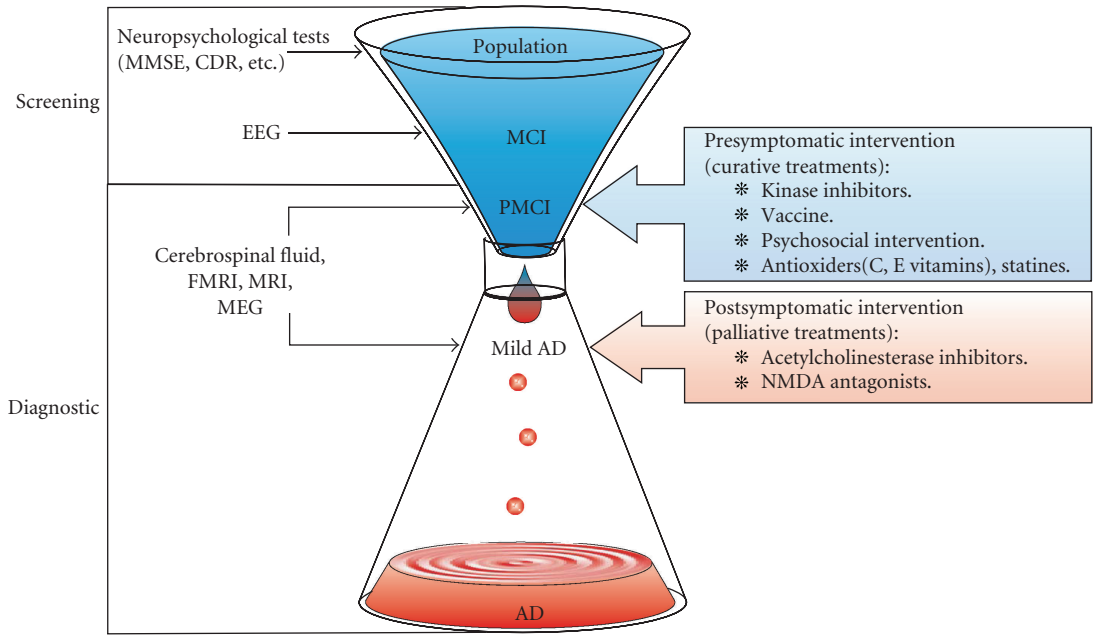

Figure 2: EEG may be used as a screening tool for early-stage AD, since EEG recording technology is inexpensive and available in most hospitals. At an early stage of AD, presymptomatic interventions (curative treatments) may be investigated. However, EEG is not yet a reliable diagnostic tool: the specificity of EEG needs to be improved.

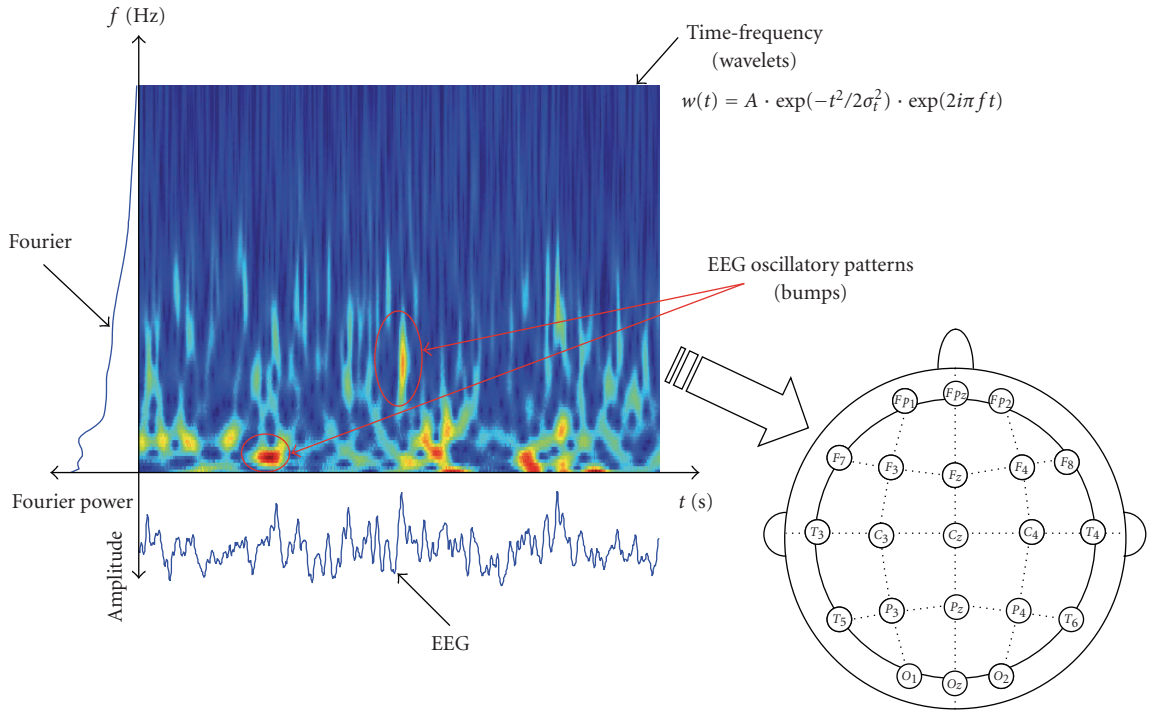

Figure 3: Possible approaches to study EEG brain dynamics. From the time-domain EEG signals, spectral information, in frequency or time-frequency domain (including EEG time-frequency patterns), may be extracted. Afterwards, the spatial information is taken into account, through QEEG or synchrony measures.

who complained of memory problems. At the time of the EEG recordings, these subjects were diagnosed with mild cognitive impairment (MCI). Later on, they all developed mild AD. The average mini mental state exam (MMSE) score in the MCI group was 26 (SD of 1.8).

The other group consists of 56 age-matched healthy subjects who had no memory or other cognitive impairments. The average MMSE of this control group was 28.5 (SD of 1.6). The ages of the two groups were 71.9 ± 10.2 and 71.7 ± 8.3, respectively.

The EEG data was investigated by an EEG expert for artifacts, and sufficiently clean EEG segments of 20 s were selected (on each of the 21 channels). Subject with less than 20 s artifact-clean data were rejected, reducing their number to 22 and 38, respectively. There was no significant difference in age data between the two groups in the subset. We used here this database with 22 patients in the early stage of Alzheimer's disease (mild cognitive impairment or MCI) and 38 control subjects. This EEG data have been analyzed in previous studies [14, 22, 26–28].

2.2. Time-Frequency Spectral Analysis. Wavelet time-frequency maps are computed using complex Morlet wavelets. The (continuous) wavelet transform **W** of a time series **x** is obtained as

$$\mathbf{W}(k,s) \triangleq \sum_{l} \mathbf{x}(l)\psi^{*}\left(\frac{l-k}{s}\right), \tag{1}$$

where $\psi(k)$ is the (complex) "mother"′ wavelet, s is a scaling factor, and $*$ stands for complex conjugate. In this paper, we use the complex Morlet wavelet:

$$\psi(k) = A \cdot \exp\left(\frac{-k^2}{2\sigma_t^2}\right) \cdot \exp(2i\pi f_0 k), \tag{2}$$

where σ_t^2 and f_0 jointly determine the number of oscillations in the wavelet. The complex Morlet wavelet family defined by $2\pi f_0 k = 7$ results in the optimal resolution in time and frequency; it has also proven to be well suited for EEG signals [29–34] (see also [35] for review).

As a benchmark for the approach based on sparse time-frequency bump models (see below), we computed statistics directly from the WTFR. In particular, we computed WTFR relative power in four different frequency bands, that is, θ (3.5–7.5 Hz), α_1 (7.5–9.5 Hz), α_2 (9.5–12.5 Hz), and β (12.5–25 Hz). We controlled the discriminative power of those 4 measures, by computing their classification error using linear discriminant analysis (LDA).

2.3. Sparsification. Next we extract oscillatory events ("bumps") from the time-frequency maps (Figure 4). Those oscillatory events are generally believed to be due to local synchrony of neural populations in the vicinity of the recording electrode [35]. We extract oscillatory bursts ("bumps") by sparse bump modeling [23–25, 28, 36]. More specifically, we used the ButIf toolbox, developed in earlier work (Figure 4, [25, 36]). We now describe this procedure in more detail.

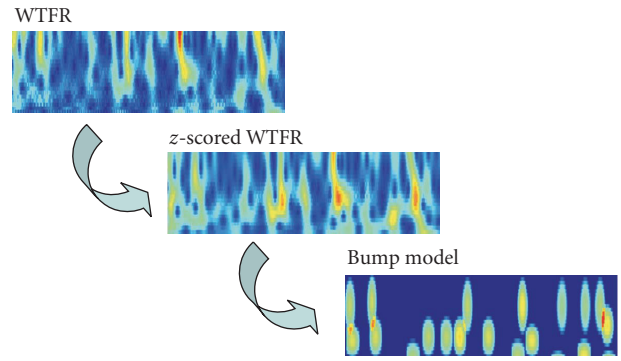

Figure 4: from wavelet time-frequency representation (WTFR) to a sparse time-frequency bump model.

Frequency-dependent z-score normalization [37, 38] was applied to each trial:

$$\mathbf{z}(f,t) = \frac{\mathbf{W}(f,t) - \mu_f}{\sigma_f}, \tag{3}$$

where μ_f and σ_f are the mean and standard deviation, respectively, of the wavelet map **W**. The resulting z-score maps $\mathbf{z}(f,t)$ are approximated by bump models z_{bump}, which are sequences of basis functions b ("bumps") with parameters θ_k (for more details about bump modeling, see [23]):

$$\mathbf{z}(f,t) \approx \mathbf{z}_{\text{bump}}(\theta) = \sum_{k=1}^{N_b} b(\theta_k), \tag{4}$$

with $\theta = (\theta_1, \theta_2, \ldots, \theta_{N_b})$. This decomposition represents the most salient oscillatory events in the z-scored map $\mathbf{z}(f,t)$. As pointed out earlier, we hypothesize that those events are characteristic for EEG dynamics and are therefore relevant for diagnosing AD. We used half ellipsoid basis functions b, and the parameters θ_k are vectors of five parameters: position in time and frequency, width in time and frequency, and amplitude. We computed the number of bumps in four different frequency bands, that is, θ (3.5–7.5 Hz), α_1 (7.5–9.5 Hz), α_2 (9.5–12.5 Hz), and β (12.5–25 Hz). We conducted linear discriminant analysis (LDA), using the number of bumps in those 4 frequency bands as input features for the classification.

3. Results

In an earlier preliminary study, we observed that bump modeling leads to improved classification results (80–93% classification using leave-one-out classification, see[22]), compared to approaches based on WTFR directly, without bump modeling (70% classification). We report here results of a more detailed study, which considers 4 separate frequency bands; so far, we had only considered the frequency band 4–25 Hz [22]. We found significant differences in the theta and beta ranges (Mann-Whitney test, $P < .01$). We compared the WTFR relative power in all four frequency

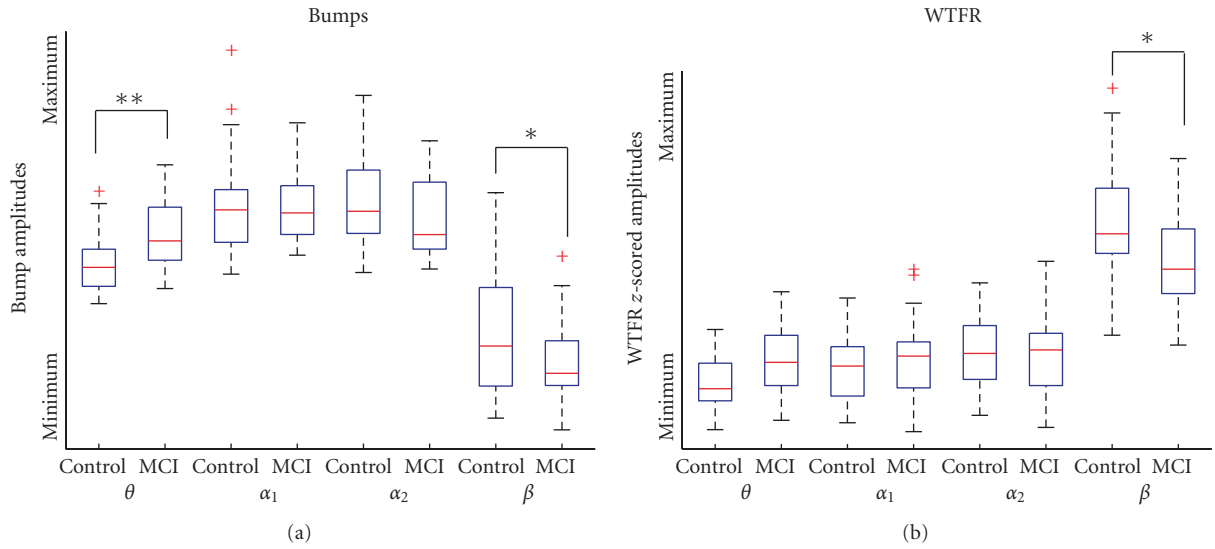

Figure 5: Boxplot comparison of the time-frequency activity between the time-frequency representation and its sparse bump representation. The center line is the median, the box represents the interquartile range, whiskers represent nonoutlier observations, and cross indicates outliers. * and ** indicate significant ($P < .01$) and very significant ($P < .001$) differences. (The relative power appears larger than in lower ranges. This is due to the topography of the wavelet maps (because we used steps of 1 Hz instead of using logarithmic scales). If we resize those values taking into account the size of the ranges, we obtain the same P values and classification results, with a lower power in the beta range as compared to low frequency ranges.)

Table 1: LDA results, for WTFR and Bump amplitude. LOO = Leave-one-out validation error (classification error). SEN = sensitivity. SPE = specificity. In both cases, the best discriminating frequency range is in the theta range. Classification, sensitivity, and specificity are improved by bump modeling.

	θ (3.5–7.5 Hz)	α_1 (7.5–9.5 Hz)	α_2 (9.5–12.5 Hz)	β (12.5–25 Hz)
WTFR	LOO = 33.3%	LOO = 46.7%	LOO = 81.7%	LOO = 48.3%
	SEN = 50.0%	SEN = 27.3%	SEN = 18.2%	SEN = 59.1%
	SPE = 76.3%	SPE = 68.4%	SPE = 18.4%	SPE = 47.4%
Bumps	LOO = 21.7%	LOO = 76.7%	LOO = 51.7%	LOO = 41.7%
	SEN = 72.3%	SEN = 18.2%	SEN = 40.9%	SEN = 68.2%
	SPE = 81.6%	SPE = 26.3%	SPE = 52.6%	SPE = 52.6%

ranges, before and after bump processing (Figure 5). The difference in theta range was enhanced by bump modeling ($P = 10^{-4}$ instead of .08), while the beta range difference was reduced but remained significant. The improvement of classification observed in [22] is therefore mostly attributed to enhanced separation of EEG activity in the theta range.

Classification results (Table 1) also improved in the theta (33.3 errors to 21.7%) and beta (48.3 errors to 41.7%) ranges, with a notable increase of specificity in the theta range (76.3 to 81.6%).

4. Discussion

This paper investigates EEG features for diagnosis AD at an early stage. We observed that bump modeling enhances the statistical differences in EEG activity in the theta range between healthy subjects and MCI patients. This observation may explain the improved classification results by bump modeling, reported in [22]. This effect is also consistent with the existing literature on Alzheimer's disease: low frequency activity (0.5–8 Hz) is generally stronger for patients with AD, while the amplitude of higher frequencies (8–30 Hz) is generally decreased in AD patients [6, 9, 11, 17, 18]. An increase of the theta range activity in the early stages of AD has often been demonstrated [5, 13], and this effect was indeed already visible using Fourier spectral analysis or WTFR, without bump modeling. However, bump modeling amplifies this effect, at least for the EEG data set at hand.

Oscillatory neuronal networks, as a model for brain dynamics, provide a unique interdisciplinary platform to study neurocognitive dynamics [39]. The analysis of EEG data, though of high relevance in cognitive research, poses a number of technical challenges as EEG signals are clearly stochastic and highly nonstationary [40]. The structural organization and associated functional role of EEG oscillations are still far from being completely understood. In

this paper, we investigated the specificity of EEG oscillatory bursts as neural correlates of early-stage Alzheimer's disease. When one computes the average of WTFR power, the structure of the time-frequency map is not accounted for. Whereas most studies focus such averaged EEG responses in time or frequency, this study considers oscillatory events in the time-frequency domain, without relying on EEG averages. The bumps are modelled on single trials, and once this structural information is extracted, we computed averages over electrodes (therefore not losing the burst/background separation). If this grand average is performed on the time frequency maps (without extracting the bump), we actually loose information (classification error increases; P values increase). We observed using our single trial models that EEG organized oscillatory events contain stronger discriminative signatures of the early stage of Alzheimer's disease than averaged spectral EEG statistics, which also explains our previously obtained classification results [22]. Our results suggest that the effect of enhanced low-frequency activity in AD patients may be primarily due to changes in time-frequency burst properties.

We speculate that those slow-wave oscillatory events may be caused by subcortical damage, induced in the early stage of Alzheimer's disease [41, 42]. Background activity in EEG is mostly attributed to cortical neural events; on the other hand, the oscillatory bursts, generated by locally synchronous neural populations, could be related to inter-area connections, including subcortical areas. Indeed, low-frequency synchrony is probably representative of subcortical connectivity [43]. Our results would then attribute the increase of slow wave activity as a probable correlate of subcortical damage induced in the early stage of Alzheimer's disease.

As we have shown recently [24], organized oscillatory bursts in EEG time-frequency activity seem to play a specific functional role in steady state visual evoked potentials, distinct from the more stationary ongoing EEG activity (activity not organized in bursts, representing 70–80% of the signal). We here provide additional evidence that EEG events carry significant information, as they can be used to distinguish normal subjects from MCI patients. This observation is consistent with the interpretation of time-frequency oscillatory events as signatures of locally synchronous neural populations. As a consequence, both background EEG and oscillatory EEG bursts may be highly relevant for understanding and diagnosing brain disorders, including Alzheimer's disease. We could not study the delta band with portions of 20 seconds only: bump modeling has limits in the lower frequency ranges [36]; we would have needed larger windows ($\approx$1 m 20 s duration). The gamma band could not be studied, the data being low-passed filtered below the gamma range. Furthermore, to study reliably gamma range power, special care should be taken to prevent electromyographic artifacts from polluting EEG signals (such as recording EMG sensors), which could not be done at the recording site. However, we insist here that studies of EEG spectrum in the gamma range are seldom led for brain disorders and may provide valuable information. Finally, one should keep in mind that the parameters of bump modeling should be chosen appropriately; otherwise one would model background activity instead of oscillatory bursts (the results presented here are robust to reasonable variations of these parameters).

5. Conclusion

This paper investigates EEG features for diagnosis AD at an early stage. We observed that bump modeling enhances the statistical differences in EEG activity in the theta range between healthy subjects and MCI patients, with a maximal specificity reached in the theta range (passing from 76.3% with WTFR to 81.6% using bumps). This observation may explain the improved classification results by bump modeling, reported in [22]. Our results suggest that the effect of enhanced low-frequency activity in AD patients may be primarily due to changes in time-frequency burst properties.

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Clinical Study

Electromyographic Activity in the EEG in Alzheimer's Disease: Noise or Signal?

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Many efforts have been directed at negating the influence of electromyographic (EMG) activity on the EEG, especially in elderly demented patients. We wondered whether these "artifacts" might reflect cognitive and behavioural aspects of dementia. In this pilot study, 11 patients with probable Alzheimer's disease (AD), 13 with amnestic mild cognitive impairment (MCI) and 13 controls underwent EEG registration. As EMG measures, we used frontal and temporal 50–70 Hz activity. We found that the EEGs of AD patients displayed more theta activity, less alpha reactivity, and more frontal EMG than controls. Interestingly, increased EMG activity indicated more cognitive impairment and more depressive complaints. EEG variables on the whole distinguished better between groups than EMG variables, but an EMG variable was best for the distinction between MCI and controls. Our results suggest that EMG activity in the EEG could be more than noise; it differs systematically between groups and may reflect different cerebral functions than the EEG.

1. Introduction

There is at present no certain diagnostic test for Alzheimer's disease (AD). Much attention is devoted to identify specific markers for AD and its presumed precursor stage, amnestic mild cognitive impairment (MCI). One research technique concerns the electroencephalogram (EEG), which has the advantages of easy availability and low cost.

Research EEG efforts focused on the search for parameters that may help distinguish between healthy ageing, MCI, and AD. AD is characterised by slowing of the EEG, which finding can be quantified using spectral analysis [1]. Resulting variables such as ratios between fast and slow activity, alpha and theta relative power, or the mean frequency have shown varying degrees of efficacy in this respect [2, 3]. Attempts have been made to increase the differences between groups by challenging the subjects, such as by a memory task or more simply by comparing "eyes open" with "eyes closed" conditions. For example, studies comparing AD with healthy controls reported increased theta power and decreased alpha suppression during eye opening and a memory task [1, 2, 4–6]. Compared to controls, EEG abnormalities in MCI consisted of decreased alpha suppression and increased alpha power during a memory task [7, 8]. Such reports suggest that the EEG may have an ancillary role in the diagnostic workup of AD and MCI, but it has not achieved a prominent place in

the diagnostic arsenal [9]. Many attempts have been made to improve the yield of the EEG for this purpose. It is commonly considered of the utmost importance to obtain a high-quality EEG, uncontaminated by artifacts such as blinks, eye movements, and electromyographic (EMG) activity, which can be extremely difficult in dementia. Eye blinks and movements most often cause low frequency potentials, and may therefore affect the measurement of low frequency signals in the EEG, that is, delta and theta waves [10, 11]. EMG activity is usually due to activity of scalp, facial, and jaw muscles and typically most strongly affects frontal and temporal EEG recordings [12]. It mostly affects the high-frequency gamma and beta bands. Over the years researchers devoted much attention to dealing with these unwanted influences. One approach is to reject contaminated epochs from analysis, either manually or through automated methods [2, 10, 13]. Others attempted to negate effects of artifacts using various techniques [14–18], and yet others chose to simply disregard affected frequency bands, largely leaving theta and alpha activity [8]. The rationale behind these intensive efforts to remove eye blinks, movements, and EMG from the EEG is probably that the latter reflects "pure" cerebral activity, whereas the "artifacts" do not. We do not doubt that the EEG reflects cerebral activity, but wondered whether the other group of parameters can be dismissed out of hand. They may be regarded as behavioural correlates, and AD ultimately affects behaviour, in a chain of events involving amongst others biochemistry, neuronal function, and cognition. It is conceivable that the amount of muscle activity is related to the degree of cognitive impairment or to neuropsychiatric symptoms such as agitation, irritability, and depression. If so, then these behavioural correlates may reflect the presence of AD. How well the EEG does so has been investigated, but how well behavioural "contaminations" do so has, to our knowledge, not been tested.

In this pilot study, we explored the discriminative value of quantitative EEG and EMG in distinguishing between AD, MCI and healthy aging. Furthermore, we examined whether EMG activity was related to neuropsychiatric and cognitive measures.

2. Materials and Methods

2.1. Participants. Thirteen age-matched controls, 13 patients diagnosed with MCI [19], and 11 diagnosed with probable AD [20] participated in the study. Patients had been referred to the outpatient memory clinic of the Leiden University Medical Centre. Control subjects without cognitive complaints were recruited through an advertisement in a local newspaper. All patients and controls underwent general medical, neurological, neuropsychological, and brain MRI investigations as part of the standardized dementia screening. Furthermore, all patient histories were reviewed and diagnoses reached in multidisciplinary consensus meetings. Within three months from the standardized dementia screening, patients and controls participated in an additional EEG examination. Eligible subjects had to be free of psychotropic medication, aged 60 years or above, and without previous history of psychiatric and neurological disorders or substance abuse. Moreover, they had no abnormalities on MRI other than white matter hyper intensities or an incidental small lacunar lesion ($\leq$5 mm diameter). The study was approved by the local Medical Ethical Committee. Written informed consent was obtained from all subjects, or from close relatives or caregivers in case of dementia.

2.2. Neuropsychiatric and Cognitive Assessment. The Geriatric Depression Scale (GDS), a patient-based interview, was used to determine the presence and severity of depressive feelings [21]. We used the Neuropsychiatric Inventory (NPI-Q) [22], an informant-based interview, to determine the presence and severity of neuropsychiatric problems (i.e., delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor activity, night-time behavioural disturbances, and eating disturbances). Per item a score from "0" to "3" could be obtained, with "0" indicating the absence of a neuropsychiatric problem and "1", "2", and "3" indicating a mild, moderate, and severe neuropsychiatric problem, respectively. NPI items were clustered based on previous research using principal component analysis [23]. Three factors were used (1) a "mood/apathy" factor including depression, apathy, night-time behavioural disturbances, and eating disturbances, (2) a "hyperactivity factor" including agitation, euphoria, irritability, disinhibition, and aberrant motor activity, and (3) a "psychosis" factor including hallucinations and delusions. Anxiety was considered a separate factor, but it was excluded from further analysis because of limited variability in scores. The Cambridge cognitive examination (CAMCOG) [24] was used to provide a measure of general cognitive functioning.

2.3. EEG Recording and Analysis. EEGs were recorded using a Nihon Kohden 2110 apparatus with 21 Ag/AgCl electrodes placed according to the 10/20 system. ECG, respiration, and horizontal eye movement leads were recorded to facilitate recognition of artifacts. The EEG was band-pass filtered from 0.16–70 Hz for display and analysis but recorded unfiltered. The sample frequency was 200 Hz and the AD precision 12 bits. The average reference montage was used, with the exclusion of electrodes Fp1, Fp2, A1, and A2. All EEGs were recorded in the afternoon. During recording, subjects sat slightly reclined in a comfortable chair, approximately 1.5 m in front of a computer screen. The light in the room was dimmed.

The EEG was registered during a 10-minute eyes-closed period, a 3-minute eyes-open period, and during memory activation. The memory activation task concerned picture memory. Subjects were consecutively shown 10 pictures of common objects on a computer screen. Each picture was presented for two seconds and subjects were asked to name the shown objects aloud. After presentation of the pictures, subjects had to close their eyes and memorise the pictures for 15 seconds. This period was later used for data analysis. Subjects were then asked to open their eyes and name as many pictures they could remember. The task was performed three times using the same 10 pictures. The number of remembered pictures was noted.

2.4. EEG Parameters. To study EEG parameters, we selected specific periods of the EEG using visual analysis. Samples had to be free of eye movements, blinks, and muscle activity. Sample selection was performed by the first author and corroborated by an experienced clinical neurophysiologist. Both were blind to clinical diagnosis. Samples had to be 4–8 seconds in length and were selected during conventional eyes closed and eyes open, and memory activation. Frequency analysis was performed using a fast Fourier transformation. We calculated absolute power in theta (4–8 Hz) and alpha (8–13 Hz) frequency bands.

Three parameters were then calculated: theta relative power during eyes closed, and alpha reactivity during both eye opening and memory activation. Alpha reactivity is defined as the percentile decrease in absolute alpha power as compared to the eyes closed condition. EEG parameters were averaged over all electrodes and over the three selected EEG samples available for each of the eyes closed, eyes open, and memory activation periods. We chose these EEG parameters as they were found sensitive to AD and MCI in previous research [1, 2, 4–6, 8]. All signal processing was performed using MATLAB (The MathWorks, Natick, USA).

2.5. EMG Parameters. To measure the amount of EMG activity, we did not select specific periods but used the entire period corresponding to the eyes closed, eyes open, and each of the three memory activation periods. The only selection involved was that periods in which the tasks were compromised by matters such as electrode correction were omitted. Frequency analysis was performed using a fast Fourier transformation. As a measure of EMG activity, absolute power was calculated in the high frequency band (50–70 Hz) and averaged over temporal (T3, T4, T5, and T6) and frontal electrodes (F3, F4, F7, and F8). These sites are sensitive to EMG activity from scalp, facial, and jaw muscles. The 50 Hz threshold was chosen to exclude any possible confusion with brain activity, that is, beta or gamma activity, that might be present at lower frequencies. In doing so, we aimed to ensure that the measured activity was the result of muscle activity only.

For analysis, we used temporal and frontal EMG during eyes closed, eyes open, and memory activation. EMG parameters were averaged over the three samples available for the memory activation periods.

2.6. Statistical Analysis. SPSS for Windows (release 14.0.1) was used for data analysis. Group differences in cognitive and neuropsychiatric outcomes, EEG, and EMG activity were assessed using ANOVA with post hoc Bonferroni tests. When data were not normally distributed we used two-sample Kolmogorov-Smirnov tests to assess group differences. Subsequently, we performed a two-tailed parametric or nonparametric correlation analysis to investigate relations between EEG and EMG activity on the one hand and cognitive and neuropsychiatric parameters on the other. We did not investigate correlations in specific diagnostic groups because of the limited number of subjects per group. The level of significance was set at $P \leq .05$.

Table 1: Clinical characteristics.

	Controls	MCI	AD
male/ female[a]	3/10	6/7	6/5
age (years)	73 (5)	73 (5)	75 (8)
education (years)	10 (3)	11 (4)	10 (4)
CAMCOG (max 106)	96 (4)	85 (6)**	68 (10)**##
Picture memory score (max 30)	25 (2)	15 (3)**	10 (4)**##
GDS (max 15)[b]	0.8 (1.2)	2.1 (1.7)	1.8 (1.6)
NPI "mood/apathy" (max 12)	—	2.0 (1.2)	2.4 (2.7)
NPI "hyperactivity" (max 15)	—	2.0 (1.9)	2.8 (1.9)
NPI "psychosis" (max 6)	—	0 (0)	0.8 (1.3)

Values in the table are means with S.D. in parentheses. ANOVA was used to assess group differences, except for: [a]χ^2-test was used and [b]Nonparametric two sample Kolmogorov-Smirnov tests were used. In view of the small number of MCI and AD patients for whom an NPI was available, we did not assess group differences. **differs from controls ($P < .01$); ##differs from MCI patients ($P < .01$). CAMCOG: Cambridge Cognitive Examination; GDS: Geriatric Depression Scale (N: 13 controls, 12 MCI and 9 AD); NPI: Neuropsychiatric Inventory (N: 5 MCI and 5 AD).

The aim of the study was to compare not only whether EEG and EMG parameters differed between groups but also whether they did so to different degrees. We assumed they could not be compared directly, because of wholly different distribution patterns including various nonnormal distributions. We also wished to avoid subjective choices regarding abnormality thresholds. To avoid such problems, we chose to plot receiver operating curves. The area under the curve serves as a quantitative indicator of how well a specific parameter distinguishes between groups, irrespective of the nature of the parameter in question. This value usually ranges between 0.5 (meaning the parameter does not distinguish between the groups at all) to 1.0 (the parameter separates the two groups perfectly). We will assume that values below 0.75 have little relevance.

3. Results

3.1. Clinical Characteristics. Clinical characteristics are shown in Table 1. Sex, age, years of education, and GDS scores did not differ between groups. Group differences were found in CAMCOG scores ($F(2,34) = 50.0$; $P < .001$). Post hoc tests showed that AD patients had significantly lower CAMCOG scores than controls and MCI patients ($P < .001$). Furthermore, MCI patients had lower CAMCOG scores ($P < .001$) than controls. There were also differences in the number of pictures correctly remembered in the memory task used during EEG registration ($F(2,34) = 72.6$; $P < .001$). Post hoc tests showed that AD and MCI patients remembered less pictures than controls ($P < .001$). Furthermore, AD patients had a lower score than MCI patients ($P < .01$).

3.2. EEG and EMG. Table 2 shows EEG and EMG data. Group differences in theta relative power were found during eyes closed ($F(2,34) = 10.6$; $P < .001$). Post hoc tests indicated that AD patients showed significantly higher theta relative power as compared with controls and MCI patients (both $P < .001$). Alpha reactivity upon eyes opening and memory activation also differed between groups ($F(2,34) = 5.3$; $P < .01$ and ($F(2,34) = 6.1$; $P < .01$) in that alpha reactivity was decreased in AD patients as compared with controls.

Group differences in frontal EMG were found during both eyes closed and eyes open ($F(2,34) = 3.8$; $P < .05$ and Kolmogorov-Smirnov $Z = 1.4$; $P < .05$). AD patients showed more frontal EMG activity than controls.

3.3. Correlation Analyses. Correlations are shown in Table 3. Theta relative power, alpha reactivity during eyes open, and alpha reactivity during memory activation were related to CAMCOG scores; lower theta relative power and higher alpha reactivity indicated higher CAMCOG scores, and thus better cognitive performance. Furthermore, frontal EMG during eyes open was related to CAMCOG scores in that increased EMG activity indicated lower CAMCOG scores.

Correlations were found between, on the one hand, frontal EMG during eyes closed, temporal EMG during eyes closed, and temporal EMG during eyes open and, on the other hand, GDS scores (see Table 3). In all cases, increased EMG activity indicated more complaints of depression. No correlations were found between EEG and EMG parameters and neuropsychiatric complaints on the NPI.

3.4. Receiver Operating Curves. ROC data are shown in Table 4. Of the 9 EEG ROCs, 4 reached levels above 0.75. Three of these concerned the comparison between AD patients and controls, and the fourth the AD-MCI comparison.

Of the 18 EMG ROCs, 3 reached levels above 0.75. Two concerned the AD-control comparison, and one the MCI-control comparison.

Table 2: EEG and EMG data.

	Controls	MCI	AD
Eyes closed			
EEG theta relative power (%)	28 (8)	29 (14)	53 (21)**##
Frontal EMG (μV^2)	2 (1)	6 (5)	7 (7)*
Temporal EMG (μV^2)	4 (4)	9 (8)	8 (10)
Eyes open			
EEG alpha reactivity (%)	67 (20)	59 (18)	37 (32)**
Frontal EMG (μV^2)[a]	6 (4)	16 (25)	24 (34)*
Temporal EMG (μV^2)[a]	10 (8)	15 (25)	18 (30)
Memory activation			
EEG alpha reactivity (%)	40 (33)	10 (32)	−7 (35)**
Frontal EMG (μV^2)[a]	3 (2)	13 (15)	21 (41)
Temporal EMG (μV^2)[a]	6 (5)	19 (26)	14 (16)

Values in the table are means with S.D. in parentheses. ANOVA was used to assess group differences, except for: [a]Nonparametric two sample Kolmogorov-Smirnov tests were used. *differs from controls ($P \leq .05$); **differs from controls ($P \leq .01$); ##differs from MCI patients ($P < .01$).

4. Discussion

EMG activity is usually regarded a source of problems in EEGs used for patient care and research purposes in dementia, because the EMG impairs the registration of the EEG. This is particularly relevant for activity at the high (beta and gamma) and low (delta) ends of the spectrum. The most important new finding of this pilot study is that EMG activity could be not only a hindrance but also reflects some aspects of AD and MCI. We base this conclusion on two lines of evidence.

Firstly, the amount of frontal EMG activity was higher in the AD group than in controls, both during the eyes open and eyes closed conditions. As such, its presence is linked to the presence of AD, presumably through an association between facial muscle activity and the expression of emotions such as depression. The ROC analysis corroborates this finding. We used this type of analysis to allow us to compare variables of a different nature, that is, EEG and EMG. This comparison shows that EEG variables on the whole distinguish better between the groups than EMG variables and also that EMG variables are not worthless in this respect. In fact, for the distinction between MCI and controls, it was an EMG variable that best distinguished between groups.

Secondly, EMG activity cannot be considered as an aspecific finding: we found significant relations between EMG activity and patient-based reports of depression. It, therefore, seems likely that the EMG reflects disease-related neuropsychiatric changes. The relation between facial EMG activity and depression has been studied previously: for instance, when depressed subjects generated sad thoughts or simply thought about a typical day in their current lives, the amount of facial EMG activity increased [25]. It can be imagined that a degree of depression in patients with memory complaints is expressed as an increased facial EMG. As one might expect, different emotions lead to different patterns of EMG activity in various muscles [26]. In the context of an EEG, it seems likely that activity of the frontalis, corrugator supercilii, and zygomatic major muscles are picked up preferentially. These muscles are indeed involved in affective reactions, such as distress and pleasure. Note that we made no effort to record these muscles with any degree of precision, so we refrain from drawing detailed conclusions in this regard.

It may well be argued that even if there is more EMG activity in AD than in controls, this has little bearing on the understanding of the pathophysiology of AD. In part we agree; the EMG reflects muscle activation and is thus a behavioural correlate, while the EEG is a direct reflection of cerebral function. Decreased EEG activity has been linked with functional disconnections among cortical areas, resulting among others from neuronal death and/or deficiency of neurotransmitters [1]. This is no doubt true, but it should be kept in mind that it is doubtful which cerebral functions are expressed in the various rhythms of

Table 3: Correlations between EEG and EMG activity on the one hand and cognitive and neuropsychiatric scores on the other hand.

	CAMCOG	GDS[a]	NPI mood/apathy	NPI hyperactivity	NPI psychosis[a]
Eyes closed					
EEG theta relative power	**−0.54****	0.32	−0.45	−0.08	−0.14
Frontal EMG	−0.25	**0.52****	0.43	0.30	−0.11
Temporal EMG	−0.12	**0.39***	−0.01	−0.32	−0.24
Eyes open					
EEG alpha reactivity	**0.53****	−0.04	0.43	0.17	−0.02
Frontal EMG[a]	**−0.43****	0.33	0.13	0.20	−0.01
Temporal EMG[a]	−0.05	**0.35***	0.42	0.07	−0.24
Memory activation					
EEG alpha reactivity	**0.43****	−0.28	0.11	0.23	−0.37
Frontal EMG[a]	−0.24	0.28	−0.21	0.07	−0.07
Temporal EMG[a]	−0.30	0.28	−0.06	−0.11	−0.36

Values in the table are Pearson's correlation coefficients. In [a]Spearman's correlation coefficients are displayed, as values were not normally distributed. $^{*}P \leq .05$ and $^{**}P \leq .01$. Significant correlations are printed in bold. CAMCOG: Cambridge Cognitive Examination; GDS: Geriatric Depression Scale (N: 13 controls, 12 MCI and 9 AD); NPI: Neuropsychiatric Inventory (N: 5 MCI and 5 AD).

Table 4: Classification accuracy of EEG and EMG parameters by receiver operating curves (ROC).

	ROC area under the curve		
	AD versus controls	MCI versus controls	AD versus MCI
Eyes closed			
EEG theta relative power (%)	**0.92**	0.50	**0.85**
Frontal EMG (μV^2)	**0.78**	**0.83**	0.52
Temporal EMG (μV^2)	0.64	0.73	0.41
Eyes open			
EEG alpha reactivity (%)	**0.82**	0.65	0.72
Frontal EMG (μV^2)	**0.86**	0.61	0.71
Temporal EMG (μV^2)	0.49	0.51	0.50
Memory activation			
EEG alpha reactivity (%)	**0.84**	0.74	0.67
Frontal EMG (μV^2)	0.74	0.73	0.47
Temporal EMG (μV^2)	0.69	0.70	0.49

Areas under the curve of over 0.75 are printed in bold.

the EEG. For example, slowing of the EEG is not specific to the type of dementia, in spite of completely different pathophysiological substrates. In fact, EEG slowing is not even specific to dementia, as this also occurs in a large variety of other conditions ranging from mechanical trauma to intoxications. One may wonder whether EEG slowing is really so much closer to the pathology of AD than EMG activity.

In the present study, the EEG generally resulted in a better discrimination between groups than the EMG, except for the MCI-control distinction, in which the EMG performed better. We do not suggest that henceforth the EMG should be used for discriminating MCI patients and controls, as we made no attempt to optimise recordings for this purpose. For similar reasons, we did not calculate measures such as sensitivity and specificity even though many attempts have been made to optimise the EEG for this purpose. Regarding optimisation, the best parameter might be the one that accurately reflects the presence of a pathogenic cause. An example is measuring the number of CAG repeats in Huntington's disease, reflecting the pathogenetic cause. The test however does not reflect the degree of affliction at all. EEG parameters do not reflect the pathogenetic cause but the degree of affliction. As this varies from normal to severely abnormal, there must be an overlap in function in early phases. This may be seen as a failure of the test to pick up any differences, but it seems more likely that the overlap truthfully represents an overlap in function. The best we can do may be to push against the detection boundary, and in this respect, it may pay to keep an open mind regarding the nature of the parameter to be measured.

Conflict of Interests

There are no potential conflict of interests, including any financial, personal or other relationships with people or organizations that could inappropriately influence the current study. The study has been approved by the local Medical Ethical Committee.

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Review Article

The Use of Auditory Event-Related Potentials in Alzheimer's Disease Diagnosis

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Event-related potentials (ERPs) are important clinical and research instruments in neuropsychiatry, particularly due to their strategic role for the investigation of brain function. These techniques are often underutilized in the evaluation of neurological and psychiatric disorders, but ERPs are noninvasive instruments that directly reflect cortical neuronal activity. Previous studies using the P300, P3a, and MMN components of the ERP to study dementing illness are reviewed. The results suggest that particularly the P300 brain potential is sensitive to Alzheimer's disease processes during its early stages, and that easily performed stimulus discrimination tasks are the clinically most useful. Finally, these data suggest that the P300 ERP can aid in the diagnosis of dementia and may help in the assessment of early Alzheimer's disease.

1. Introduction

Alarmingly increasing prevalence of Alzheimer's disease (AD) due to the aging population in developing countries, combined with lack of standardized and conclusive diagnostic procedures, make accurate diagnosis of Alzheimer's disease, especially for its early stage also known as amnestic mild cognitive impairment (MCI), a major public health concern. While no current medical treatment exists to stop or reverse this disease, recent dementia-specific pharmacological advances can slow its progression, making early diagnosis all the more important. Behaviourally, both AD and MCI are traditionally diagnosed in relation to abnormalities in brain functions such as memory, cognition, perception, and language. Furthermore, the differentiation of probable AD from other dementing illnesses is generally obtained by excluding alternative causes for cognitive dysfunction. It is important therefore to determine whether AD and MCI can be characterized by functional deficits other than high-level abnormalities already described and whether, with further development, they are specific and sensitive enough to contribute to the search of early markers of the disease process.

In an attempt to facilitate the diagnosis of AD, several noninvasive biomarkers have been proposed, including event-related potentials (ERPs). ERPs are voltage changes time-locked to some physical or mental occurrence in the ongoing electrical brain activity (recorded as EEG). Depending on the type of sensory stimulus, the ERPs can be divided into somatosensory, visual, or auditory ERPs. This review concerns the auditory modality.

In auditory ERP studies, perhaps the most commonly used experimental approach is the active oddball paradigm. In this paradigm, typically two classes of stimuli are presented, one occurring frequently (standard) and the other occurring infrequently (target), and the subject is required to distinguish between the two stimuli and to respond to the stimuli that are predesignated as targets. Variations of this paradigm include the passive oddball paradigm, in which the subject is instructed to ignore the stimuli, and so-called novelty oddball paradigm, in which a third class of stimuli (novelty) are also presented intermixed with the standard and target stimuli.

ERPs offer a psychophysiological method for studying attentional processes, language, and memory functions, yielding information not available from behavioral studies.

A number of studies have suggested that ERPs are useful indices for assessing changes in cognitive brain functions. In particular, the P300 component of the ERP has been widely applied in the scientific study of age-related cognitive dysfunction, because it reflects attentional and memory processes. This ERP is most commonly elicited in a active oddball paradigm when a subject detects an occasional target stimulus in a regular train of standard stimuli. In the novelty oddball paradigm, in turn, deviant or unexpected tones elicit a frontal subcomponent of P300, namely, the P3a, which is considered as an electrophysiological marker of the orienting response [1]. Furthermore, in the passive oddball paradigm, at around 200 ms the deviant tones elicit a component called mismatch negativity (MMN). The MMN is thought to reflect the mismatch between a trace in a sensory memory (of the standard stimulus) and the representation of the current stimulus to which the trace is compared, and is considered to be an index of the preattentive stage of auditory information processing [2].

The present paper briefly reviews from the literature (especially from [3]) the background of clinical MMN and P300 applications.

2. P300 Responses

Auditory P300, a positive deflection occurring at about 300 ms from stimulus onset, is one of the most widely studied components of the ERP. It is generated by the activation of multiple neocortical and limbic regions, and has two functionally different components: the earlier P3a that is maximal over frontocentral regions, and the later P3b (hereafter called P300 in this review) that is maximal at posterior scalp locations [4].

3. Psychophysiology of P300

The P300 is parietocentral positivity that occurs when a subject detects an informative task relevant stimulus (first described by Desmedt et al. [5]; Sutton et al. [6]). It is most commonly elicited in an active oddball paradigm when a subject detects an occasional target stimulus in a regular train of standard stimuli. The P300 probably represent concurrent activity in multiple regions of the brain, including temporoparietal neocortical areas and higher limbic structures [7–16].

The major theoretical interpretation of the P300 component is that it indexes updating of activity in corticolimbic circuits in processes requiring attention and working memory [17, 18]. This context updating theory has its roots in Sokolov's model of the orienting response, which has been postulated to result from a change in the organism's neural representation of the stimulus [19]. P300 amplitude is also proportional to the amount of attentional resources devoted to a given task [20–22] and has been associated with superior memory performance [23, 24]. P300 amplitude can therefore be viewed as a measure of CNS activity that reflects the processing of incoming information when it is incorporated into memory representations of the stimulus and the context in which the stimulus occurs. Variation in P300 amplitude is, therefore, assumed to reflect the degree or quality with which that information is processed.

The P300 has a latency to peak of anywhere from 300 to 1000 ms, depending on task complexity and the clinical sample tested. A frequently observed phenomenon is that the P300 latency increases when categorization of the stimulus becomes more difficult. A general consensus seems to be that P300 is evoked after the stimulus has been evaluated [25]. Thus, the latency of P300 has been regarded as a measure of stimulus evaluation time [26, 27]) and is generally unrelated to response selection processes [28, 29]. It is therefore independent of behavioral reaction time [30, 31]. Indeed, it is just these properties that make the P300 a valuable tool for assessing cognitive function: because P300 latency is an index of the processing time required before response generation, it is a sensitive temporal measure of the neural activity underlying the processes of attention allocation and immediate memory. In addition, P300 latency is negatively correlated with mental functions in normal subjects, with shorter latencies associated with superior cognitive performance (e.g., [32–35]). The neuropsychological tests that are best correlated with P300 latency are those that assess how rapidly subjects can allocate and maintain attentional resources. This association is also supported by results indicating that P300 latency increases as cognitive capability decreases from dementing illness [27, 35–40]. Thus, P300 latency is directly associated with cognitive capability in both normal and patient populations.

4. Clinical Applications of P300

Changes in the latency, amplitude, and topography of the P300 correlate with clinical findings in a wide range of disorders and brain injuries. Since the P300 has been related to the fundamental cognitive events of stimulus evaluation and immediate memory in normals, and because its peak latency is correlated with neuropsychological tests of cognitive function, this ERP component may provide an objective index of the degree of dementing illness which can be distinguished from the electrophysiological changes found in normal aging. Indeed, the initial suggestion that the P300 component might be a useful tool for investigating cognitive functions came from studies of normal aging and dementia, since peak latency was found to be prolonged in individuals with dementing illness compared to similarly aged normal subjects [41, 42]. The extent of deviation varied with the aetiology of the disorder, being greatest with metabolic causes and brain tumours and least with degenerative disorders, such as AD [41]. The P300 latency changes were reversed by treatment in patients with metabolic encephalopathy, with latency returning to normal values when the disorder was corrected and cognitive functions were again normal [43, 44].

Several studies have now verified that P300 is an objective and sensitive tool for demonstrating cognitive impairment in AD, as these patients have increased P300 latency and decreased P300 amplitude compared to elderly controls

subjects [35, 45, 46]. P300 is sensitive to AD processes already during its early stages [47], and similar P300 alterations have also been demonstrated in MCI [48–50]. P300 amplitude or latency alterations may also identify preclinical changes in participants who are at relatively high risk for AD because of genetic predisposition [48, 51]. P300 may thus reveal neurophysiological changes prior to the emergence of clinical deficits, which could advance the early detection and diagnosis of AD.

P300 latency increases systematically as cognitive function becomes worse in dementing illness, even though component size is not directly associated with the degree of mental impairment [27, 40, 52]. Recently, in a followup study, it was shown that the abnormalities in P300 in AD and MCI latency correlated with the severity of cognitive impairment. Furthermore, upon followup, one year later after the baseline study, the P300 latencies demonstrated significantly more prolongation than their baseline measures in AD and MCI patients, although their neurophysiological evaluation showed no statistical decline, suggesting that the P300 latency may reflect cognitive decline more sensitively than neuropsychological tests in the longitudinal followup of AD patients [53]. It has also been suggested that P300 latency is a valuable tool for the evaluation of cholinesterase inhibitors treatment in demented patients [54]. However, P300 latency does not seem to be capable of predicting which MCI patients will convert to AD [48], and therefore seems to have no predictive value for AD diagnosis.

Some reports have suggested that ERP measures may distinguish between subcortical (e.g., Huntington's and Parkinson's disease) and cortical (Alzheimer's, cerebral vascular accident) dementias [55, 56]. Other studies have indicated that P300 latency can separate individuals with dementia from those with depression-associated pseudodementia [37, 57].

Associations between P300 latency and the level of cognitive function also have been reported in neurological disorders, in confusional states, and for posttraumatic syndromes (cf. [34, 36, 38, 43, 44, 58–61]). Furthermore, the P300 component has been used to study psychiatric disorders such as alcoholism, depression, and schizophrenia (e.g., [62–67]). Taken together, these findings suggest that P300 may be clinically useful as an index of cognitive function, although its diagnostic utility is questionable (cf. [27, 37, 40, 68]). The P300 continues to be an important signature of cognitive processes such as attention and working memory and of its dysfunction in neurologic and mental disorders [69].

5. Psychophysiology of P3a

The P3a is a frontocentrally maximal positive ERP wave elicited by deviant or unexpected events [4, 70], and it is considered as an electrophysiological marker of the attentional switching, that is, the orienting response [1]. P3a is generated by a complex cerebral network, including the prefrontal, cingulate, temporo-parietal, and hippocampal regions [7, 71–74] and it is recorded over widespread anterior and posterior scalp sites [73]. It has been distinguished from P300 by a shorter peak latency, a more frontally oriented scalp topography and different elicitation conditions [4].

6. Clinical Applications of P3a

The P3a is affected in several psychiatric and neurological disorders. An enhanced P3a amplitude over the left frontal region has been found in chronic alcoholism [75]. An enhanced P3a are found in children with depression [76] and ADHD [77]. In addition, patients with closed head injuries show larger P3a amplitudes than control subjects [78, 79].

There are only a few studies published about P3a in AD and the findings have been to some extent inconsistent. Some authors found that AD patients are characterized by longer P3a latency than control subjects suggesting delayed orientation to deviant stimuli in AD [49, 80]. Furthermore, these authors suggested that separation of P3 subcomponents (P3a and P300) by dipole source analysis may increase sensitivity and specificity in correctly detecting AD patients from healthy subjects [49, 80]. On the other hand, some authors found no difference in the P3a between AD patients and controls but instead showed that the P3a was different in AD patients compared with patients with vascular dementia whereas the P300 was similar in these patients [81].

7. Psychophysiology of MMN

The mismatch negativity (MMN) is a frontal negativity at around 100–200 ms. It is generated automatically whenever the stimulus deviates physically from the immediately preceding context [82, 83]. MMN can be elicited by changes in simple tones, such as frequency or duration, and also by complex sounds such as phonemes [2]. The MMN is commonly derived by subtracting the ERP to the standard stimulus from that to the deviant stimulus. The MMN is thought to reflect the mismatch between a trace in a sensory memory (of the standard stimulus) and the representation of the current stimulus to which the trace is compared and is considered to be an index of the preattentive stage of auditory information processing [2]. In addition, by measuring the decay of the MMN amplitude as a function of the interstimulus interval, it is possible to estimate the duration of sensory memory. The MMN is generated mainly in the auditory cortex in the temporal lobes [84, 85]. Furthermore, a frontal MMN generator [86], has also been implicated.

8. Clinical Applications of MMN

MMN is an important ERP measure as it may reveal deficits of both sensory memory storage and of fundamental automatic mismatch detection mechanism [87, 88]. MMN is attention independent and therefore particularly suitable for studies with subjects who do not cooperate at all or cooperate very poorly. Clinical research lines using the MMN involve schizophrenia, dyslexia, autism spectrum disorders, coma, alcoholism, and dementia (for a review, see [89]).

Early studies on the aging effects on the MMN show that the MMN is smaller and prolonged in the ERPs of the normal old compared to those of the young (e.g., [90, 91]). In subsequent studies, Pekkonen et al. [92, 93] found that with frequency changes this effect was confined to conditions with long inter-stimulus intervals (ISIs), indicating that it is sensory memory rather than perception that is affected by aging. Similarly, several studies have found fairly unaffected MMN in AD at short ISIs [94]; (for review, see [95]), whereas MMN was reduced at long (3s) ISI in these patients [96]. These results suggest that AD appears to reduce the duration of auditory sensory memory when sound frequency is involved.

Interestingly, the pattern with duration MMN is quite different, with the age-related MMN-amplitude decrement being present even with short ISIs (for a review, see [95]). However, in patients with AD automatic stimulus discrimination to duration change in the auditory cortex is preserved as compared with normal aging [97]. These findings imply that although the preattentive discrimination to duration deviance is attenuated in aging, it is not further damaged in the early phase of AD. This may be due to the fact that the neurodegenerative changes underlying AD mainly affect mesial temporal structures like hippocampus, whereas the lateral aspects of the temporal lobes, where the MMN is generated, are less damaged [97].

In summary, studies on MMN in AD demonstrate that older controls and patients with AD produce MMNs that are reduced in amplitude relative to the younger subjects, but the differences between older controls and AD subjects are relatively small. Also, the fact that the AD subjects can produce significant MMN responses suggest that they do have a relatively intact MMN, albeit reduced in amplitude compared to controls [94]. In all the aforementioned studies, patients had minor to moderate cognitive impairment and taking into account the acknowledged cholinergic hypothesis in AD, probably their cholinergic defect was not sufficient to cause MMN generator impairment per se at short ISIs, but in some studies, impaired the duration of the memory trace [96].

As reviewed here, the value of the MMN in the early diagnosis of AD is somewhat limited. However, more pronounced MMN alterations have been found in demented Parkinson's disease (PD) patients relative to normal controls or patients with AD and dementia with Lewy-bodies, indicating that demented PD patients to a larger degree than the control groups have a deficit in automatic auditory change detection [98]. Furthermore, MMN may aid in the differentiation of normal pressure hydocephalus (NPH) from NPH with concomitant AD [99]. Thus, the MMN may aid in the differentiation of AD from other dementing illnesses. These findings also have implications for understanding cognitive and behavioural functioning in patients with dementia.

9. Conclusion

Alzheimer's disease is a neurodegenerative disorder, causing neuronal death that leads to cognitive function decline. Two misfolded proteins, β-amyloid that causes plagues and hyperphosphorylated-τ that causes neurofibrillary tangles are often blamed, yet, the genesis of these proteins, and in fact the true cause of the disease, are still unknown. While no current medical treatment exists to stop or reverse this disease, recent dementia-specific pharmacological advances can slow its progression, making early diagnosis all the more important.

Application of the auditory ERPS to the study of dementing illness and AD has produced positive findings. The P300 response, in particular, has become popular in studies of dementia. Because the P300 response is related to fundamental aspects of cognitive function in normals, it should be useful in the diagnosis of dementia, especially that of the Alzheimer's type. In general, this assertion is supported by a wide variety of previous findings that include the spectrum of dementias. Although the P300 does not appear to differentiate between types of cortical dementias, it does accurately reflect the level of cognitive dysfunction caused by these disorders. Furthermore, the auditory evoked potentials (including the MMN) might offer an additional tool to index cholinergic dysfunction in aging and in neurodegenerative diseases such as AD. Moreover, when variables which affect P3 measures such as task parameters and population differences are well controlled, the P3 ERP can differentiate between early AD patients and normal controls. Given these effects, it is reasonable to suppose that further refinement of the test procedures would facilitate the delineation of differences in the P3 response for the early diagnosis of AD.

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Review Article

Transcranial Magnetic Stimulation Studies in Alzheimer's Disease

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Although motor deficits affect patients with Alzheimer's disease (AD) only at later stages, recent studies demonstrated that primary motor cortex is precociously affected by neuronal degeneration. It is conceivable that neuronal loss is compensated by reorganization of the neural circuitries, thereby maintaining motor performances in daily living. Effectively several transcranial magnetic stimulation (TMS) studies have demonstrated that cortical excitability is enhanced in AD and primary motor cortex presents functional reorganization. Although the best hypothesis for the pathogenesis of AD remains the degeneration of cholinergic neurons in specific regions of the basal forebrain, the application of specific TMS protocols pointed out a role of other neurotransmitters. The present paper provides a perspective of the TMS techniques used to study neurophysiological aspects of AD showing also that, based on different patterns of cortical excitability, TMS may be useful in discriminating between physiological and pathological brain aging at least at the group level. Moreover repetitive TMS might become useful in the rehabilitation of AD patients. Finally integrated approaches utilizing TMS together with others neuro-physiological techniques, such as high-density EEG, and structural and functional imaging as well as biological markers are proposed as promising tool for large-scale, low-cost, and noninvasive evaluation of at-risk populations.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder clinically characterized by a progressive cognitive decline that affects memory and other cognitive functions, as well as mood and behavior [1]. It is the most common type of dementia and nowadays it affects more than 35 million people all over the world. The disease is characterized by extracellular formation of Aβ amyloid plaques and intracellular deposition of neurofibrillary tangles in specific cortical areas; this process leads to loss of neurons and white matter, amyloid angiopathy, inflammation, and oxidative damage [2]. Transcranial magnetic stimulation (TMS) is a safe, noninvasive and painless technique today widely employed to explore brain functions [3, 4]. From about 15 years, it provides a valuable tool for studying the pathophysiology of Alzheimer's disease. This paper intends to review the most relevant studies in the literature in order to provide to the reader a clear picture of what we have learned by using TMS in the study of AD. A PubMed-based literature review of English-language studies was performed to acquire publications on AD and TMS. Key search words were "dementia, Alzheimer's disease, transcranial magnetic stimulation, and motor cortex excitability."

This work is schematically divided in to several sections: after the introduction, in Section 2 we briefly discuss basic principles of TMS and some types of paradigms used by researchers in studying AD patients; in Section 3 we explain why TMS is important for studying AD pathophysiology and what are the main AD alterations highlighted with this neurophysiological technique; in Section 4 we briefly introduce studies that used TMS to make differential diagnosis

of dementia; in Section 5 we discuss TMS employment as a treatment tool and in Section 6 we provide concluding remarks and topics of future research.

2. TMS

Transcranial magnetic stimulation (TMS) is a safe, non-invasive, and painless technique today widely employed in studies designed to explore brain functions [3, 4]. It was introduced by Barker and colleagues in 1985, inspired by transcranial electric stimulation studies. In TMS short current pulses are driven through a coil positioned on the scalp of the subject [6]. The transient magnetic field generated in the brain produces an electrical current able to depolarize the cell membrane, resulting in opening of voltage-gated ion channels and consequently giving rise to the action potential. The electric field induced by TMS depends on the position and orientation of the coil over the head of the subject and also by structural anatomical features and by the local conductivity of the scalp itself [7]. Different types of stimulation, declined in several type of paradigms, are currently possible (e.g., single pulse, paired-pulse, repetitive): we will focus on those more widely used in studying Alzheimer's disease.

2.1. Single Pulse. Applying a single TMS pulse over primary motor area, a series of epidurally recordable corticospinal volleys are generated which reflect the transsynaptic activation of superficial cortical neurons. Volley's temporal summation at the spinal motoneuron level elicit a motor evoked potential (MEP) in contralateral target muscles [8]. This approach is useful to study the disease processes or the neuroactive drugs [9–12] that affect regulatory mechanism of cortical excitability [13]. Single TMS pulses are also very useful to track plastic changes which originate from physiological and pathological manipulations involving the motor system and can be used for mapping motor cortical outputs. Cortical mapping procedures, with single TMS pulses focally applied on several scalp positions overlying the motor cortex, take into account the number of cortical sites eliciting MEPs in a target muscle and its "center of gravity" (COG, [9, 10]). The location of the COG of the MEP map corresponds to the scalp location at which the largest number of the most excitable corticospinal neurons can be stimulated. Therefore, changes in the COG are considered able to indicate true changes in the topographical organization of motor cortex representations.

2.2. Paired-Pulse (SICI and ICF, SAI). TMS paired-pulse (ppTMS) protocols consist in the erogation of two individual different kinds of stimuli separated by a predetermined interval of time (interstimulus interval -ISI-). In a well-known paradigm [12, 15] able to test intracortical inhibitory/facilitatory balance, a subthreshold magnetic conditioning stimulus (S1) is followed by a suprathreshold magnetic test stimulus (S2) delivered on the same target area through the same coil. The effect of S1 on the size of control MEP is thought to originate at the cortical level [14, 16, 17]. It is in fact known that a supra-threshold stimulus determines a corticospinal output leading to a MEP, while a sub-threshold stimulus only excites local, cortical interneurons [18]. Thus, by combining a sub-threshold pulse with a suprathreshold pulse one can assess the effects of inter-neurons on cortical output [19, 20]. The test responses are inhibited at interstimulus intervals (ISIs) of 1–5 ms and are facilitated at ISIs of 8–30 ms; these phenomena are referred as short intracortical inhibition (SICI) and intracortical facilitation (ICF). Based on the time course of cortical inhibition and facilitation and on results of pharmacological manipulations during ppTMS, several authors have suggested that SICI is mediated by GABA-A receptors [21] whereas ICF is mediated by glutamatergic N-methyl-D-aspartate (NMDA) receptors, [19, 20]. The balance between SICI and ICF is altered in several neurological conditions showing abnormal cortical excitability [22, 23].

Another paradigm, widely used in AD, to study intracortical inhibitory mechanisms is the short-latency afferent inhibition (SAI). This approach consists of a conditioning electric stimulation applied on the median nerve at the wrist preceding a contralateral TMS test pulse by 20–25 ms, a timing compatible to the activation of the primary sensori-motor cortex. The resulting MEPs are inhibited with respect to those evoked by the test pulse alone. The origin of this phenomenon is cortical [24–26] and probably it depends on the central cholinergic activity; Di Lazzaro and colleagues in fact clearly demonstrated that SAI can be abolished by scopolamine, a muscarinic antagonist [27].

2.3. Repetitive TMS. Repetitive TMS (rTMS) consist of single TMS pulses delivered in trains with a constant frequency and intensity for a given time. Repetitive TMS is capable to temporarily modify the function of the underlying cortical area because rTMS may exert excitatory or inhibitory actions on underling cortical activity, depending on TMS parameter used, as well as on the task at hand. An important feature of rTMS is the capacity, depending on the frequency of application, to increase or decrease the level of cortical excitability. This is the basis for the reported clinical benefits in diseases linked to brain excitability dysfunctions and the reason why this technique is increasingly used with therapeutic and rehabilitative functions [28, 29].

3. TMS for Studying AD Pathophysiology

Neurophysiological aspects usually studied in Alzheimer's disease by means of TMS are alteration of motor cortex excitability and cortical reorganization of motor output. TMS studies have in fact clearly demonstrated the existence of cortical hyperecitability and subclinical motor cortical reorganization mostly in the early stages of AD.

The cortical hyperexcitability is believed to be a compensatory mechanism to execute voluntary movements [5], despite the progressive impairment of associative cortical areas. At present, it is not clear if these motor cortex excitability changes might be the expression of an involvement of intracortical excitatory glutamatergic circuits or an impairment of cholinergic and/or gabaergic activity [5]. In fact, although

the best hypothesis for the pathogenesis of AD remains the degeneration of cholinergic neurons in specific regions of the basal forebrain, the application of specific TMS protocols, such as the paired-pulse TMS (ppTMS) and the study of the short-latency afferent inhibition (SAI; [30–32]), points out the role of other neurotransmitters, such as γ-aminobutyric acid (GABA), glutamate, and dopamine [33, 34].

3.1. Alteration of Motor Cortex Excitability in Alzheimer's Disease. Even though TMS evaluations in AD have not yielded absolutely converging findings, recent studies, but one [35], strongly support the hypothesis of early motor cortex global hyperexcitability in AD [5], opposed to the progressive hypoexcitability to TMS normally found with aging [36, 37]. Most of these studies showed that resting motor threshold (rMT) is generally reduced in AD and in subcortical ischemic vascular dementia (VaD) compared to healthy age-matched controls [18, 30, 32, 38–42]; however several other reports have not found reduction of motor thresholds [5, 43–45]. To date it is not yet possible to give an univocal pathophysiological interpretation of the hyperexcitability, however it could be determined mainly by two different mechanisms:

(i) *increase of excitability* of the intracortical excitatory circuits;

(ii) *impairment of intracortical inhibitory circuits* resulting in a disinhibition of the motor cortex.

As the main excitatory neurotransmitter in the brain is glutamate, the first mechanism would imply an involvement of glutamatergic transmission in AD. Indeed, several studies suggest that abnormalities of glutamatergic neurotransmission might play an important role in AD, and the glutamatergic hypothesis of AD has been proposed as an auxiliary mechanism to the cholinergic hypothesis [5]; this would be due to an imbalance between non-NMDA and NMDA neurotransmission [5, 46–50].

However, the hypothesis of impairment of intracortical inhibitory circuits leading to disinhibition of the motor cortex in AD should also be taken carefully into consideration because several recent studies have demonstrated an abnormality of two inhibitory mechanisms accessible via TMS in patients with AD, that is, SICI and SAI, respectively mediated by GABA-A receptors and cholinergic neurons activities. Liepert and colleagues in 2001 used ppTMS according to Kujirai and colleagues [15] in mildly to moderately demented AD patients. They found a reduced SICI compared to an age-matched control group and a correlation between the amount of disinhibition and the severity of dementia. Later, in 2004, Pierantozzi and colleagues applied the same ppTMS protocol in two groups of early-onset demented patients with a neuropsychological profile suggestive of AD and frontotemporal dementia (FTD). They found a significant reduction of MEPs inhibition at ISI 2-3 ms in early-onset AD patients but not in controls and in FTD patients and speculated that these changes may be ascribed, at least in part, to an impaired endogenous cholinergic transmission (see also [44]) as they might be reversed by middle-term treatment with galantamine and other acetylcholinesterase inhibitors [30, 43, 44]. In 2010 also Olazarán and colleagues used the same ppTMS protocol in eleven patients with mild cognitive impairment (MCI) that converted to AD and 12 elderly control subjects. Cognitive assessment and ppTMS were performed at baseline in the two groups and after 4 and 21 months of treatment with donepezil in the AD group and ICF and SICI were found reduced in AD patients. However, there was high interindividual variability, and statistical significance was only attained at a 2-ms interstimulus interval (ISI). A trend towards recovery of 2-ms SICI was observed after treatment with donepezil. Baseline cortical excitability at 300 ms was associated with better cognitive performance in AD patients. Anyway, although the SICI is considered to be mediated by GABA-A receptors [21], to date it is not clear if the SICI impairment observed in AD patients is really an expression of an involvement of GABAergic activity [51] as biochemical investigations of biopsy brain tissue from patients in the early phases of AD have not shown significant alterations in the concentration of GABA and no disturbance of GABA transporters [52, 53].

Converging evidence also suggests that SAI, an inhibitory phenomenon [24, 26, 54] considered as a putative marker of central cholinergic activity, is reduced in AD and that AChEI (acetylcholinesterase inhibitors) therapy can rescue it [18, 32, 55] pointing out the fact that probably the central cholinergic dysfunction occurs in early stages of Alzheimer's disease [55]. However also other neurotransmitters were recently claimed to be involved in AD; for example, recently Martorana and colleagues [56], to test whether cholinergic disfunction could be modified by dopamine, designed a neurophysiological protocol consisting of the study of SAI before and after a single L-Dopa administration in AD patients and in healthy subjects. They observed that SAI was reduced in AD patients with respect to normal subjects, and that L-dopa administration was able to restore SAI-induced modification only in AD. They explained these data with a relationship between acetylcholine and dopamine systems.

Finally, very recently we explored changes in cortical excitability and reorganization in AD during long-term AchEIs therapy [14, 57]. We compared motor cortex functionality in 10 AD patients before and after one year of AchEIs therapy and we found the examined parameters of motor cortex physiology unchanged in patients with stabilized cognitive performance during the therapy (Tables 1 and 2). Therefore, thought the study was performed in a limited number of patients, we suggested that serial TMS analysis might be a useful, non-invasive and low-cost method to monitor rate of change in motor cortex hyperexcitability in AD, as well as AchEI CNS bioavailability and long-term pharmacological response. This idea is also supported by other experiments using the evaluation of SAI for the assessment of response to treatment [18, 31].

In conclusion, clinical and neuropsychological assessment are current standards to evaluate response to therapy and they are well validated, but they are somewhat dependent on examiner's expertise and, most of all, on patient's motivation. TMS could be helpful in reducing interindividual variability and achieving a more direct measure of disease progression. To date there are not univocal explanations of

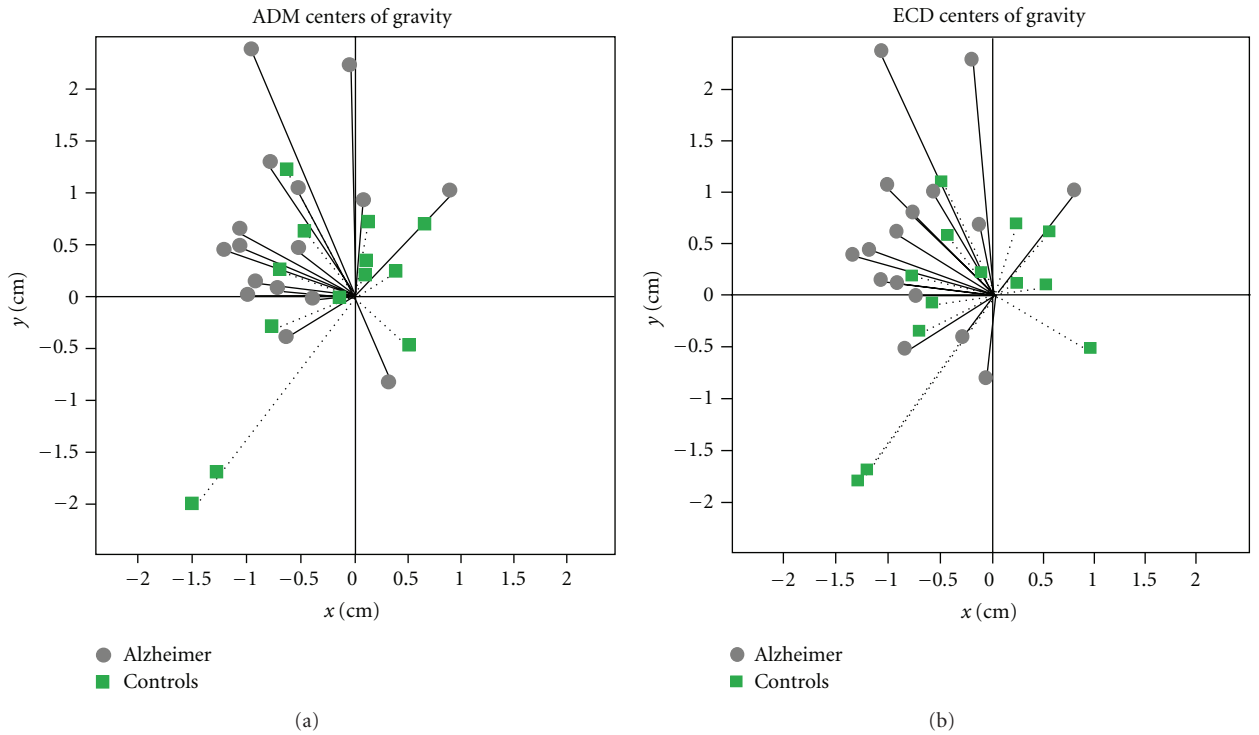

Figure 1: ADM: Abductor Digiti Minimi Muscle, ECD: Extensor Digitorum Communis Muscle. This graph shows that the map centre of gravity of the two muscles considered separately is in controls widely distributed around to hot-spot, while in patients it is evidently located anteromedial to it (modified from [5]).

Table 1: Mini mental state evaluation trend over two years in patients examined. T_1: basal evaluation, T_2: 1 year after AchE-ib treatment, T_3: 1 year after the last TMS session, DS: standard deviation. Patients, both as a group and as individual cases, could be considered cognitively stabilized at T_2 and at T_3 and formed an homogeneous group (modified from [14]).

PATIENT	MMSE at T_1	MMSE at T_2	Difference between MMSE at T_1 and T_2	MMSE at T_3	Difference between MMSE at T_1 and T_3	Total difference	
1	23	22	1	22	0	*1*	
2	23	21	2	20	1	*3*	
3	20	20	0	19	1	*1*	
4	21	20	1	18	2	*3*	
5	21	20	1	19	1	*2*	
6	21	20	1	18	2	*3*	
7	23	21	2	20	1	*3*	
8	19	18	1	16	2	*3*	
9	19	18	1	16	2	*3*	
10	23	23	0	22	1	*1*	
			1		*1.3*	*2.18*	Media
			0.67		*0.67*	*0.95*	DS

TMS findings because the pathophysiology of AD refers to a complex involvement of different neurotransmitter systems in many brain areas. For example GABAergic dysfunctions revealed by paired-pulse TMS studies, could represent an epiphenomenon of the complex cortical excitability balance. This equilibrium is probably related to age, disease duration, and degree of cognitive impairment. In other words AD should be viewed as a pathological mosaic composed of numerous facets, in which the neurotransmitter question is only a piece of the problem.

3.2. Cortical Reorganization of Motor Output in AD. Motor symptoms are considered late events in the natural history of AD and their early occurrence makes the diagnosis less likely [5]. The delayed involvement of the motor system has been variably explained A smaller burden of neuropathological

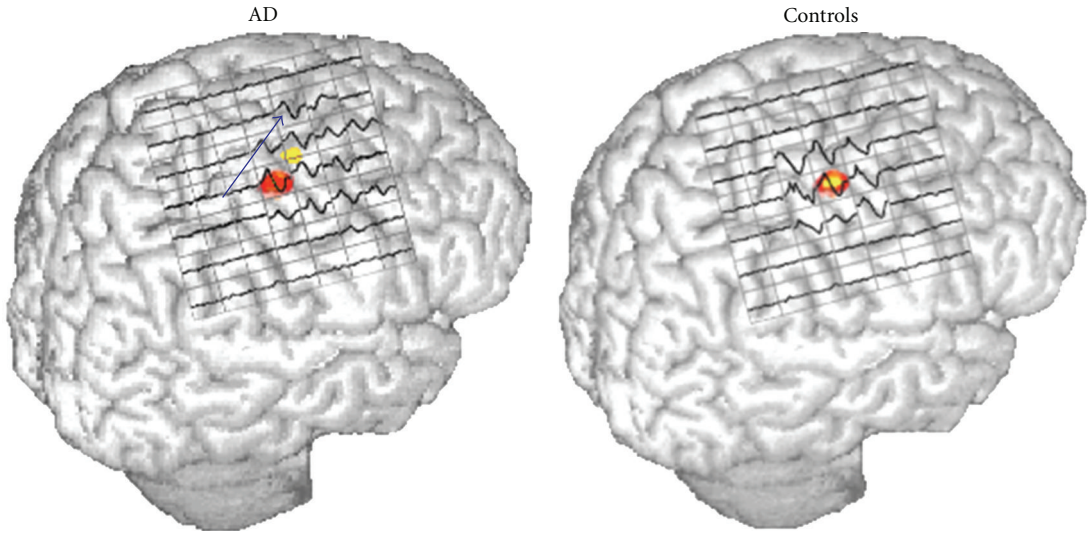

Figure 2: In AD patients is present a significant frontomedial shift of the center of gravity of MI output. In fact, comparing AD (a) and Controls (b) cortical maps how the hot-spot (red area) is not coincident with the center of gravity (yellow area) is evident (modified from [5]).

Table 2: Motor cortex excitability parameters trend in patients examined. T_1: basal evaluation, T_2: 1 year after AchE-ib treatment, ADM: Abductor Digiti Minimi Muscle, ECD: Extensor Digitorum Communis Muscle, SD: standard deviation. The table shows the AchEI therapy effect was not significantly impacting on TMS parameters (Pillai's trace = .996; $F(5,5) = 2.440$; $P = .175$). Consistently, looking at single measures, the authors did not find any significant change ($P = .154$ for threshold, $P = .416$ for ADM area, $P = .484$ for ECD area, $P = .682$ for ADM volume, $P = .368$ for ECD volume) (modified from [14]).

TMS Parameter	Hemisphere	Time			
		T_1		T_2	
		Mean	SD	Mean	SD
Threshold (%)	Right	40.8	5.8	38.7	6.8
	Left	39.6	4.9	37.4	5.6
Area ADM (N)	Right	5.3	2.5	4.9	2.4
	Left	5.4	3.5	4.4	3.5
Area ECD (N)	Right	5.7	2.6	5.3	2.5
	Left	6.1	4.3	5.2	3.5
Volume ADM (microV)	Right	26.8	12.9	27.0	15.1
	Left	29.4	18.9	25.8	19.5
Volume ECD (microV)	Right	33.3	15.6	29.7	15.8
	Left	38.4	27.6	31.9	21.0

changes in the motor cortices, compared with other brain areas, a rich dendritic arborization and progressive neuronal reorganization compensatory for neural loss, have all been hypothesized. Recent neuropathological studies, though, have shown that the density of neurofibrillary tangles (NFTs) and senile plaques (SPs) in the motor cortex is comparable to that of other cortices generally considered more specific targets for AD pathology, such as the enthorinal cortex, the hippocampus, and the associative parietal and frontal areas [58]. Despite early modifications of motor cortex seem to be part of the neurodegenerative process in AD [58], the lack of early clinical manifestations might be ascribed to its ability to reorganize via alternative circuits, due to its natural distributed network with multiple representations of the motor maps [59]. The motor cortex receives a major cholinergic input from the Nucleus Basalis of Meynert, one of the most affected brain areas. TMS was employed to study the motor cortex of AD patients demonstrating presence of subclinical motor output reorganization from the early stages of the disease [5]. Comparison with age- and gender-matched controls showed, in the AD patients, increased motor cortex excitability and frontal shift of the cortical motor maps for hand and forearm muscles (Figure 1). Specifically, while in normal controls the center of gravity (CoG) of the motor cortical output, correspondent to the TMS excitable scalp sites, coincides with the site of maximal excitability, or "hot spot", [60], in AD patients the CoG showed a frontal and medial shift, with no changes in the "hot spot" location

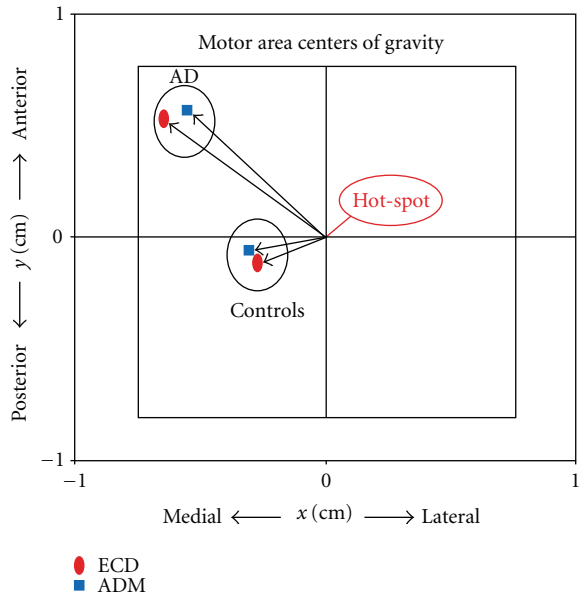

Figure 3: AD: Alzheimer disease, ADM: Abductor Digiti Minimi Muscle, ECD: Extensor Digitorum Communis Muscle, Hot-Spot: scalp site of maximal excitability. This picture shows that the coordinates of the map center of gravity compared to the hot-spot appear on average significantly different in the two groups: in controls the center of gravity matches with the hot spot and is located in the center of the map. In patients there is a marked frontal and medial shift of center of gravity compared to Hot-Spot. (modified from [5]).

(Figures 2 and 3). Increased excitability and frontomedial "migration" of the excitable motor areas could be explained by neuronal reorganization, possibly including the dysregulation of the inhibitory frontal centers (the "suppressory" motor cortex or area 4 S) and their integration with the distributed excitatory network subtending motor output. The frontomesial migration of the CoG does not seem to be due to gross tissue changes secondary to atrophy; were this the case, in fact, the "hot-spot" would have also similarly shifted, with no dissociation from the CoG of the map [5]. The motor cortex, for the above-mentioned reasons, seems capable of "self-defensive" reorganization, leading to late appearance of clinically evident symptoms. A more recent evidence of an altered synaptic plasticity in AD has been also demonstrated by Inghilleri and colleagues in 2006. They applied brief trains of high-frequency rTMS to motor cortex and recorded MEPs from the contralateral hand muscles. The researchers observed a progressive increase in MEP size in normal age-matched controls and opposite changes in AD [42]. This finding was interpreted as an altered short-term synaptic enhancement in excitatory circuits of the motor cortex.

4. TMS As Potential Instrument for Differential Diagnosis of Dementia

Recently Pierantozzi ([44], see also above) proposed the ppTMS paradigm as a noninvasive and reproducible tool to obtain an early differential diagnosis between cholinergic (AD) and non-cholinergic forms of dementia (FTD); the authors, in fact, observed a significant loss of MEPs inhibition at ISI 2-3 ms in early-onset AD patients but not in FTD patients and they speculated that these changes may be ascribed, at least in part, to an impaired endogenous cholinergic transmission.

In this vein it was also demonstrated [32, 61, 62] that SAI is normal in FTD and in most of patients with VaD whereas it is reduced in AD and dementia with Lewy bodies (DLB). All together these results seem interesting with a view to find a tool to early differentiate different kind of dementia but further studies are required to confirm these data and to introduce this approach in the daily clinical practice.

5. TMS to Improve Cognitive Performance in MCI and AD Patients

In the last 5 years rTMS has been proposed as a possible treatment to improve cognitive performance not only in normal subjects but also in patients affected by dementia in which it may represent a useful tool for cognitive rehabilitation. Particularly on one hand it was demonstrated that rTMS induce a transient improvement in the associative memory task in normal subjects and that it is associated with recruitment of right prefrontal and bilateral posterior cortical regions [63], on the other hand further studies have demonstrated that rTMS on dorsolateral prefrontal cortex improves naming performance in mild AD patients and also in the advanced stages of the disease [64, 65]. Moreover recently rTMS [66] was applied to AD patients to assess the duration of its effects on language performance and it was found that a 4-week daily real rTMS treatment is able to induce at least an 8-week lasting effect on the improved performance.

Bentwich and colleagues [67] combined rTMS (applied on six different brain regions) with cognitive training; they recruited eight patients with probable AD, who were treated for more than 2 months with cholinesterase inhibitors. These patients were subjected to daily rTMS-cognitive training sessions (5/week) for 6 weeks, followed by maintenance session (2/week) for an additional 3 months. They demonstrated a significant improvement in Alzheimer Disease Assessment Scale-Cognitive (ADAS-cog) and in Clinical Global Impression of Change (CGIC) after both 6 weeks and 4.5 months of treatment. These findings represent direct evidences that rTMS is helpful in restoring brain functions and could reflect rTMS potential to recruit compensatory networks that underlie the memory-encoding and other congnitive processes [68].

6. Conclusions and Future Perspectives

Initially developed to excite peripheral nerves, TMS was quickly recognized as a valuable tool to noninvasively investigate and even activate the cerebral cortex in several neuro-psychiatric disorders, such as dementia; to date the all findings available suggest that TMS is a valuable tool to study the neurophysiological basis of cognitive disorders. TMS

furnished several interesting patho-physiological information and, although the cholinergic deficit seems to be the most accepted hypothesis, recent results indicate that AD should be considered as a complex neurodegenerative disease, involving different neurotransmitter systems. The subsequent discovery that repetitive TMS could have long-lasting effects on cortical excitability spawned a broad interest in the use of this technique and, despite the current outcomes from initial trials include some conflicting results, initial evidence supports the idea that rTMS might have some therapeutic value in AD. To date, few studies have been conducted at the predementia stage and correlations between cortical excitability and cognitive performance have not been clearly addressed.

Finally as altered functional connectivity may precede structural changes, an objective method for the investigation of early functional changes in cortical connectivity might be useful in the early diagnosis and followup of AD [69]. With this view the combined use of TMS with other brain mapping techniques will greatly expand the scientific potential of TMS in basic neuroscience and clinical research and will provide substantial new insights in the pathophysiology of neuropsychiatric diseases. In recent years, several commercially available devices have been introduced that allow recording electroencephalographic (EEG) responses to TMS of a given scalp site with millisecond resolution. The latency, amplitude, and scalp topography of such responses are considered a reliably reflection of corticocortical connectivity and functional state [14, 57, 70]. Combining TMS with EEG enables a noninvasive, finally direct, method to study cortical excitability and connectivity that is intrinsic neural properties and the connections of thalamocortical circuits can be explored without involve peripheral stimulation or requiring the active engagement of subjects in a cognitive task. EEG-TMS is a promising tool to better characterize the neuronal circuits underlying cortical effective connectivity and its disruption in Alzheimer's disease and other kind of dementia [69].

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Research Article

Combining Transcranial Magnetic Stimulation and Electroencephalography May Contribute to Assess the Severity of Alzheimer's Disease

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Alzheimer's disease (AD) is the most common form of old age dementia, and mild cognitive impairment (MCI) often precedes AD. In our previous study (Julkunen et al. 2008), we found that the combination of transcranial magnetic stimulation (TMS) and electroencephalography (EEG) was able to find distinct differences in AD and MCI patients as compared to controls. Here, we reanalyzed the small sample data from our previous study with the aim to test the sensitivity of the TMS-EEG characteristics to discriminate control subjects ($n = 4$) from MCI ($n = 5$) and AD ($n = 5$) subjects. Furthermore, we investigated how the TMS-EEG response characteristics related to the scores of the dementia rating scales used to evaluate the severity of cognitive decline in these subjects. We found that the TMS-EEG response P30 amplitude correlated with cognitive decline and showed good specificity and sensitivity in identifying healthy subjects from those with MCI or AD. Given the small sample size, further studies may be needed to confirm the results.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder which leads to dementia through a progressive cognitive decline. In Europe, AD affects over 5% of population aged above 70 years [1]. This makes it the most common cause of dementia in old age. It has been postulated that the impairment of the lateral cholinergic pathway originating from the Meynert's nucleus would characterize AD and contributes to its typical symptom of memory loss [2, 3]. AD-related pathology leads to the degeneration of the large cortical pyramidal neurons [4], and subsequently impairment of functional connectivity takes place [5]. Before the diagnosis of AD can be set, subjects often suffer from impaired episodic memory [6]. The stage characterised by mild memory or other cognitive loss is called mild cognitive impairment (MCI), and it has been proposed as a prodromal state of AD. Thus, subjects with MCI have an increased risk to develop AD [7–9]. Understanding the pathophysiology of MCI would be essential for predicting and possibly in the future preventing the development of AD. It is possible that altered functional connectivity precedes structural changes, and therefore, a sensitive method to detect those early functional changes would be useful in the diagnostics of MCI and AD. Early identification of AD would be desirable, as it could help aiming the current treatment to the appropriate subjects. With the prospects of obtaining treatments that modify the course of AD, accurate identification of subjects who will develop AD is essential.

Earlier it has been shown that the primary motor cortex experiences changes during the development of AD, which also relate to the severity of the disease [10]. Structural

changes in M1 are mild and appear late as compared to other brain areas, and therefore, motor function also appears intact in early AD [11–14]. Several earlier TMS studies have found that AD patients have reduced resting motor threshold (MT) of the primary motor cortex [3, 15–21]. Alagona et al. reported that the resting MT correlates inversely with the disease severity [15]. This implies that the inhibitory control is reduced in AD, which is also supported by reported shortening of cortical silent period [21]. Additionally, previous studies have reported reduction in short-latency afferent inhibition (SAI) in AD [18, 22–24]. SAI has been considered as a marker of central cholinergic activity [25] and is likely of cortical origin [26, 27]. Hence, motor cortex functions, especially intracortical inhibition, suffer during the development of AD. Earlier, Sakuma et al. [23] showed that SAI is not impaired in MCI, suggesting that the cholinergic activity shown to be impaired in AD may still be normal in MCI. Several studies have been conducted to solve this question and supporting as well as contradicting results have been published [28–31]. Hence, the cholinergic changes related to MCI should be interpreted carefully, as the cholinergic regulation in MCI is still unclear. Furthermore, in AD, there is a tendency towards a reduced short-latency intracortical inhibition (SICI), a different form of inhibition evoked by using paired-pulse TMS [3, 18, 19]. SICI has been connected with intracortical $GABA_A$ activity [32].

Combining TMS with electroencephalography (EEG) offers a direct noninvasive method to study cortical reactivity and connectivity in physiological and pathological conditions [33–38]. Previously, we have shown that TMS-EEG can reveal abnormalities in functional cortical connectivity and reactivity in the AD subjects [39]. Our main finding was that the P30 response of TMS-EEG was significantly reduced in AD as compared to controls and MCI, and that the reduction was localized to the ipsilateral temporoparietal area as well as contralateral frontocentral area, that is, sensorimotor area, connected to M1. In the past, TMS-EEG response, when focused on M1, has been shown to exhibit several distinguishable peaks: N15, P30, N40, P60, and N100 [33, 35, 36, 38, 40–43]. Prior studies have related the early peaks N15 and P30 to the M1 activation. P30 has been suggested to reflect activity around the premotor cortex on the stimulated side, and it has been reported that P30 may increase due to long-term potentiation induced by repetitive TMS [41]. Furthermore, P30 has been suggested to involve pathways between subcortical structures such as thalamic nuclei or basal ganglia and cortex [40]. Also, P30 has been shown to vanish with nonoptimal orientation of the stimulation coil in respect to the cortical structures [40]. Therefore, the use of neuronavigation in combination with TMS allows controlling of the stimulation direction in respect to the subject's brain anatomy and results in optimized motor responses [44], and likely optimized TMS-EEG responses.

We wanted to investigate subject-specific differences in intracortical connectivity between healthy subjects, and MCI or AD patients. We utilized and reanalyzed our previously published data [39], which indicated that especially the P30 amplitude of the TMS-EEG response could be decreased in AD. We further evaluated the sensitivity of the P30 amplitude changes in discriminating healthy subjects from those exhibiting cognitive impairment (MCI and AD). Furthermore, we tested whether P30 amplitude would directly relate to commonly categorizing scores of dementia rating scales. On the basis of the findings of our previous study, we hypothesized that P30 amplitude would decline as the disease becomes more severe and correlate with the dementia rating scales.

2. Materials and Methods

2.1. Subjects. In the present study, our previously published data was further analyzed. A small size sample including four control subjects (age: 78 ± 3 years, 3 females, 1 male), five MCI subjects (age: 74 ± 8 years, 2 females, 3 males), and five AD subjects (age: 73 ± 8 years, 2 females, 3 males) was recruited for the original study. All subjects were right handed. Each subject gave written informed consent, and the study was approved by the local ethics committee. Categorizing of these subjects to their groups was done based on a standard rating [45] and is explained in more detail in the original paper [39]. Briefly, the MCI subjects fulfilled the following characteristics [7]: (1) subjective memory impairment corroborated by an informant, (2) objective memory impairment, that is, a score of 0.5 in the clinical dementia rating (CDR) scale [45] with at least 0.5 on the memory subscale and a score of 1.5 SD below the average of a normative age-matched sample group in at least one memory test, (3) normal global cognitive function (Mini-Mental-State Examination score (MMSE) of at least 20 [46]), (4) normal activities of daily living, and (5) no dementia according to the NINCDS-ADRDA criteria [11]. The MCI subjects were classified as multidomain amnestic MCI [47]. Diagnosis of AD was made according to the NINCDS-ADRDA criteria for probable AD [11]. All the AD patients were on cholinesterase inhibitors, while other subjects had no medication affecting cognition at the time of measurements.

2.2. Measurement System and Protocol. Navigated TMS was used to probe the motor cortex of the subjects (Figure 1), that is, the primary motor cortex (M1) of the subjects was mapped for the representation area of the thenar musculature of both hands. The stimulation system consisted of a Magstim BiStim stimulator (Magstim Ltd., Whitland, UK) and a 70 mm figure-of-eight TMS coil with monophasic pulse form. Stimulation-triggered EEG responses were recorded with 1450 Hz sampling frequency and 16 bit precision using a 60-channel TMS-compatible EEG amplifier (Nexstim Ltd., Helsinki, Finland). Navigation of the TMS system utilized T1-weighted 3D magnetic resonance images (imaged with Siemens Magnetom Avanto, Siemens, Erlangen, Germany). The navigation was conducted using eXimia navigation system (version 2.0, Nexstim Ltd., Helsinki, Finland). Resting state MT at the "hotspot" was determined using a threshold-hunting protocol [48]. For measuring TMS-induced muscle responses, electromyography was recorded (ME6000, Mega Electronics Inc., Kuopio, Finland)

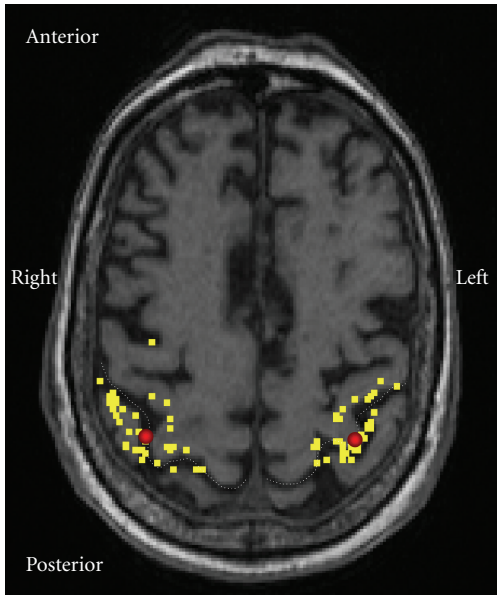

Figure 1: Motor cortex representation area of a control patient. TMS was focused at the "hotspot" of thenar muscle representation on the primary motor cortex (M1). The yellow dots present stimulation locations during the mapping of the hotspot in the vicinity of M1. The red spots indicate the hotspots, which were located within normal variation in each group [57].

from the opponens pollicis muscle using pregelled disposable Ag-AgCl surface electrodes. TMS-induced EEG responses were recorded from >50 trials elicited with an interstimulus interval of 3–5 s with a stimulation intensity of 110% of the determined MT. For a more thorough system description, the reader is referred to our previous paper [39]. Both hemispheres were separately investigated, and the stimulation order of the hemispheres was randomized.

2.3. Analysis of TMS-EEG. The offline analysis of EEG was performed using Matlab 7.2 (Mathworks Inc., Natick, MA). Zero padding for 10 ms after the TMS pulse was applied to dampen the TMS-induced artefact. Segmented EEG was bandpass filtered to 1–50 Hz. Any segments contaminated by blinks, as observed from vertical electro-oculogram, were removed from the analyses. Also, in some cases, a bad channel signal due to poor contact was replaced with a signal linearly interpolated from the neighbouring good channels. Manual artefact removal was conducted, prior to rereferencing all electrodes to common average. Baseline correction for 100 ms before each stimulus was conducted prior to averaging the segments. Averaged TMS-EEG responses over all trials were used in the statistical comparisons (Figure 2). Our interest was in the P30 response, earlier shown to be influenced by AD [39]. Analysis of the P30 responses was conducted from an electrode close to the site of stimulation based on the most distinguishable and shortest-latency response, as it has been reported that P30 originates ipsilaterally to the stimulation at the close proximity of the primary motor cortex (M1) [33].

2.4. Statistical Analyses. To test how well the P30 amplitude would be able to discriminate the groups from each other, receiver operating characteristic (ROC) curve analysis was conducted. Area under the ROC curve (AUC) was computed to determine how well the groups could be discriminated based on the P30 amplitude. The asymptotic significance for the AUC was computed with the null hypothesis of AUC = 0.5. The optimal cut-off point for the ROC curve was determined as the closest point to the diagonal line connecting points (0, 1) and (1, 0) in the ROC plot.

Differences in P30 amplitude between the groups were analysed applying a mixed linear model, and using group and hemisphere as fixed variables and subject as a random variable. Restricted maximum likelihood estimation was used in the model. Mean effects between the groups were analysed using post-hoc analysis with least significant difference adjustment (LSD). Also, individual mean amplitudes for the P30 (hemispheric values averaged, $P30_{mean}$) were used in the comparisons. Then, Mann-Whitney test was applied in comparison of the differences between the groups. Correlations between the scores of dementia rating scales and P30 amplitude were conducted using Spearman's rank correlation (ρ). The tests for correlation significance were two tailed. The correlated dementia scores were the global score and sum of boxes score of the clinical dementia rating scale (CDR-SOB) as well as MMSE. Statistical tests were conducted using SPSS 17 (SPSS Inc., Chicago, IL). Level of statistical significance was set at $P < .05$.

3. Results

The resting MTs (average of both hemispheres) for the opponens pollicis muscle of the control, MCI, and AD group were 44 ± 11, 48 ± 12, and 41 ± 4% of the maximum stimulator output, respectively. No significant differences were observed between the groups. The hemispheric data and data for pooled samples were presented in our previous study [39], where we found that the MT of the left hemisphere in MCI subjects (50 ± 13% of the maximum stimulator output) was significantly higher ($P < .05$) than in AD patients (42 ± 4% of the maximum stimulator output). Additionally, on the right hemisphere, the MT of the controls (40 ± 11% of the maximum stimulator output) was significantly lower ($P < .05$) than in MCI subjects (48 ± 13% of the maximum stimulator output).

Dementia scales for the subject groups were distinctive of the different disease conditions. MMSE for control, MCI, and AD group was 27 ± 4, 25 ± 3, and 22 ± 5, respectively. The global CDR values were 0 for controls, 0.5 for MCI subjects, and 0.5 ($n = 4$) or 1.0 ($n = 1$) for AD patients. Corresponding values for the CDR-SOB were 0.0 ± 0.0, 1.9 ± 1.1, and 3.2 ± 2.5, respectively. CDR and CDR-SOB values in controls were significantly lower ($P < .001$) than in MCI and AD subjects, while MMSE was nonsignificantly higher ($P = .055$) in controls as compared to AD group. Also, no significant difference was observed between controls and MCI subjects in MMSE ($P = .437$).

The P30 peak was lower in amplitude in the AD patients than in the controls (Figure 3, Table 1). No significant

Table 1: Group-wise values of P30 amplitude.

	P30 amplitude (μV)		
	Control	MCI	AD
Left hemisphere	32.0 ± 6.0	25.6 ± 12.7	17.7 ± 7.1
Right hemisphere	33.0 ± 14.6	16.3 ± 5.9	11.5 ± 4.9
$P30_{mean}$	32.5 ± 9.8	21.1 ± 8.2	16.0 ± 6.9*

*$P < .05$ as compared to controls, linear mixed model (pooled values), and Mann-Whitney test (mean or hemispheric values).
Abbreviations:
MCI: Mild cognitive impairment
AD: Alzheimer's disease
$P30_{mean}$: P30 amplitude, mean of P30 amplitudes on both hemispheres.

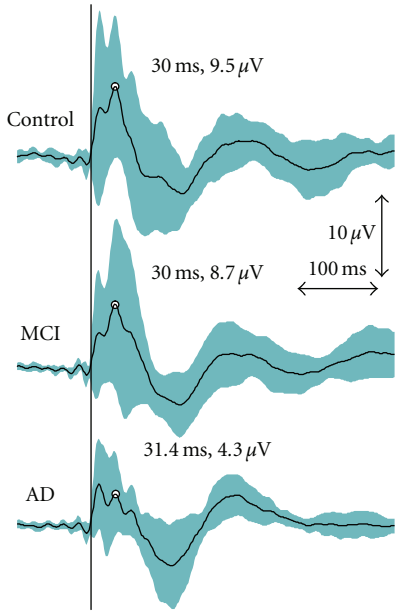

Figure 2: Grand average curves for TMS-evoked EEG responses as measured from the central electrode (CZ). The mean peak for the P30 has been indicated. However, P30 was analyzed for individuals from the electrode chosen based on the shortest latency and clearest identification on the stimulated hemisphere. The turquoise area represents the 95% confidence interval for the TMS-EEG responses. The vertical black line indicates the moment of stimulation.

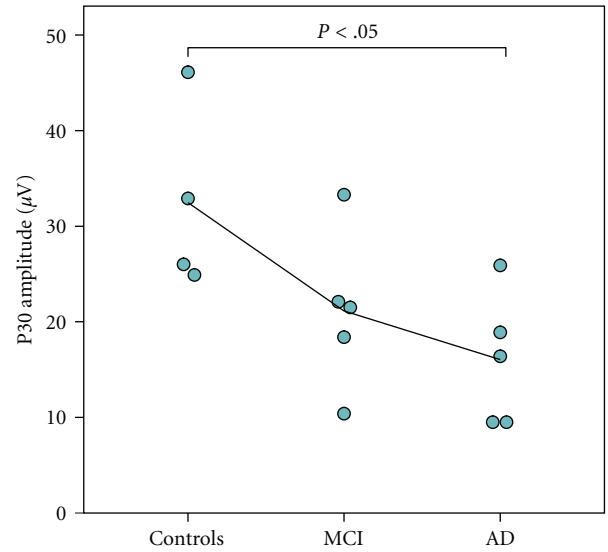

Figure 3: Group-wise P30 amplitudes. The individual values are presented as a mean value of P30 amplitude measured from both hemispheres. Black line represents the group-wise mean value when moving from controls to MCI and AD.

difference was observed between the controls and MCI subjects ($P = .054$) or between the MCI and AD groups ($P = .336$). No significant differences were observed in the latencies between the groups (data not shown). Also, no significant interhemispheric differences in P30 were observed ($P = .097$).

The different groups were discriminated from each other by the ROC curve analysis (Figure 4). The AUC indicated that the discrimination of controls from the MCI and AD groups is possible based on TMS-induced P30 peak amplitude (AUC = 0.900, $P = .024$, $P30_{mean}$). The optimal cut-off point was found to be 24.5 μV (sensitivity of 0.75 and specificity of 0.80). Similarly, as the amplitude of the P30 peak was lower in the AD group as in the other groups, the ROC curve indicated that the discrimination of the AD group from controls and MCI may be possible (AUC = 0.882, $P = .053$, $P30_{mean}$). The optimal cut-off point in this case was 20.2 μV (sensitivity of 0.80 and specificity of 0.78).

If only the discrimination of AD patients from controls was estimated, the AUC increased to 0.950 ($P = .027$, $P30_{mean}$). The optimal cut-off point was 25.4 μV (sensitivity of 0.80 and specificity of 0.75). Discrimination of MCI from AD using ROC curve was found more difficult (AUC = 0.720, $P = .251$, $P30_{mean}$). The optimal cut-off point then was 18.7 μV (sensitivity of 0.60 and specificity of 0.60). However, the more important discrimination of MCI subjects from controls was found stronger although the AUC was 0.850 ($P = .086$, $P30_{mean}$). The optimal cut-off point was 25.5 μV (sensitivity of 0.75 and specificity of 0.80), which was very close to similar as in discriminating AD patients from controls.

Significant correlations were observed between the P30 amplitude and the dementia scales. An inverse correlation was found between the global CDR and P30 amplitude as well as between CDR-SOB and P30 amplitude (Figure 5). As the global CDR is a classification variable, its correlations with P30 amplitude should be interpreted with care.

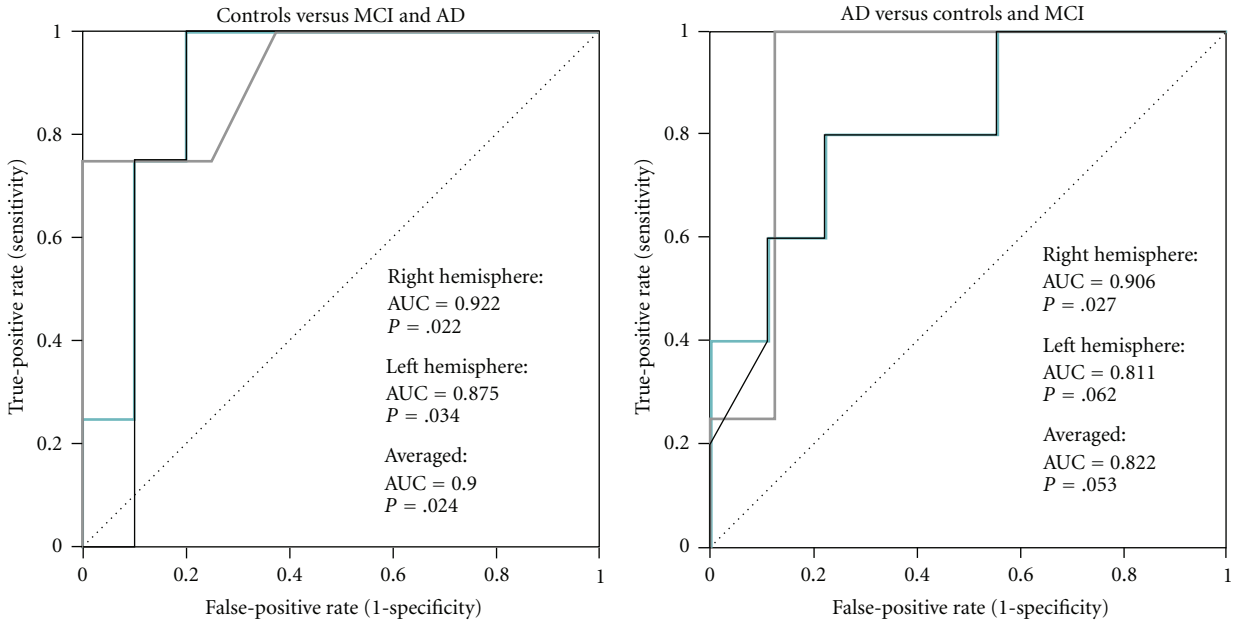

Figure 4: Receiver operating characteristic (ROC) curves for distinguishing (a) controls from MCI and AD, and (b) and AD patients from MCI and control subjects based on TMS-EEG P30. Turquoise line indicates the ROC curve for averaged data, while the grey and black lines indicate ROC curves for the right and left hemisphere, respectively. The area under the ROC curve (AUC) has been given separately for the averaged ($P30_{mean}$) and hemispheric data. The asymptotic significance has been indicated with the null hypothesis of AUC = 0.5 (diagonal line).

Table 2: Correlation coefficients (Spearman's ρ) between the P30 amplitude and dementia rating scales.

	Mini-mental state examination	Clinical dementia rating—global†	Clinical dementia rating—sum of boxes
Left hemisphere	0.456	-0.678^{**}	-0.788^{***}
Right hemisphere	0.631^{*}	-0.705^{**}	-0.849^{***}
$P30_{mean}$	0.537^{*}	-0.698^{**}	-0.808^{***}

$^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$.
†As the global CDR is a classification variable, its correlations with P30 amplitude should be interpreted with care.
Abbreviations:
$P30_{mean}$: P30 amplitude, mean of P30 amplitudes on both hemispheres.

A positive correlation was found between the MMSE and P30 amplitude (Table 2).

4. Discussion

We have previously shown that TMS-evoked P30 amplitude is reduced in the AD subjects in the temporoparietal area, ipsilateral to the stimulation side as well as in the contralateral frontocentral cortex corresponding to the sensorimotor area [39]. In the present study, we further investigated our previously published data and found that the discrimination of control subjects from MCI and AD subjects may be possible with good sensitivity (Figures 3 and 4). Further, consistently with our hypothesis, we found that there is a significant relation between the commonly used dementia rating scales and the analyzed TMS-EEG response P30 amplitude, when TMS is focused on the M1 with suprathreshold intensity (Figure 5). Our results suggest that the use of TMS-EEG in the evaluation of AD and its initial signs could be feasible as distinct changes occur in the measured responses during the development of AD.

The greatest limitation of this study was that the group sizes were small. In spite of that, the findings of the present study showed clearly significant differences between the groups. In the future, these results should be further verified by other studies with larger group sizes. Nevertheless, it was clear that the discrimination of probable mild AD patients and MCI subjects from control subjects seemed feasible. Furthermore, the present study was able to show a correlation between the P30 amplitude of the TMS-EEG and the dementia rating scales (Figure 5, Table 2). Such relation has not been reported earlier. Therefore, it seems that the P30 peak is indeed related to cognitive decline, or perhaps to the developing motor deficits that the AD patients may exhibit in the advanced stage of the disease [11]. Due to the small sample size, the study may suffer a lack of power to provide reliable answers to its aim, that is, some of the intergroup relations and differences may have been missed. Even with

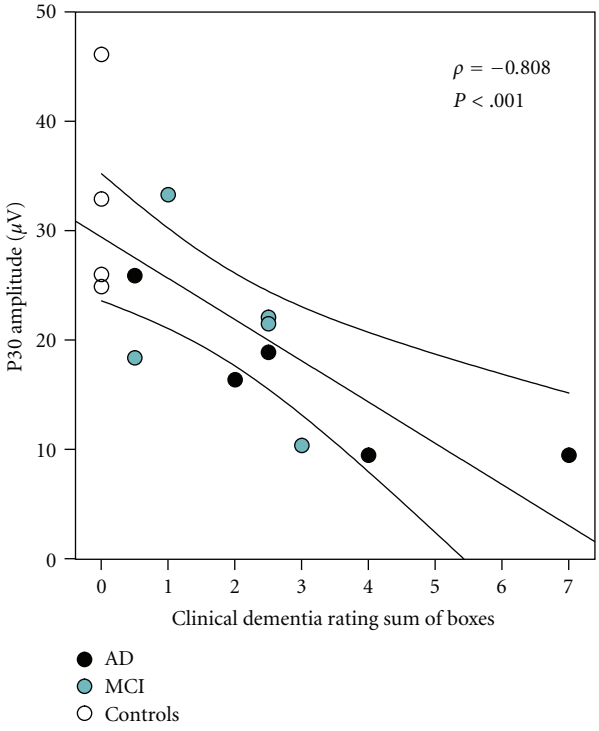

Figure 5: Scatter plot indicating the relation between the clinical dementia rating sum of boxes and P30 amplitude (average of each subject's left and right hemisphere measurement, $P30_{mean}$). The thin curved lines represent the 95% confidence intervals for the curve fit.

the small sample size, the found effect size for discriminating controls from mild AD patients based on the $P30_{mean}$ was large (Cohen's $d > 0.8$), as was the effect size for the controls and MCI difference (Cohen's $d > 0.8$). A medium size effect was observed between the MCI and AD (Cohen's $d > 0.5$). However, the statistical significance of those comparisons was too weak in the last two cases. This encourages further studies with larger sample sizes.

As opposed to the localized (single-channel) P30 responses reported in the present study, our previous study investigated the global mean field power (GMFP) of the P30 peak [39]. Hence, for comparison, the global mean field power (GMFP) was computed for the P30 response peaks ($P30_{GMFP}$) [49]. We found that the $P30_{GMFP}$ correlated strongly with the single-channel $P30_{mean}$ ($\rho = 0.810$, $P < .001$). This correlation is affected by the differences in the P30 spread between the groups, and hence the correlation may not be an ideal indicator for similar behavior. In the discrimination of the different groups, $P30_{GMFP}$ was weaker than the single-channel $P30_{mean}$, that is, in the ROC analysis, controls were not discriminated as easily from the MCI and AD (AUC = 0.775, $P = .120$) or the AD group from MCI and control groups (AUC = 0.756, $P = .125$). Furthermore, the $P30_{GMFP}$ exhibited some correlations with the dementia scales ($P30_{GMFP}$ versus MMSE, $\rho = 0.311$, $P = .279$; $P30_{GMFP}$ versus CDR, $\rho = -0.515$, $P = .060$; $P30_{GMFP}$ versus CDR-SOB, $\rho = -0.755$, $P = .002$). Therefore, to us it seems that the localized P30 amplitude is more sensitive in observing cognitive decline as compared to global field values. This finding may be influenced by the modified spread of the P30 component in AD, which was observed in our previous study, and which affects the GMFP [39].

The CDR is a standard assessment tool that yields global and CDR-SOB scores. The global CDR score is often used to stage dementia severity [45]. However, the CDR-SOB score is a more detailed general index and is more sensitive in assessing mild dementia [50–52]. Based on the CDR-SOB, the AD patients in this study had very mild or mild dementia [52]. In agreement with our hypothesis, we found significant correlations between the P30 amplitude and the dementia scales (Table 2). As the CDR-SOB is a detailed and one of the most used dementia scales, it also related best to the P30 amplitude as was seen from their strong correlation (Figure 5). Also, the other applied dementia scales correlated with P30. Therefore, it seems that P30 indeed relates to the severity of the AD even in a mild stage of the disease as the patients were in the present study. Since our recent study showed some effect of cognitive decline on the N100 [39], we analyzed the N100 response from the TMS-EEG at the vertex for comparison with the P30 amplitude. We found that none of the dementia scales correlated significantly with the N100 amplitude (N100 versus MMSE, $\rho = -0.029$; N100 versus CDR, $\rho = 0.333$; N100 versus CDR-SOB, $\rho = 0.177$). Therefore, P30 appears more specific than N100 in identifying cognitive decline with TMS-EEG. The reason for this may be that TMS-induced N100 response also includes an auditory component, which does not affect P30 [42].

Currently, the origin of P30 is not precisely described. It has been suggested to originate from the ipsilateral sensorimotor/premotor cortex border [41] or the ipsilateral supplementary motor area [53]. As discussed by Mäki and Ilmoniemi, the P30 may not reflect activation directly at the location activated by the stimulus. However, it may still reflect the degree of excitation in M1 [33]. Bonato et al. showed that P30 vanishes if the activation of M1 is induced with TMS coil oriented nonoptimally, which supports the idea that P30 is descriptive of cortical activation related to M1 excitation [40]. Considering the findings of the present study, the decrease in P30 in AD as compared to healthy controls may reflect impaired cortical activation in response to M1 activation. However, if we consider the earlier findings relating MEPs with P30, the P30 measured in the present study would not directly relate to motor activation, as the earlier reports have indicated a positive correlation between the two [33, 40]. In our earlier study [39], we showed that the correlation between the induced MEPs and P30 exhibits a nonsignificant negative trend when correlated over different patient groups ($\rho = -0.224$, $P = .441$). When comparing the mean values of MEP amplitudes, the controls exhibit the lowest mean MEP amplitude of 1.0 mV while showing the highest P30 amplitude. Instead, the highest mean MEP amplitude of 2.9 mV was in the AD group with the lowest P30 amplitude (Figure 3). This suggests that P30 is not only related to the excitation of M1, but also other mechanisms may influence it when AD progresses. Ferreri et al. [38] suggested that P30 may be connected to $GABA_A$ receptors, provided that P30 modulation is related to fast inhibitory

postsynaptic potentials. Hence, considering the earlier findings suggesting reduction in $GABA_A$ -mediated SICI of AD patients [3, 18–20], the reduction in P30 amplitude in relation to cognitive decline could be explained by possibly affected $GABA_A$ activity in AD patients, even if the effect is not directly caused by the disease. However, based on the present study, we cannot reveal the mechanism affecting P30, and future studies are required.

As the P30 has been suggested to relate to motor function/control in response to TMS of the M1 [33, 40], it is obvious that it may also be affected by the motor function impairment related to the development of AD. Furthermore, as the connectivity of the AD patients is also impaired, the subcortical contributor to the P30 may suffer leading to a decrease in P30 amplitude (Figure 5). The indications of P30 decrease are already present in the MCI subjects (Figure 4) although they are insignificant ($P = .054$) in the present study, likely due to the low number of subjects. One possibility is that the P30 decline in AD is a result of the missing connections or cortical atrophy, and the actual function, which is still unclear, is related to the cortical hyperexcitability [19, 54] or cholinergic dysfunction leading to disinhibition [17–19, 55]. Hence, we will further study on how the dementia symptoms relate to the connectivity and the components of the TMS-EEG in our future studies with larger material.

We cannot rule out the possible effect of medication in our findings, as the AD patients were on cholinesterase inhibitors. However, in our previous study [39], we found that the later part of the TMS-EEG response appeared partly similar to that of the controls, meaning that not the entire TMS-EEG response is influenced by either the AD or the medication, or that the cholinesterase inhibitors are compensating for some of the changes. The effect of cholinesterase inhibitors on the motor cortex excitability has been studied earlier. Korchounov et al. [56] found that the MTs or SPs were not affected by the acetylcholinesterase inhibitor in healthy subjects, while the intracortical inhibition and facilitation were affected between 2 and 6 hours of the medication intake. The motor cortex disinhibition in AD has been shown to recover partly by the use of cholinesterase inhibitors [55]. Studying the effect of cholinesterase inhibitors on the TMS-EEG response of healthy subjects, possibly in combination with paradigms such as SAI or paired-pulse TMS, could help to understand the origin of P30.

5. Conclusions

We found differences in TMS-induced P30-component amplitude between the controls and AD patients, indicating impaired/altered connectivity in AD. In addition, we found that the cognitive decline correlated with the P30 amplitude. Further investigations with larger sample sizes are needed to support our conclusion that TMS-EEG could be a potential noninvasive biomarker for identifying MCI and AD subjects and separating those from healthy population, and for identifying connectivity changes occurring during the development of AD.

Conflict of Interests

Professor J. Karhu works part time as Chief Medical Officer in Nexstim Ltd., the manufacturer of navigated brain stimulation instruments.

Acknowledgment

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Case Report

An Unusual Cause of Dementia: Essential Diagnostic Elements of Corticobasal Degeneration—A Case Report and Review of the Literature

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Corticobasal degeneration (CBD) is an uncommon, sporadic, neurodegenerative disorder of mid- to late-adult life. We describe a further example of the pathologic heterogeneity of this condition. A 71-year-old woman initially presented dysarthria, clumsiness, progressive asymmetric bradykinesia, and rigidity in left arm. Rigidity gradually involved ipsilateral leg; postural instability with falls, blepharospasm, and dysphagia subsequently developed. She has been previously diagnosed as unresponsive Parkinson's Disease. At our clinical examination, she presented left upper-arm-fixed-dystonia, spasticity in left lower limb and pyramidal signs (Babinski and Hoffmann). Brain MRI showed asymmetric cortical atrophy in the right frontotemporal cortex. Neuropsychological examination showed an impairment in visuospatial functioning, frontal-executive dysfunction, and hemineglect. This case demonstrates that association of asymmetrical focal cortical and subcortical features remains the clinical hallmark of this condition. There are no absolute markers for the clinical diagnosis that is complicated by the variability of presentation involving also cognitive symptoms that are reviewed in the paper. Despite the difficulty of diagnosing CBD, somatosensory evoked potentials, motor evoked potentials, long latency reflexes, and correlations between results on electroencephalography (EEG) and electromyography (EMG) provide further support for a CBD diagnosis. These techniques are also used to identify neurophysiological correlates of the neurological signs of the disease.

1. Introduction

Corticobasal degeneration (CBD) is an uncommon, sporadic, neurodegenerative disease described for the first time by Rebeiz et al. [1]. It can be associated with an extraordinary variety of motor, sensory, behavioural, and cognitive symptoms [2].

It is an asymmetrical parkinsonism affecting a limb, typically an arm: rigidity is the most common manifestation of the parkinsonian syndrome followed by bradykinesia, gait disorder (postural instability and falls), and tremor; asymmetrical limb dystonia is common as well. Other cardinal signs include higher cortical dysfunctions such as apraxia (limb more common than orofacial, eyelid-opening). Dementia, progressive nonfluent aphasia, speech apraxia, progressive-supranuclear-palsy- (PSP-) like syndrome and posterior cortical atrophy syndrome are other presentations of CBD [3, 4].

CBD is a tauopathy (characterised by abnormal deposition of the microtubule-associated protein tau), similar to frontotemporal dementia and progressive supranuclear palsy (PSP) [5].

The typical pathological findings in CBD include focal asymmetric cortical atrophy, nigral degeneration, taupositive neuronal, and glial lesions in both gray and white matters [6].

To achieve more accurate clinical diagnosis, neuropsychological, electrophysiological, and imaging methods could be applied to differentiate this disease from the other parkinsonism syndromes [3, 4].

In comparison with other neurological diseases, the symptoms of CBD are particularly difficult to understand and the patients have considerable difficulties in describing

their experience. A better understanding of the disease may help clinicians to make diagnosis, providing patients with comprehensive information about prognosis and difficulties they will encounter during the course of the disease, improving their quality of life as well as their careers.

2. Case Report

A 71-year-old woman, primary school graduate, formerly farmhand, was referred to our Department of Neurology with left rigid-akinetic syndrome and cognitive dysfunction.

She had no previous medical or family neurological history; she just reported in the previous months frequent falls and postural instability.

She initially presented with slowly progressive dysarthria and speech abnormalities two years before. Cognitive symptoms included impairment of spoken-language production and attention/concentration deficits.

Several months later clumsiness and rigidity in her left upper limb appeared. Her main complaint was difficulty in using her left arm and hand, which gradually progressed. The limb became severely rigid and adopted a dystonic posture associated with pain and functional disability.

Her clinical features slowly deteriorated and, 1 year later, involved also the left lower limb with gait disorder associated to postural instability and falls. Subsequently, the patient underwent brain MRI and 18F-fluorodeoxyglucose-positron emission tomography (PET).

Brain MRI showed moderate atrophy, more pronounced on the right side. She has been previously diagnosed as Parkinson's Disease but with no response to levodopa or dopaminergic medications.

Asymmetrical hypometabolism involving the right frontal cortex was also confirmed by PET.

Her clinical symptoms gradually progressed and, four months later, blepharospasm and mild dysphagia appeared.

When she was admitted to our Neurological Centre, the neurological examination revealed: blepharospasm; hypomimia and asmmetric bradykinesia; left upper-arm-fixed-dystonia; spasticity in left lower limb and pyramidal signs (Babinski, Hoffmann, and grasp reflex); moderate disturbance of gait with short steps, tendency to drag her left leg, bradykinesia, and propulsion requiring assistance.

We performed a complete neuropsychological examination (for more details see Table 1). Mini Mental State Examination score was 23/30. The other tests revealed impairment in visuospatial abilities, severe visuospatial neglect (Figure 1), constructional and ideomotor apraxia, poor word fluency with mild visual confrontation anomia, and nonverbal oral apraxia. Learning and memory were minimally affected.

Brain MRI showed asymmetric cortical atrophy in the right frontotemporal cortex (Figure 2).

No abnormalities were found on EEG examination, even if, a deeper analysis showed a focal slow wave activity in the right parietotemporal area.

Related to clinical features, based upon diagnostic criteria proposed by Boeve et al. [4], she has been diagnosed as "corticobasal degeneration (CBD)".

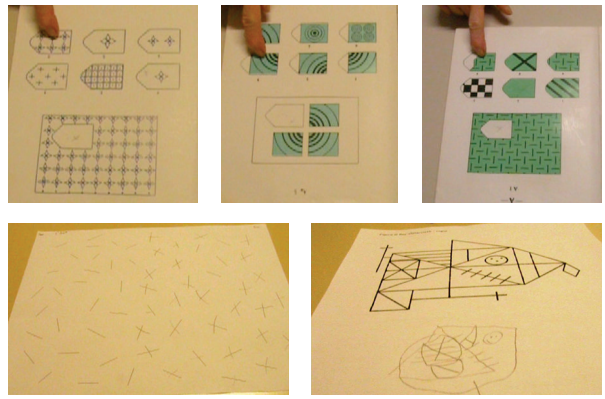

Figure 1: Neuropsychological examination show emineglect (Raven's colored matrices and barrage test) and constructional apraxia (Rey-Osterrieth complex figure).

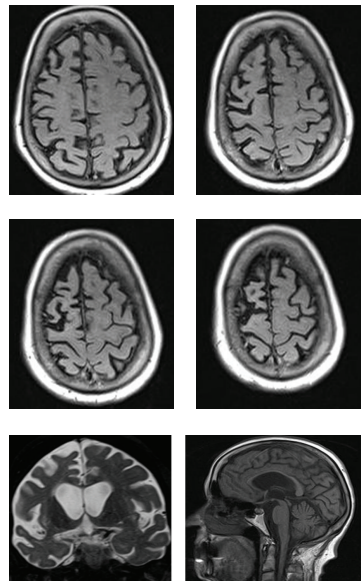

Figure 2: Axial, T2-weighted and fluid-attenuated inversion recovery (FLAIR), MRI images of the brain, demonstrating asymmetric cortical atrophy in the right hemisphere of the patient.

The diagnosis was based on the gradual onset of a parkinsonian disorder associated with cortical dysfunctions and other supportive features such as cognitive dysfunction, asymmetric atrophy on MRI imaging, and asymmetric hypoperfusion on PET.

3. Discussion and Review of the Literature

3.1. Clinical Presentation. Clinically CBD begins in the sixth, seventh, or eighth decade [7], with slight predilection for women [8, 9]. Typically the primary symptoms develop in a profoundly asymmetric way, affecting either one arm or, less frequently, a leg, which appears to be rigid, dystonic, akinetic, or apraxic. Clinical features include a series of motor, cognitive and neuropsychiatric symptoms, that can

Table 1: Complete neuropsychological examination performed by the patient.

	Obtained score	Cut-off	Result
Rey Auditory Learning Test			
Immediate recall	40	28,53	Normal
Delayed recall	8	4,69	Normal
Recognition recall	14/15, 4/30; accuracy % 95	92	Normal
Digits forward	5	7±2	Below normal
Digit backward	2	5±2	Below normal
Corsi span Forward	3	7±2	Below normal
Corsi span Backward	2	5±2	Below normal
Rey-Osterrieth Complex figure delayed recall	2,5; correct 9,5	9,46	Normal
Barrage Test	Dx (26/30); Sx (5/30)	59	Below normal
	Time 95″	>105″	
Deux Barrage	5/13, 22/67; accuracy % 57	95	Below normal
	Time 210″	>133″	Prolonged time of execution
Rey-Osterrieth Complex figure Test	4,5; correct 7	28,87	Below normal
Ideomotor Praxia	8,5	9	Below normal
Buccofacial apraxia	10	9	Normal
Raven's colored Matrices	6; correct 10,5	18,96	Below normal
Verbal Fluency			
Phonetc cues	10; correct 18,6	17,35	Normal
Semantic cues	12; correct 14,3	10,3	Normal
Naming (B.A.D.A.)	24	28	Below normal

be explained by impairment of the cortical and subcortical structures.

Motor symptoms include progressive asymmetric rigid-akinetic parkinsonism usually involving the upper limbs, without resting tremor [10], focal stimulus-sensitive or action myoclonus [4, 11], blepharospasm, speech abnormalities, gait disorder with postural instability and falls, and asymmetric limb dystonia, generally of the upper limbs, sometimes evolving towards the development of a dystonic clenched fist [3, 12].

Eye movements are usually preserved, although a delay in the initiation of saccades may occur, in absence of pursuit and optokinetic nystagmus impairment [13, 14].

Involvement of higher cortical functions results in often symmetric ideomotor apraxia, firstly affecting the limb, then, as the disease progresses, eyelid-opening, tongue, lips. The alien-limb phenomenon, that is seen in 50% of the cases [15], can be defined as "a circumstance in which one of the patient's hands behaves in a way which the patient finds foreign, alien or at least uncooperative"; it commonly co-occurs with cortical sensory loss [11, 16].

Cognitive decline is a common feature of the disorder [17], occasionally the presenting feature of the disease [18]. The prominent characteristics are impairment of spoken-language production (typically nonfluent aphasia), frontal executive impairment, calculation and visuospatial skills impairment, whereas semantic and episodic memory may be spared [17].

Neuropsychiatric symptoms may include depression, apathy, anxiety, irritability, disinhibition, delusions, and obsessive compulsive disorder [19].

3.2. Electrophysiology. Abnormalities on magnetoencephalography [20], an exaggerated electromyographic-electromyographic (EMG-EMG) coherence [21], and an alteration in cortical excitability evaluated by means of transcranial magnetic stimulation (TMS) [22] were noted in patients with CBD [23]. On the other hand, conventional electroencephalography (EEG) may be normal when the first clinical symptoms appear, and often remains unchanged as the disease progresses. Nevertheless, an unilateral slowing may be evident in some patients, which may occasionally generalise to the whole cortex as the disease evolves [24, 25]. In a study involving six patients, Vion-Dury and coworkers, using a quantitative standard EEG (EEGq) with spectral analysis, found indeed the occurrence of several EEG abnormalities (generally enhanced by hyperventilation or intermittent photic stimulation), such as an increase of slow rhythms (delta or theta frequency range) and occasionally the occurrence of sharp waves [25]. These abnormalities were

lateralised in five patients (more often after hyperventilation) and were bilateral in one, confirming the asymmetrical features of CBD [25]. Moreover, Huang et al. showed that the EEG recordings with jerk-locked back average do not present any jerk-locked cortical potentials [23].

In CBD, the cortical sensory evoked potentials (SEPs) are not enlarged as in cortical reflex myoclonus, and back-averaged cortical potentials do not precede each myoclonic jerk [26–28]. Clinical and imaging evidence suggests that the localized parietal cortical damage is a pivotal factor for the absence of a giant SEP in these patients [29]. An asymmetric alternation of inhibitory and excitatory balance at the level of cortical neurons leading to a particularly enhanced cortical excitability may moreover play an important role in the generation of myoclonus [27, 28]. The loss of the inhibitory input from the somatosensory cortex to the relatively intact motor cortex, which results from the prominent asymmetric parietal atrophy, may give rise to the asymmetric hyperexcitable motor cortex without giant SEP [30, 31], even-though the existence of an alternative hyper-excitable thalamo-cortical pathway cannot be excluded [32]. In effect, motor cortex disinhibition has been clearly demonstrated in CBD by means of TMS applied in several paradigms in different neurophysiological studies [32–34]. By applying single pulse-TMS, Lu and coworkers discovered a relatively higher motor evoked potential (MEP) amplitude and a significantly shorter cortical silent period in the affected hand of CBD patients [26]. They therefore supposed that the relatively enlarged MEP may be explained postulating that an increased number of motorneurons are being recruited by the descending volleys from the motor cortex [26], while the shorter silent periods may reflect mainly defective inhibitory processes [32]. The result from paired pulse-TMS studies also supported the last hypothesis [22, 23, 35]; for example, Frasson et al. [22] showed that, in patients with CBD, paired magnetic stimuli delivered at short (inhibitory) interstimulus intervals (ISIs) invariably elicited enlarged MEPs; moreover, asymmetric corticocortical disinhibition [22, 36], as well as asymmetric TMS maps organization [32, 37], has been observed in patients with CBD.

In conclusion, several mechanisms could explain this abnormal motor cortical excitability, namely, loss of inhibitory neurons in the cortex or thalamus, effect of morphological changes in cortical neurons mainly in the somatosensory cortices, disruption of some neuronal circuits, or the existence of alternative cortical-subcortical pathways [33, 38]. Further electrophysiological studies are necessary to better circumstantiate these hypothesis.

3.3. Imaging in Corticobasal Degeneration. Morphologic imaging of the brain, although normal in the early phases of the disease, may demonstrate asymmetrical cortical atrophy, in particular of the frontal and parietal lobe, more evident contralaterally to the side most severely clinically affected [39, 40]. Asimmetrical atrophy in the basal ganglia, corpus callosum, lateral ventricles, and cerebral peduncles may be present.

Functional imaging studies might be useful in the differential diagnosis of patients with suspected CBD, showing asymmetrical hypoperfusion on SPECT and asymmetrical hypometabolism on PET involving the parietal-frontal cortex and basal ganglia [41].

Other neurodegenerative disorders sometimes overlap the CBD, making its clinical diagnosis difficult. All criteria stress the combination of an akinetic-rigid syndrome with apraxia, alien limb syndrome, and cortical sensory deficits. A universally recognized feature is the asymmetry of clinical presentation, further corroborated by a contralateral asymmetrical atrophy on the structural and hypometabolism on the functional neuroimaging.

3.4. Neuropathology in Corticobasal Degeneration. Neuropathologically CBD presents as asymmetrical focal atrophy of the cerebral cortex focused on the peri-Rolandic posterior frontal and parietal cortex, especially the motor and sensory areas [42]. There is a relative sparing of temporal and occipital cortex, except in some forms presenting with dementia or primary progressive aphasia, which are characterised by a more symmetric and more severe involvement of the frontal and temporal lobes [6].

Basal ganglia are also involved with substantial atrophy in the lateral two-thirds of the substantia nigra, and, to a lesser extent, of putamen, pallidum, thalamus, and hypothalamus [43].

Histologically CBD is characterised by large pale ballooned neurons (neuronal achromasia), with tau-positive cytoplasmatic inclusions and astrocytic plaques (annular clusters of tau-positive deposits within the distal processes of astrocytes), typically distributed in atrophic cortices [5, 6, 42].

Molecularly CBD is a taupathy, characterised by accumulation of abnormal filamentous inclusions of hyperphosphorylated tau-protein in neurons and glia, similarly to progressive supranuclear palsy (PSP), and some forms of frontotemporal dementia with parkinsonism (FTD) [5, 44]. This molecular overlap, especially with PSP is very argued, and whether they are the extremities of the spectrum of a single disorder or two different disorders with a similar genetic predisposition is not clear [3, 18].

3.5. Diagnostic Criteria and Growing Importance of Cognitive Symptoms. The symptoms can be gathered in four categories: natural history and presentation, motor, sensory motor, and cognitive symptoms. The first three categories include characteristics which have been taken into account in almost all the previous diagnostic criteria. Up to 1994, dementia was an exclusion criterion of CBD; from 2003, on the base of new criteria, cognitive impairments support diagnosis, so the inclusion of the cognitive criteria reflects the growing recognition of the importance of cognitive assessment in the diagnosis of CBD [3, 45].

The core features of disease are insidious onset and progressive course, no identifiable cause (tumor, infarct) of symptomatology, cortical dysfunction includes at east one of the following: (i) focal or asymmetric ideomotor apraxia, (ii) alien-limb phenomena, (iii) cortical sensory loss, (iv) visual or sensory hemineglect, constructional apraxia, (v) focal

or asymmetric myoclonus, (vi) apraxia of speech/nonfluent aphasia: extrapyramidal dysfunction as reflected by one of the following: (i) focal or asymmetrical appendicular rigidity lacking prominent and sustained L-dopa response, (ii) focal or asymmetrical appendicular dystonia.

The supportive investigations are variable degrees of focal or lateralized cognitive dysfunction, with relative preservation of learning and memory, on neuropsychometric testing, focal or asymmetric atrophy on computed tomography or magnetic resonance imaging, typically maximal in parietofrontal cortex, focal or asymmetric hypoperfusion on single-photon emission computed tomography and positron emission tomography, typically maximal in parietofrontal cortex/basal ganglia/thalamus [3].

3.6. Differential Diagnosis. Predominant parkinsonian features might not be easy to distinguish from idiopathic PD and atypical parkinsonian syndromes (e.g., PSP and multiple system atrophy, MSA). Akinetic-rigid syndrome, early inbalance and poor response to dopaminergic treatment are typical symptoms for CBP, PSP, and MSA, in contrast with PD. PSP is clinically and pathologically related to CBD, but with differences in symmetrical versus asymmetrical parkinsonism, and in the pattern of rigidity, which tends to be more nuchal/axial in PSP and more limb-accentuated in CBD. Also, while the superanuclear gaze palsy can occur in both conditions, in CBD it tends to affect the horizontal more than the vertical gaze and the saccade latency (delay in initiating saccades) more than saccade velocity (the speed of saccades).

In patients with cognitive presentation, the diagnosis depends on the specific case: pronounced visuoper-ceptual deficits related to dementia with Lewy bodies (DLB), language involvement to primary progressive aphasia (PPA), and prominent behavioral features to frontotemporal dementia (FTD) [3].

4. Conclusion

CBD can present with various clinical syndromes. The diagnosis of this heterogeneous disorder is difficult and misdiagnoses are frequent. It is important to explain the nature of the motor as well as the cognitive deficits to the patients as well as to all people involved in their care.

As a motor disorder, CBD has been recognized for over 30 years. However, more recent findings suggest that there is a neuropsychological syndrome associated with CBD. The most prominent neuropsychological features of CBD include limb apraxia, ideomotor and ideational apraxias. Executive function and language impairments are also reported.

The characterization of the natural history of patients with the CBD (clinical, laboratory, neuropsychological, radiological features) is important to improve the accuracy of diagnosis.

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Case Report

Nonconvulsive Seizures and Dementia: A Case Report

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Nonconvulsive status epilepticus (NCSE) is a severe medical condition that shows increased incidence in the elderly and is frequently underdiagnosed because of its pleomorphic presentation. We report an NCSE in a 76-year-old woman affected by dementia with acute change of cognitive status and behavior. Intravenous diazepam solved clinical and electroencephalographic manifestations. Neuropsychological assessment after NCSE conclusion showed impairment of several fields that remained unchanged at 3-month followup. NCSE should be considered when sudden and transient cognitive fluctuations appear in the elderly. Epileptic events in dementia occur frequently and are often underrecognized; this could be a misleading factor when considering a quick progression of mnesic performances. Moreover, recent findings both in animal models and in humans demonstrated the deep link between epilepsy and dementia, also supporting the hypothesis that epileptiform activity could contribute to cognitive impairment.

1. Introduction

Epileptic events, even a status epilepticus (SE), should be considered when fluctuations of cognition and awareness occur in elderly people, especially if dementia coexists [1, 2]. In particular, the nonconvulsive status epilepticus (NCSE) is a pleomorphic condition, usually underdiagnosed, defined by the association of changes in consciousness without major motor signs and continuous or repeated epileptic dis-charges beyond 30 minutes on EEG [3]. It appears most often as clinical confusion, corresponding either to absence status (AS) or complex partial status epilepticus (CPSE) [4–9]. According to experimental and clinical observations that focal epileptic activity tends to generalize less often in old age, elderly people show an increased incidence of NCSE—in particular acute symptomatic CPSE—especially in association with neurodegenerative, cerebrovascular, or neoplastic disorders [1, 4–6, 10].

Furthermore, several clinical and experimental data support a close linkage between pathophysiological processes sustaining epilepsy and cognitive impairment of dementia. In fact, both the ictal and postictal effects of the seizures themselves and the effects of the interictal epileptiform EEG discharges may have an impact on cognition [11]; on the other hand, patients with Alzheimer disease (AD) and other types of dementias are at 5–10 fold increased risk of epilepsy compared to age-matched controls [12]. Finally, β-amyloid was recently demonstrated to favour epileptiform activity and cognitive deficits in transgenic mouse models of AD [13, 14].

We report an NCSE in a 76-year-old woman affected by dementia.

2. Case Report

A 76-year-old woman was admitted to our department complaining of an acute worsening of cognitive status and a fluctuating level of consciousness. One year ago, she received a diagnosis of dementia. She has also been suffering from recurrent complex partial seizures for 15 years, and she was taking two antiepileptic drugs (valproicacid, 1000 mg/die and oxcarbazepine, 600 mg/die); the monthly seizure frequency was two. Moreover, she was suffering from hypertension and depression and received several medications (ticlopidine, sartan/hydrochlorothiazide 50 + 12.5 mg, paroxetine 20 mg/die). Finally, in her history, there was a nonspecified cerebrovascular accident 16 years ago.

Her relatives defined her actual behaviour as different from the usual one, and they noted a fluctuating cognitive status in the last weeks. Upon examination, she looked distracted and vacant. She replied to questions only after a brief pause and with inadequate answers. She had trouble speaking, and she was uncooperative and disoriented. Some minutes later she presented a restriction of consciousness (fixed gaze and unresponsive to any kind of stimuli) with motor signs (oro-alimentary automatisms and jerking of right foot) lasting some minutes. Then, only persisted consciousness restriction.

The EEG examination that was performed during the episode showed a subcontinuous theta-delta activity with sporadic low-voltage spikes prevalent in the bilateral frontotemporal regions longer than 30 minutes from symptoms' onset, and thus leading to the diagnosis of CPSE (Figure 1). She was promptly given intravenous diazepam (5 mg) with resolution of clinical and electroencephalographic manifestations. After diazepam administration the patient fell asleep. The EEG recording revealed clear interictal epileptiform waves on the left frontotemporal area during stage 2 NREM sleep (Figure 2). Brain MRI performed on the fourth day showed a T2-weighted abnormal hyperintensity in the left insular cortex consistent with a vascular gliotic area. A severe impairment of memory and attention with minor deficits of language and praxia were evident at the neuropsychological assessment on the fifth day after CPSE. MMSE score was 12/30. She was discharged with an increased dose of oxcarbazepine (1800 mg/die). Neuropsychological evaluation demonstrated an unchanged cognitive performance at 3-month followup.

3. Discussion

Transient events including syncope, episodes of inattention, or confusion are frequent in elderly people, mainly in patients affected by dementia [1, 2]. In our patient, with a known cognitive impairment, the acute change in behavior and cognition, associated with a restriction of consciousness, leads to the suspicion of an epileptic event. The EEG provided evidence of an electroclinical pattern of CPSE that explained the patient's symptoms.

Rapid cognitive decline in demented patients could mimic several disorders: metabolic encephalopathy, prolonged postictal confusion, psychiatric disorders, substance intoxication, transient global amnesia, and transient ischemic attack [15]. NCSE should be included in the differential diagnosis, as a potentially treatable cause of altered awareness in the elderly. NCSE appears to have a gradual development of symptoms (impaired consciousness; "epileptic twilight state" with confusion, strange behavior, and automatisms). Therefore, its identification is usually difficult, especially when clinical manifestation only consists of mild changes in behavior. In our patient, the presence of preexisting epilepsy and dementia fortified the presumption of a status epilepticus (SE) [1, 6, 8, 16]. Furthermore, she was in treatment with paroxetine that reduces the seizure threshold [17]. Several previous studies have demonstrated the frequency of a delayed diagnosis of an NCSE in elderly due to the absence of certain clinical parameters [18]. Husain and colleagues tried to define a profile of clinical features highly suggestive of NCSE (risk factors for seizures such as history of epilepsy, dementia and stroke, and impaired mental state) in order to select those patients who need an emergency EEG [19]. The EEG is fundamental to obtain an early diagnosis and should be promptly considered as a standard protocol in acute de novo confusion in these patients with high level of suspicion for NCSE [3]. Moreover, EEG findings are necessary to localize the epileptic focus and to distinguish a CPSE from an absence status, since in the first one, a rapid cessation is required due to prolonged episodes that may be accompanied by neurological deficits. Benzodiazepines are the most commonly recommended agents [20, 21]. The aims of therapy when treating NCSE are the improvement of individual's cognitive function and to clear EEG tracing from epileptiform discharges [6, 15]. Our patient's critical EEG definitely improved during treatment. No causative medical disorders were recognized at blood test. We supposed that the patient was affected by symptomatic focal epilepsy, and her poor antiepileptic therapy compliance in association to a lower seizure threshold was the cause of SE.

The hypothesis of an "epileptic pseudodementia" has been later confuted by cognitive assessment followup that proved a stationary neuropsychological impairment. The patient's relatives noted a very different behavior prior to admission. We could hypothesize that she might have experienced some other prolonged epileptic events that were not recognized. Animal models and some observation in humans have shown that NCSE could be responsible for long-term deficits also in neuropsychological field. How much morbidity adds ictal confusion to a preexisting cognitive impairment remains highly debated. The authors confirm the influence of causative medical disorders, the treatment, and perhaps the persistence of seizure activity in complications and sequels of NCSE [6, 15]. Both ictal and interictal epileptiform EEG discharges could have an additional and independent effect on cognition. Nevertheless, some authors downsize their role except for cryptogenic partial epilepsies that seem to be associated with a higher risk of cognitive impairment [22]. In our case, the left frontotemporal epileptic discharges should be compatible with clinical features of language and memory impairment and well match with the insular vascular gliotic area revealed by MRI. Thus, it could be argued that previous stroke caused the ischemic insular lesion and then symptomatic epilepsy.

Finally, interesting recent studies have speculated on several mechanisms that could link epilepsy to cognitive decline and vice versa. Cordonnier and De Reuck [23, 24] reported that epileptic seizures, both early and late-onset, after stroke were independent predictors of new-onset dementia. They speculated that preexisting vascular pathologies that may predispose to both epileptic seizures and new-onset dementia could be white matter changes, silent infarcts, or microbleeds. Alternatively, this could be due to an underlying preclinical degenerative disorder such as Alzheimer's disease. The recent findings in AD animal models of causal relationship between Aβ-induced aberrant excitatory neuronal activity and cognitive decline raised

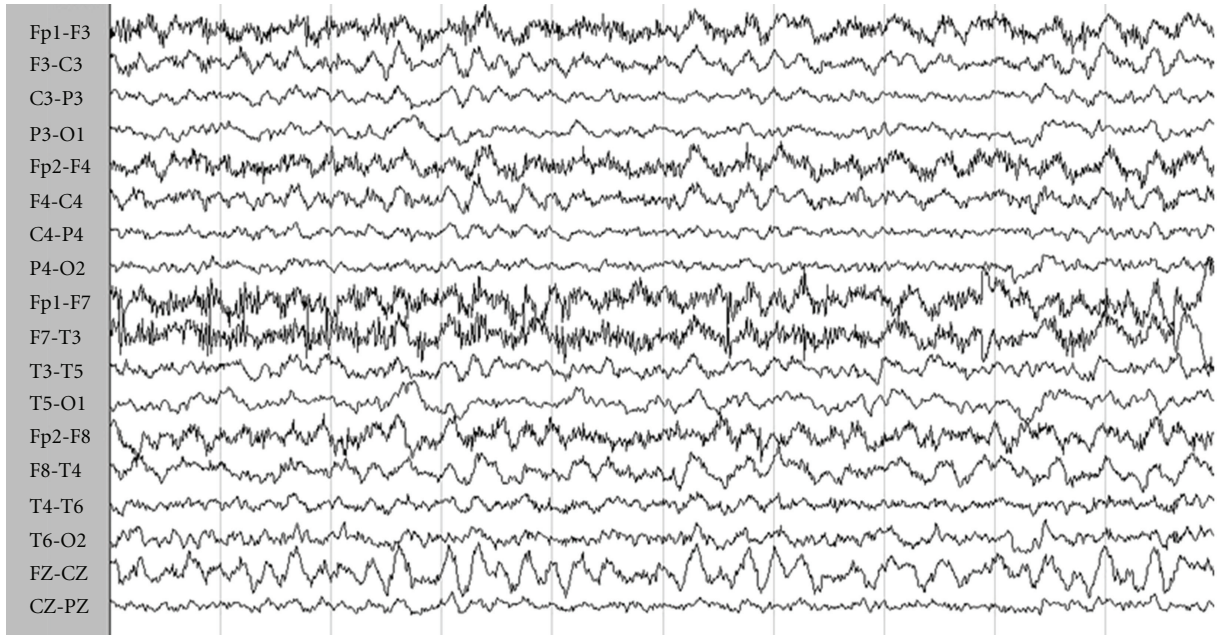

Figure 1: *Ictal EEG.* The EEG during the episode showed a subcontinuous theta-delta activity with sporadic low-voltage spikes prevalent in the bilateral frontotemporal regions.

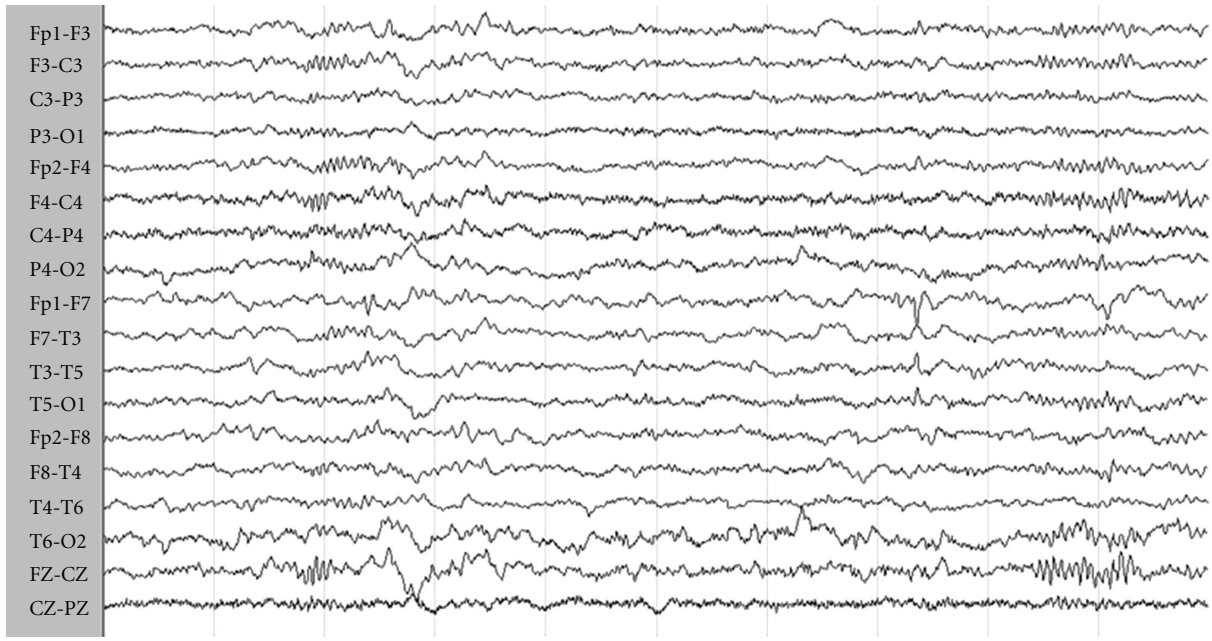

Figure 2: *EEG activity after diazepam administration.* After diazepam administration, the patient fell asleep, and EEG recording showed sharp waves on the left frontotemporal area during stage 2 NREM sleep.

the possibility that also in humans epileptiform activity could represent a primary mechanism that may contribute to cognitive deficits [13, 25, 26]. However, the long-term effect of seizure activity on the neurodegenerative disorder is unknown. Finally, the putative epileptogenic mechanism in patients with combined recurrent seizures and a progressive neurodegenerative disorder may relate to the findings of neuronal loss and gliosis involving selected regions such as the medial temporal lobe [25].

4. Conclusion

Epileptic events in dementia are frequent and often under-recognized, and this could be a misleading factor when

considering a quick progression of mnesic performances. NCSE should be always considered when sudden and transient changes in behavioral or cognitive baseline condition are presented in an elderly patient, especially if affected by dementia when there are no other evident causes. It is mandatory to recognize the suggestive features for NCSE in an early stage and to perform a prompt EEG to diagnose and treat this epileptic condition.

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Review Article

Management of Demented Patients in Emergency Department

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The hospitalization of the elderly with acute illness is one of the most discussed in the organization of health services, it is not yet clear whether the hospital is really the best response to the needs of the elderly, especially those with cognitive impairment. Despite evidence of possible adverse effects of hospitalization (immobilization, acute confusional state resulting in sedation, risk of falls, intestinal sub-ileus), there has been an increasing use of the hospital, particularly to specialist services. Regardless of the benefits from the shelter (instrumental diagnosis and prompt treatment of acute somatic disease), in people with dementia it needs to identify the characteristics of the person (cognitive impairment, functional status, somatic comorbidity, social and familial status), the personal needs and, therefore, diagnostic and therapeutic targets which must be assumed for that sick person during hospitalization. To this end, it is fundamental the role of assessment and diagnostic orientation that takes place in the Department of Emergency and Acceptance (DEA), which mainly receives patients at the hospital. Even before the hospital recovery it is therefore essential to check how many elderly patients with cognitive impairment that belong to the DEA, and what are their needs.

1. Epidemiological Data

Over the past 10 years an increasing proportion of elderly people, especially those with dementia, had recourse to the Department of Emergency and Acceptance (DEA): the elderly, in respect to young and adult people, on average, have more urgent requests, stay longer in the department (both for diagnosis and for therapy), use more resources and staff time [1]. Despite a great number of tests and procedures, diagnoses tend to be less accurate: this condition is explained by the atypical presentation of many diseases, the clinical and pharmacological comorbidity, which tend to complicate the presentation, the diagnosis, and the treatment of acute or chronic disease. In addition, older people often belong to the DEA for diseases that require intensive care: a study carried out for 5 years in 352 hospitals in the USA and England, it was found that the percentage of admission in polyfunctional intensive therapy (PIT) of patients over 65 years is very high (above 50%). In the total group of patients belonging to the DEA, the subsequent admission to the PIT was mainly for medical conditions (53% in England, 63% in USA), and less for acute surgical diseases (48 vesus 41%, resp.) [2]. The data shows that elderly patients who belong to the DEA, and among these also patients suffer from dementia, are presented to the hospital for somatic diseases or acute and severe surgical procedures that require often intensive treatment. It should be noted, moreover, a different intensively diagnostic/therapeutic attitude between different countries: USA PIT hospitalization of elderly patients from the DEA has increased, especially for acute somatic diseases. This reflects in part the difference in prevalence in the elderly population, and probably represents a different attitude in the decisions of hospitalization of elderly patients between the two countries. A study conducted in Italy showed that 21% of people who belong to the DEA are over 65 years. The percentage of those who are hospitalized increased with age: it goes from 11% of those under 65 years, to 56% of the over nineties. The majority of patients hospitalized in medical departments from DEA is over sixty-five (60%), but represents only 25% in surgical wards. Among all patients hospitalized and then hospitalized for the DEA, 6% suffer from severe dementia. The sick elderly patient who suffers from dementia that reaches the DEA, therefore, is often hospitalized because of the seriousness of his condition requires acute somatic hospital treatment. Moreover, because of the greater disease severity, the duration of hospital stay

in patients over eighty years is longer than the hospital stay of younger females (7.9 versus 5.8, resp., days for males, 6.8 versus 4.1 in women). An increase in patients, over 85 years, who belong to the DEA: 71% versus 65% of the general population. 71% versus 65% of the general population. Among these patients, more than 80% are suffering from dementia, of which 30% suffer from severe dementia, and 20% from the moderate form of disease (patients followed at home by a caregiver). Another interesting fact that emerges from the study is the cause of hospitalization: 43% of the patients are evaluated for acute somatic pathology, and 33% for chronic heart failure. The percentage increases for each age group; over-85-year group always (including the dementia for 80%) that have the highest percentage (41%) of hospitalization for acute somatic illness. The recent studies paint a scene so disturbing: a high number of elderly patients and, among these, a high percentage of people with dementia, belong to a structure for acute, historically more prepared to manage acuities in young and adult. The future scenario must necessarily change, since the number of patients with these characteristics tends to increase over time [1]. Among the possible explanations for this phenomenon, apart from the increase in the average age of the population and worsening of chronic somatic illnesses and comorbidity (especially in people with dementia) in general, it increases the vision of the DEA as a replacement more quickly and technological than the caregivers, and the lack of an adequate social/assistance support at home [3].

2. The Main Pathological Conditions

The majority of patients with dementia pertains to the DEA for an acute somatic or surgical illness, or a chronic heart failure. The diseases that most often drive the elderly to apply for an urgent evaluation are cardiovascular diseases (angina, heart failure, arrhythmias, and syncope) or respiratory diseases (acute exacerbation of chronic bronchitis, bronchial asthma, and pneumonia), in addition, cancer (cancer of the lung, breast, and large bowel), and neurological diseases (acute cerebrovascular disease, altered state of consciousness) [4]. Among surgical emergencies, the most common diagnosis is related to trauma and fractures, caused mainly by falling to the ground. Other diseases that result in the arrival at the DEA are clinical emergencies that require different level of intervention: sometimes less technological and more clinical (dehydration, urinary tract infections, intestinal subileus, delirium, behavioral disturbances, and subsequent guidance of therapeutic prescription) others more specific to the setting of care (acute respiratory failure from respiratory infection, acute myocardial infarction, and sepsis). Finally, in some cases, the patient with dementia is sent to the DEA for clinical problems related to an incorrect home management: oversedation from psychopharmacological treatment, side effects from medications (iatrogenic hypotension, hypoglycemia jatrogena). See Table 1 for a summary.

In these situations a careful medical and medication history is the necessary instrument (low-tech, but related to the practice of good clinical practice) that would lead to the diagnosis and solution of the problem. It should also be considered that there is a different prevalence of somatic diseases in different stages of Alzheimer's disease and other dementias. Those that are usually associated with mild to moderate dementia are the tumours, diabetes, gastrointestinal disease, while those associated with severe dementia are pneumonia and other infectious diseases, stroke, malnutrition, hip fractures, bed sores [5]. See Table 2 for a summarization.

In this case, dementia complicates the management of chronic diseases, compromising the ability of patients to detect the presence of an incipient fault, to measure the severity of the disease, to accurately report symptoms, and to follow closely the prescriptions [6].

3. The Evaluation of the Patient in the Emergency Department

A difficult problem in clinical management and in supporting people with dementia is the impairment in the ability to report somatic symptoms: this ability seems directly related to insight of disease, different from person to person. Patients with dementia generally tend to subreport symptoms of organic disease, and therefore may be at increased risk of somatic disease: a result could be that many potentially treatable medical conditions are overlooked. Furthermore, the clinical manifestations of somatic diseases may be atypical in patients with dementia, the onset of acute illness or exacerbation of persistent disease may occur, rather than with classic signs and symptoms, with confusion: hyperkinetic or hypokinetic delirium, the second even more difficult to detect and interpret. Finally, somatic diseases may occur with sudden onset of behavioral problems, or a modification if in their background: usually there is an increase in frequency and severity of BPSD (behavioural and psichological symptoms of dementia), such as agitation, insomnia, busy, deliria, or hallucinations. A study showed that there is a clear difference between painful somatic symptoms reported spontaneously by the person with dementia, compared to those required by an observer [7]. Considering both the symptoms reported spontaneously and those evoked after request, patients with MCI and very mild complained significantly more symptoms than cognitively intact patients. The number of painful symptoms changed in patients suffering from dementia of varying severity (from very mild to severe): a greater severity of cognitive impairment corresponded to a lower number of somatic symptoms reported. Since the diagnostic orientation in medicine is mainly based on reported symptoms, it is possible that many diseases, potentially treatable, may not be diagnosed in the person with cognitive impairment. This condition is central in the clinical treatment of organic disease in patients with dementia, because the nonresponse (and the consequent failure to treat) of somatic disease significantly affects both somatic health and evolution of cognition and functional status [8].

4. Clinical Assessment

The assessment of somatic diseases in the course of dementia is a phase of the multidimensional assessment, which often

Table 1: The diseases that most often drive the elderly to apply for an urgent evaluation.

Medical emergency
Cardiovascular diseases (angina, heart failure, arrhythmias, syncope)
Respiratory (acute exacerbation of chronic bronchitis, bronchial asthma, pneumonia)
Cancer (cancer of the lung, breast, large bowel)
Neurological diseases (acute cerebrovascular disease, altered state of consciousness)
Chirurgical emergency
Trauma and fractures
Clinical emergency
Dehydration, urinary tract infections, intestinal sub-ileus, delirium, behavioral disturbances and subsequent guidance of therapeutic prescription
Acute respiratory failure from respiratory infection, acute myocardial infarction, sepsis
Clinical problems related to an incorrect home management
Oversedation from psychopharmacological treatment, side effects from medications (iatrogenic hypotension, hypoglycemia jatrogena)

Table 2: Principal pathologies associated with patients with dementia.

For mild to moderate dementia:
Tumours, diabetes, gastrointestinal disease
For severe dementia:
Pneumonia and other infectious diseases, stroke, malnutrition, hip fractures, bed sores

suffers from the problems associated with comorbidity, or that is, entirely neglected. One of the targets of care of patients with dementia is in fact the prevention of complications (infection, malnutrition, incontinence, or delirium) which result in an increased risk of hospitalization and increased mortality in short and medium term [6]. A careful management of possible comorbidity could therefore slow the functional decline and limit the complications. In patients with dementia, even in the early stages of the disease, medical history should be collected or at least confirmed by the principal caregiver or by a person who knows the personal history. The doctor involved in the evaluation of the patient should be able to detect the presence of signs and somatic symptoms in the acute phase.

The risk that you may incur, then, rather than an overestimation of pain in patients with dementia is the underestimation of the symptom in older cognitively compromised patients. The question is to understand how it is possible to detect somatic symptoms in patients who have communication problems and memory disturbances. It is evident that, while for chronic symptoms we must rely on memory and observation of the caregiver, for the detection of acute pain you can take advantage of signs that may accompany the symptoms and be directly observed. Firstly, a sudden change in cognitive status of a patient is always an alarm bell. When family members report a rapid deterioration, or an unusual confusion, the possibility that the patient has pain should always be investigated. We must observe the gestures and movements, asking the patient to report the discomfort. The same process must be implemented when the patient experiences a sudden agitation, insomnia, or when they show unusual apathy and drowsiness. Determining the amount of pain is much more difficult. The correct attitude is to try any way because of the pain and to treat both the disease and the symptom. The risk of a too conservative practice is to leave the most compromised patients—those who cannot communicate their pain in any way—alone with their pain. In addition to symptom assessment, the assessment of somatic health of the patient with dementia is based on the concepts already defined by the multidimensional geriatric assessment associated with the clinical evaluation of the patient. In the person with dementia, the examination is of particular importance in order to capture significant signs, that are the indicator of an underlying organic disease not reported or underestimated by the patient and the family. Similarly, given the difficulty of communication of the patient, the clinical signs should be carefully considered: the difficulty breathing or tachypnea is a sign of an underlying respiratory or cardiac disease, regardless of the reported symptom (dyspnea). Finally, incorrect posture could be due to side effects of a prolonged neuroleptic treatment, and antalgic attitudes give an indication related to the districts affected by pain. Furthermore, the presentation of somatic or acute surgical diseases can be atypical, for example, pneumonia rarely occurs with fever, chest pain, and cough, but simply with a catastrophic effect on functional status, an event that represents the most significant clinical manifestation. In front of nonspecific and atypical symptoms and signs of acute somatic illness (lethargy, delirium, and rapid functional decline), it is important that the evaluation of patients with dementia, which refers to the DEA, is the most complete and accurate. In DEA the beats are tight, and there is often a need to evaluate many patients quickly, with the risk of neglecting the details: for this reason it is possible that the atypical signs of the diseases of the patient with dementia are neglected, resulting in delay on diagnosis and treatment of disease. It is therefore necessary,

Table 3: Clinical assessment of patients with dementia.

Anamnesis: medical history collected or at least confirmed by the principal caregiver or a person who knows the history Risk of underestimation of the symptom in older cognitively compromised
Objective examination: patient visit in order to capture significant clinical signs Useful indicator of an underlying organic disease not reported or underestimated by the patient and the family
Pharmacological anamnesis: drug history of the patient Many drugs may cause side effects, especially when administered by not clinical prepared persons
Vital signs: for better understanding of the patient's general condition Determination of blood pressure, heart rate, oxygen saturation (blood gas, or), body temperature, and glycemia

with complex patients, to retrieve that good clinical practice that researches all possible causes, starting with a thorough medical history. Events interpreted as normal for adults are not normal for the elderly suffering from dementia the recent onset of fever, decreased hydration, push to try different pathologies with a patient who does not communicate and which shows only a drowsiness. Still, the drug history is important, especially if we think that many drugs (e.g., oral hypoglycemic agents, antihypertensives, neuroleptics) may cause side effects, especially when administered by persons not prepared by the clinical point of view (family members). The assessment of vital signs, finally, is essential for a better understanding of the patient's general condition: the determination of blood pressure, heart frequency, oxygen saturation (or blood gas), body temperature, and glycemia. On the basis of the geriatric history and the clinical evaluation, it becomes easier to guide implementation of blood chemistry and instrumental analysis in DEA while avoiding unnecessary and expensive tests, both in terms of patient suffering (execution time, discomfort for the patient and their families) that in economical terms. The evaluation of the patient with dementia which refers to the DEA, therefore, requires more attention than the adult, as it needs a specific and careful approach, which considers every possible cause of somatic or surgical illness to achieve a good diagnostic orientation, a prerequisite for the selection of the correct treatment regimen. Table 3 reports the principal clinical assessments of patients with dementia.

5. The Path in DEA

When patients with dementia belong to the DEA for somatic problems or the exacerbation of cognitive or behavioral disorders, the key problem is to understand the real necessity and usefulness of hospitalization; that is, if the issue in which the patient with dementia is presented to the DEA is solved in the same emergency room, or if it becomes necessary hospitalization for diagnosis and treatment. In fact, in some cases nonspecific symptoms (confusion, agitation, anxiety, or, conversely, apathy, and drowsiness) may represent the onset of an acute somatic disease (lung infection, acute heart failure, acute myocardial infarction, and fractures), which requires correct hospitalization. In this case, the diagnostic, clinical and instrumental capacity of the staff of the DEA would lead to a disease orientation that should be treated in a hospital. Sometimes, on the contrary, from the evaluation of the DEA, medical conditions requiring hospitalization emerge: it is often the patient's family that led him to the DEA, frightened by a series of nonspecific symptoms that cannot be understoond (conduct disorder, bone and joint pains, abdominal pain from chronic constipation, and dyspepsia). The minor clinical problems can be addressed directly in the DEA, for which the patient can be treated on site (pain therapy, oral antibiotics, and enema evacuees) and be returned to their home, or in nursing homes of origin. This attitude has a twofold advantage: firstly it solves the problem directly to the patient and his family members, reducing the discomfort and inconvenience of a hospitalization. On the other hand, it allows the patient to return to their place of residence, thus avoiding the risk of delirium, which is high for the hospitalized patient with dementia. Certain negative conditions must be, however, remember: even today, too often, the patient suffering from dementia is an uncomfortable patient. When the patient arrives at the DEA, the doctor knows that, most likely, he will tract a number of problems that characterize a complex patient. Often the risk is to reduce the attention, to make a superficial assessment, assuming a series of chronic pathologies, and therefore not worthy of consideration. Superficiality and carelessness, unfortunately, do not allow an overall assessment of the patient, with the risk of failing the expectations of the patient and family members, or to neglect the real problem of the patient (e.g., to deal with the agitated patient with sedatives without thinking about the cause that could be pneumonia). Finally, particular attention should be paid to the environment: the DEA is often a noisy, crowded place, where all patients are understandably suffering from an illness, seeking an answer quickly, not including delays or procedures, also because few medics find the time to stop and explain it. Stress related to pain, noise, and unfamiliar environment are reflected even more heavily on the patient suffering from dementia, who find themselves in a "tower of Babel" where just few stop talk to them, trying to understand their problems and to cheer them up. Little attention is given to their needs, including physiological ones: if they have to wait in the DEA for several hours before the visit, it is difficult for them to ask for help, as they suffer from dementia, they do not pay attention to their needs: hydration, using the bathroom, eating, and caring for their somatic pain. The risk is to accentuate the symptoms, including behavioural ones, and arrive at the time of the visit with a patient even more confusing and therefore, in our

eyes, even more incomprehensible. The future of the DEA, if it is to become efficient and effective, is to specialize in these patients, who will increasingly need quick and competent responses [9].

6. Conclusions

A large number of people who come to the DEA suffer from a severe form of dementia: 12% of patients who are admitted to medical ward from the emergency department suffer from severe dementia, so it is possible to envisage a double rate if we include patients with dementia in mild to moderate impairment. The hospital and the staff of the DEA, in general, are not prepared to deal with the continuing (and increasing gradually over time) requirement of care by people with dementia, regardless of its severity. In fact, with increasing age, it increases the clinical complexity of patients that belong to the hospital. It is necessary that the staff of the DEA is prepared (and not just on the field) to the assessment and planning of the elderly patient with dementia: how to recognize cognitive, sensory deficits, to identify the patient's functional status and social resources at home are fundamental factors that drive both the diagnostic orientation and treatment choices (hospital care versus at home care). The risk you take is to use the outdated disease-oriented method that does not help the understanding of geriatric pathologies. As noted in a recent study, most physicians working in the DEA in the USA reported higher levels of anxiety as a result of the large number of elderly patients who belong to the hospital, and their inability to cope with the complexity of the patient. The low level of experience, and the lack of specific training in geriatric medicine for acute care and in relation to the elderly and their families, are factors contributing to increased stress for staff [9]. The future scenario should include a plan to improve the quality of care, through a specific theoretical and practical training for all personnel working in an emergency ward: the objective is to train skilled professionals to handle the urgency of the young and adult, but also specialized in the treatment of acute diseases of the elderly patients with dementia [10].

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