

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 zero-time 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 zero-time 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 awoken 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 awoken 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, awoken human brain [54–58] and have been linked to intelligent quotient, memory, and cognition [51]. Whereas high-frequency alpha rhythms 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 $\epsilon 4$ genotype (Apo-E $\epsilon 4$) and late-onset AD. Apo-E $\epsilon 4$ 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 $\epsilon 2$ and $\epsilon 3$, AD patients with $\epsilon 4$ showed higher theta and lower beta spectral power [75]. Furthermore, the AD ApoE $\epsilon 4$ 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 $\epsilon 4$ 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 lose 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,

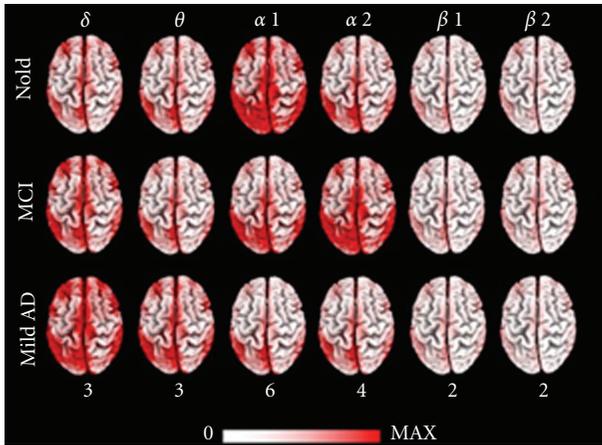


FIGURE 1: Grand average of low-resolution brain electromagnetic tomography (LORETA) solutions (i.e., normalized relative current density at the cortical voxels) modeling the distributed EEG sources for delta, theta, alpha 1, alpha 2, beta 1 (13–20 Hz), and beta 2 (20–30 Hz) bands in normal elderly (Nold), 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 $\epsilon 4$ affects sources of resting EEG rhythms in MCI and AD was assessed in 89 MCI with 34.8% $\epsilon 4$ incidence and 103 AD with 50.4% $\epsilon 4$ incidence [112]. Alpha 1 and 2 sources in occipital, temporal, and limbic areas were of lower amplitude in subjects carrying the ApoE $\epsilon 4$ allele. For AD homozygous for ApoE $\epsilon 4$ allele, abnormal temporo-parietal and occipitoparietal EEG or MEG rhythms were found [74, 88]. However, in addition to ApoE $\epsilon 4$ 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 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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