Resting State Cortical Electroencephalographic Rhythms in Alzheimer's Disease

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Abstract: Physiological brain aging is characterized by a loss of synaptic contacts and neuronal apoptosis that provoke age-dependent decline of cognitive functions. Neural/synaptic redundancy and plastic remodelling of brain networking, also secondary to mental and physical training, promotes maintenance of brain activity in healthy elderly for everyday life and fully productive affective and intellectual capabilities. However, age is the main risk factor for neurodegenerative disorders such as Alzheimer's disease (AD) that impact on cognition. Oscillatory electromagnetic brain activity is a hallmark of neuronal network function in various brain regions. Modern neurophysiological techniques including electroencephalography (EEG) can index normal and abnormal brain aging to facilitate non-invasive analysis of cortico–cortical connectivity and neuronal synchronization of firing, and coherence of rhythmic oscillations at various frequencies. The present review provides a perspective of these issues. It is concluded that discrimination between physiological and pathological brain aging clearly emerges at the group level, with applications at the individual level also suggested. Integrated approaches utilizing neurophysiological techniques together with biological markers and structural and functional imaging are promising for large-scale, low-cost and non-invasive evaluation of at-risk populations.

Keywords: Alzheimer's disease (AD), resting state, electroencephalography (EEG), low resolution brain electromagnetic tomography.

1. INTRODUCTION

Since its introduction, the electroencephalogram (EEG) was viewed with a great enthusiasm as the only methodology allowing a direct, on-line view of the "brain at work" [1]. It offers appreciable promise as a means to characterize significant deviations from the 'natural' aging found in Alzheimer and other dementias [2]. From the 1970s and 1980s with the introduction of structural imaging technologies such as computer assisted tomography (CAT) and magnetic resonance imaging (MRI), these newer methods produced non-invasive views of *in vivo* brain anatomy with considerable resolution that contributed to their clinical and therefore economic utility. Over the course of the following two decades, 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) have supplanted the role of EEG in basic and clinical studies. However, these functional brain imaging methods with their high spatial resolution for anatomical details are relatively limited in their temporal resolution when measuring functional brain activation (seconds to minutes). Thus, these neuroimaging techniques cannot discriminate in series or parallel activation of different relays within a distributed network [3]. As these imaging methods were being developed, similar advances were being made for EEG measures in part because neuroelectric signals can track information processing with millisecond precision, and may measure natural brain aging and to discriminate it from neurodegeneration [4, 5].

In recent years, an increasing attention has been paid to the application of quantitative EEG (qEEG) and/or event-related potentials (ERPs) as useful clinical markers of early disease or progression [6], in large part as a result of recent and dramatic improvements in the ease of use of the technology and in access to sufficient computing power and

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the 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 place with low impedance. A positive ERP peaking 600 ms after the zerotime of stimuli to be encoded (P600) has been reported to be impacted in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) [7, 8]. Furthermore, a positive ERP peaking 300 ms after the zerotime of oddball stimuli (P300) has been reported to be impacted in dementia [6]. Thus, theoretical and empirical support exists for the application of ERPs as a measure of individual variation of cognitive function along pathological aging [9]. However, recording of ERPs requires a peculiar set up between the stimulation device and EEG machine, about 40-60 minutes of time for the exam in a 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 review outlines the impact of EEG techniques for the measurement of physiological and pathological brain aging and attempts to provide a reasonably comprehensive analysis of brain aging by the analysis of resting state EEG rhythms in elederly subjects with various degrees of cognitive decline. Its major goal is to highlight the emerging neurophysiological findings to determine whether these techniques provide sufficient innovative and potentially useful information for the assessment of normal aging and dementia, both at a group- and single-subject level.

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 allow control over the contribution of volume currents from far-field generators [10, 11]. Hence, EEG signals generated from extracerebral sources (e.g., electrocardiogram, electromyogram, electroretinogram, eye movements etc.) can be isolated from those produced by the brain, with 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 spatial resolution of the signals has been reduced from about 7 to 2 cm by applying surface Laplacian estimation with a regularized 3D spline function, which 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, 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 also is unreliable when computed at the borders (i.e., temporo-parietal electrodes), and its maxima often do 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 cortico–cortical connectivity. 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. Finally, the direction of the information flow within the EEG rhythms between pairs of electrodes can be estimated by a direct transfer function (DTF) [17-22].

Source reconstruction of the electromagnetic brain scalp signals can be achieved *via* different methods. Relevant literature on brain aging is particularly linked to the use of low-resolution electromagnetic tomography algorithm (LORETA) technique that computes 3D linear solutions from multi-channel input to localize generators in the brain from the EEG field distribution on the scalp by employing a three-shell spherical head model of the scalp, skull, and brain compartments [23-25]. Source analysis is reference free, since the same source distribution is obtained for EEG data referenced to any electrode including a common average. 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 [26-29]. LORETA solutions consist of voxel z-current density values that are used to predict EEG spectral power density at scalp electrodes. A normalization method yields current density at each voxel for the power density averaged across all frequencies (0.5–45 Hz) of electromagnetic brain rhythms and voxels of the brain volume.

3. RESTING STATE EEG RHYTHMS AND PHYSIOLOGICAL AGING

Resting state EEG rhythms typically change across physiological aging, with gradual modifications in spectral power profile indicating a pronounced amplitude decrease of alpha (8-13 Hz) and a global "slowing" of the background EEG, wich increases in power and topographic location in the slower delta (2–4 Hz) and theta (4–8 Hz) frequency ranges [30-33]. A recent study in a large sample of healthy subjects (N = 215, 18–85 years) confirmed an age-dependent power decrement of low-frequency alpha rhythms (8–10.5 Hz) in parietal, occipital, and temporal regions, as well as a decrease of occipital delta power [34].

Aging effects on parieto-occipital alpha rhythms presumably reflect the activity of dominant oscillatory neural network in the resting awake brain. This activity is modulated by thalamo–cortical and cortico–cortical interactions facilitating/inhibiting the transmission of sensorimotor information and the retrieval of semantic information from cortical storage [35-37]. Low frequency alpha is primarily related to subject's global attentive readiness, whereas high-frequency alpha reflects the

oscillation of specific neural systems for the elaboration of sensorimotor or semantic information [33, 38, 39]. 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 [40].

Neuroelectric output does not scale linearly with inputs received, so 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 pre-frontal and the right parietal regions between young and elderly, suggesting that the aging brain engages right parietal region to assist the pre-frontal cortex [41].

4. RESTING STATE EEG RHYTHMS AND DEMENTIA

Dementia is one of the most frequent chronic diseases of the elderly. Its prevalence increases with age and affects nearly 30% of all octogenarians [42] with heavy social costs and impact on family and caregivers. Neuropathological hallmarks 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. Microscopic signs include neurofibrillary tangles (intracellular aggregations of tau protein filaments) and amyloid plaques (extracellular aggregates of amyloid beta-peptides) that are particularly concentrated in the hippocampus, entorhinal cortex, and post-central parietal neocortex [43]. Tangles are mainly found in hippocampal and parahippocampal limbic structures, whereas extensive diffuse and neuritic amyloid plaques – circumscribed by proinflammatory and proapoptotic reactions – form deposits throughout the cortex [44]. A progressive decrease of use-dependent synaptic plasticity and of interneuronal connectivity and its association with the degree of dementia is considered the neurophysiological hallmark of brain aging [45]. However, in pre-clinical conditions plastic compensatory remodelling appears to continue that maintains neural function, such that the neuronal and synaptic death may occur in the absence of dementia symptoms for an unknown duration, possibly for years or decades.

When compared to the resting state EEG rhythms of healthy normal elderly (Nold) subjects, AD patients evince high power for delta and theta and low power for posterior alpha (8–12 Hz) and/or beta (13–30 Hz) frequencies [28, 46-50]. Some of these EEG changes could discriminate among different dementia diagnoses, as a strong decline of posterior slow-frequency alpha sources appears specific for mild AD group compared to the vascular dementia, fronto-temporal dementia and normal elderly groups. In addition, abnormal wide amplitude of the theta sources characterized cerebro-vascular dementia patients [28]. EEG abnormalities were associated with altered regional blood flow/metabolism and with impaired global cognitive function as evaluated by mini-mental state examination (MMSE) [49, 51-53].

Of note, early stages of AD (even preclinical) are typically associated to slowing down of resting occipital alpha rhythms, namely a decrease of the individual alpha frequency (IAF) peak in power density [54]. Therefore, the IAF 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.

Genetic risk factors such as Apo-E ε 4 alleles are associated with abnormalities of resting state EEG rhythms in AD [55-58] with relatively specific EEG measures.

Compared to AD patients with ε2 and ε3, AD patients with ε4 demonstrated faster theta and lower beta spectral power [56]. Furthermore, the AD patients with ε4 were characterized by higher theta power and lower beta power at baseline, whereas they had higher delta power and lower alpha power at 3 years at follow-up [57]. Moreover, AD patients with ApoE ε4 has been related to selective decrease in functional cortico–cortical connectivity, which was suggested by the reduction of right and left temporoparietal, right temporofrontal, and left occipitoparietal alpha coherence [55]. Thus, genetic risk factors for AD are 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 [55, 59-63], suggesting a linear temporal interdependence of coupled EEG rhythms from simultaneously engaged neural sources. Such findings imply that functional coupling of cortical rhythms is modulated by cholinergic systems, and that a decrease of cortical EEG coherence may be a fine-grained marker of AD, since it is characterized by defective basal forebrain cholinergic inputs to cortex and hippocampus [64].

Most EEG studies of AD have reported a prominent decrease of alpha band coherence [45, 55, 58-63, 65-67]. This result also has been found to be associated with ApoE genetic risk, which is hypothesized to be mediated by cholinergic deficit [55]. However, delta and theta band coherence changes in AD is not homogeneous, as some studies demonstrate a decrease of slow-band EEG coherence, whereas others find an increase [59, 63, 65, 68]. To improve the functional coupling evaluation EEG and MEG data have been analyzed with procedures inspired by the theory of nonlinear dynamics, which provide a measure of signal dynamic coordination [69]. AD patients produce a nonlinearly defined "complexity", which is a measure of signal dynamic coordination. 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 [70, 71]. Nonlinear analysis also has been used to model brain flexibility in information

processing, defined as the capability to affect information processing states from identical initial conditions. AD patients demonstrate a decrease in information processing flexibility, so 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 [69]. This measure has been shown to be significantly decreased at 10–12 Hz, 14–18 Hz, and 18–22 Hz bands when comparing AD to MCI and/or Nold subjects [72-75].

In addition or in parallel to the cortico–cortical 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 [93]. Animal models suggest that acetylcholine loss produces a decrease of high-frequency EEG couplings and an increase of slow-frequency couplings [78]. Loss or a significant drop in EEG synchronization in faster rhythms also has been correlated with decreased MMSE scores in MCI and AD patients [69]. Linear and nonlinear EEG analysis improves classification accuracy of AD compared to unaffected controls, and these methods correlate with disease severity [69, 73, 74].

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 [76]. The length of the follow-up is of paramount importance and indicates the reason for a lack of findings over a 12-month period [77]. 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 [79]. Resting EEG alpha power is decreased from experimental damage to this cholinergic pathway [80]. Furthermore, the cholinergic basal forebrain has been found to be responsive to the treatment with cholinesterase inhibitors more for AD than other dementias [83]. Conversely, brainstem cholinergic innervations of the thalamus are relatively spared in AD patients [79]. Long-term (1 year) treatment of acetylcholinesterase inhibitors (AChEI) demonstrate less temporal and occipital alpha reduction for responders compared to non-responders and a combined effect on delta and low alpha [81, 82]. 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 [84].

5. RESTING STATE EEG RHYTHMS AND MILD COGNITIVE IMPAIRMENT

Assessing pre-clinical 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. Epidemiological and clinical follow-up 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 disease progression [85-87]. A recent study [88] 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 [88]. 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 [47, 67, 89-92]. 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 [40, 78, 93]. As a consequence, the increased excitability of thalamocortical connections would desynchronize the resting alpha rhythms and enhance the cortical excitability as seen in AD (see Section 4.5). Hence, changes of low-frequency alpha power in MCI and mild AD suggest a progressive impairment of the thalamo–cortical and cortico–cortical systems that govern visual attention. This hypothesis is consistent with clinical findings of increasing deficits of visuo-spatial abilities in MCI and mild AD [94]. Similarly, limbic sources imply a progressive impairment of thalamo–cortical and cortico–cortical systems regulating attention tone for memory functions.

Decreases in cortico–thalamic modulation and increase of slow EEG rhythms correlated to progressive cortical hypoperfusion have been found in AD [53, 95]. Abnormal delta and alpha sources in the posterior brain regions could therefore index the progressive decline of cognitive visuo-spatial functions across MCI and mild AD thereby supporting a transition between these conditions [85-87]. An intriguing aspect includes the peculiar magnitude increase of the parieto-occipital high-frequency (10.5–13 Hz) alpha sources in MCI compared to mild AD and normal elderly [88]. Furthermore, prospective studies have demonstrated that increased delta/theta activity, decreased alpha and beta, and slowed mean frequency may be predictors of progression from MCI to dementia [47, 67]. 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 follow-up of at-risk populations. A multicentric EEG study [96] exhibited the findings from a major EEG study of these factors in MCI subjects. The hypothesis that presence of ApoE ε4 affects sources of resting EEG rhythms in MCI and AD was assessed in 89 MCI with 34.8% ε4 incidence and 103 AD

with 50.4% ε4 incidence [96]. Alpha 1 and 2 sources in occipital, temporal, and limbic areas were of lower amplitude in subjects carrying the ApoE ε4 allele. For AD homozygous for ApoE ε4 allele, abnormal temporo-parietal and occipitoparietal EEG or MEG rhythms were found [55, 69]. However, in addition to ApoE ε4 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 [97]. EEG measures were obtained from 84 MCI with 42% B haplotype and 65 AD with 40% B haplotype. Slow alpha (from parietal, occipital, 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 non-carriers 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 [98-100]. 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 [101]. 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 [102]. 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 ablt to to predict decline from MCI to AD at long term for with an overall predictive accuracy of about 90% [103]. 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 [47, 63, 67, 104-109]. These findings are encouraging for future development of this prognostic and perhaps diagnostic approach [110].

Rossini *et al*. (2006) [111] 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 follow-up. 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 follow-up, 45 subjects were classified as stable MCI (MCI Stable), whereas the remaining 24 had converted to AD (MCI Converted). Results showed that at baseline, fronto-parietal midline coherence as well as delta (temporal), theta (parietal, occipital and temporal), and low-frequency alpha (central, parietal, occipital, temporal, 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 review 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 article 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, 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. The results would be welcome for prognosis and providing an objective evaluation of innovative pharmacological and cognitive rehabilitation treatments for dementing illness.

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