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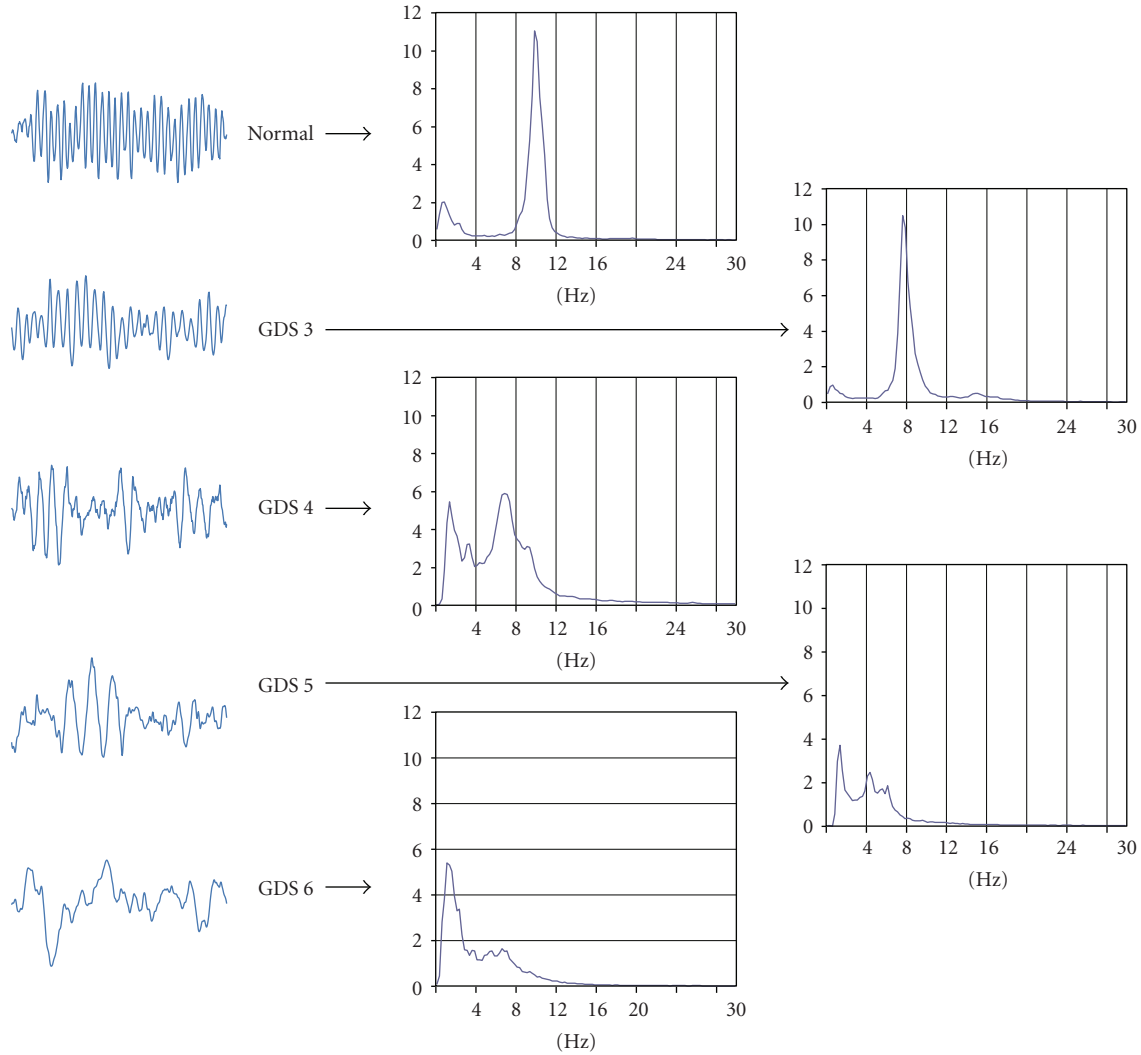
FIGURE 1: Sample of visual EEG and EEG spectrum on 4 clinical classes of severity (Global Deterioration Scale: GDS, from 3 to 6; for more details see text). EEG frequency bands (X-axis) and percent value of each band (Y-axis) are shown.

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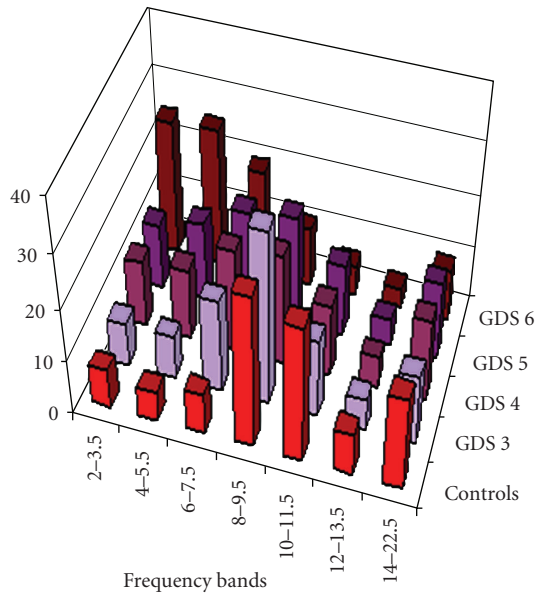
Figure 2: Histogram showing the relationship between 7 EEG frequency bands (2–3.5; 4–5.5; 6–7.5; 8–9.5; 10–11.5; 12–13.5;14–22.5 Hz) and disease's severity (normal controls and 4 clinical classes of severity; GDS 3 to 6).

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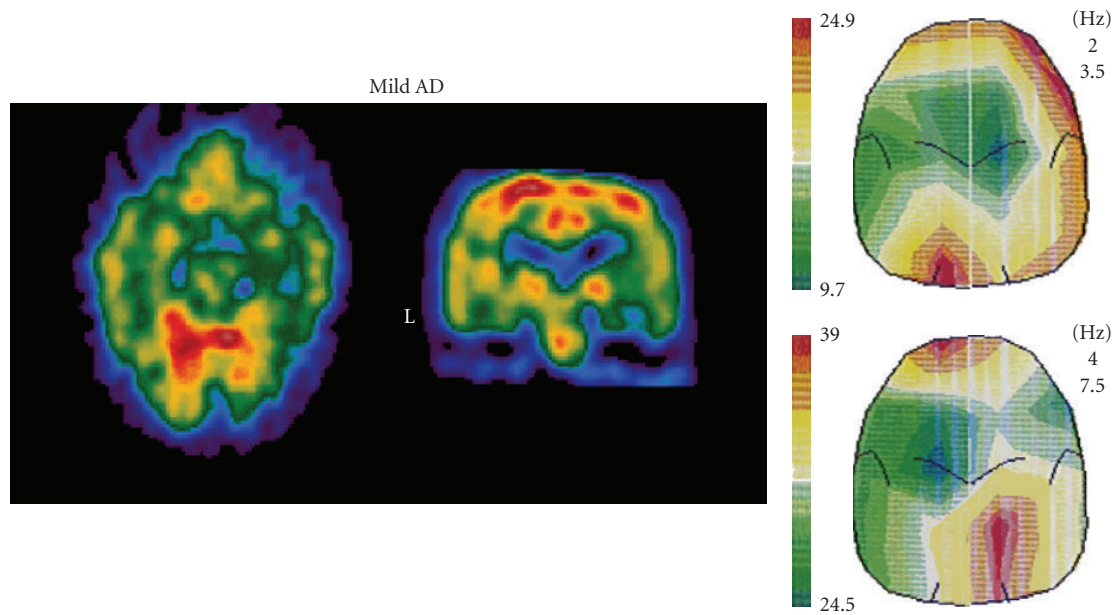
FIGURE 3: Sample of SPECT neuroimaging (Tc-99 HMPAO) and EEG brain mapping in a mild AD patient. Topographic scalp distribution of the EEG power on the 2.0 to 3.5 Hz frequency band (top right) and 4.0 to 7.5 Hz frequency band (bottom right) is shown. For more details, see text.

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.
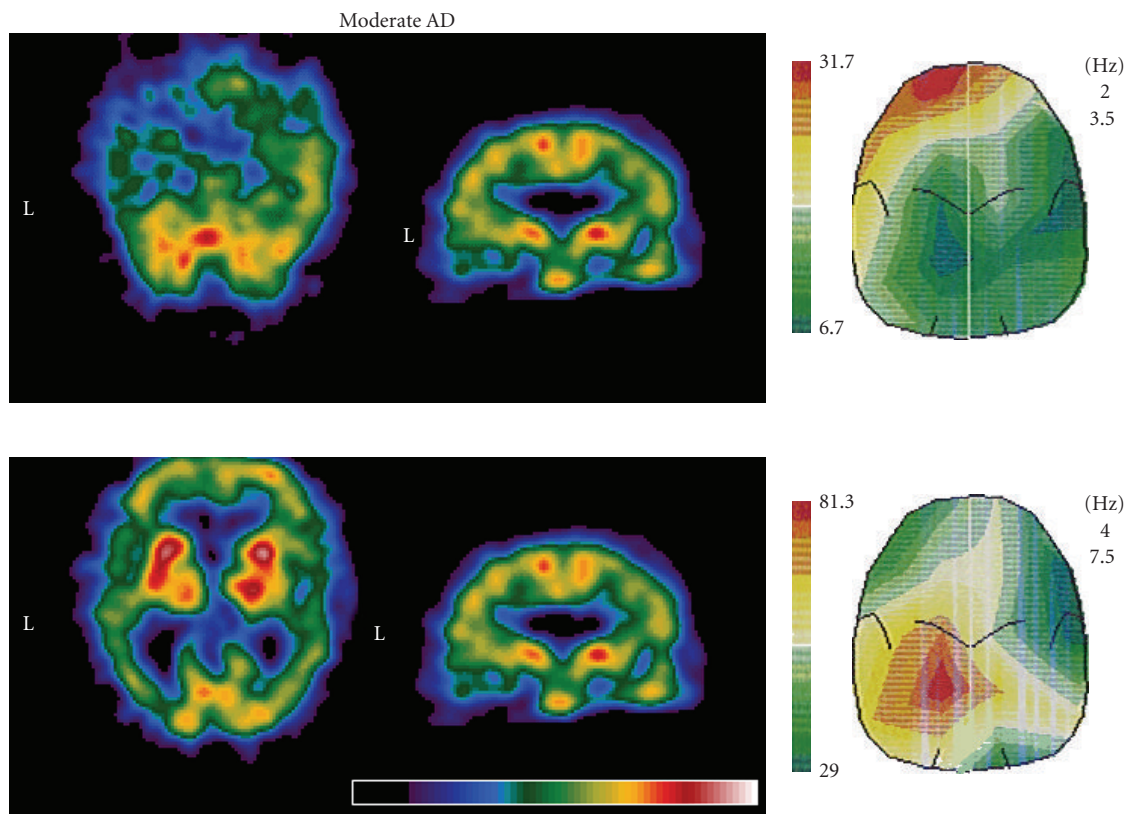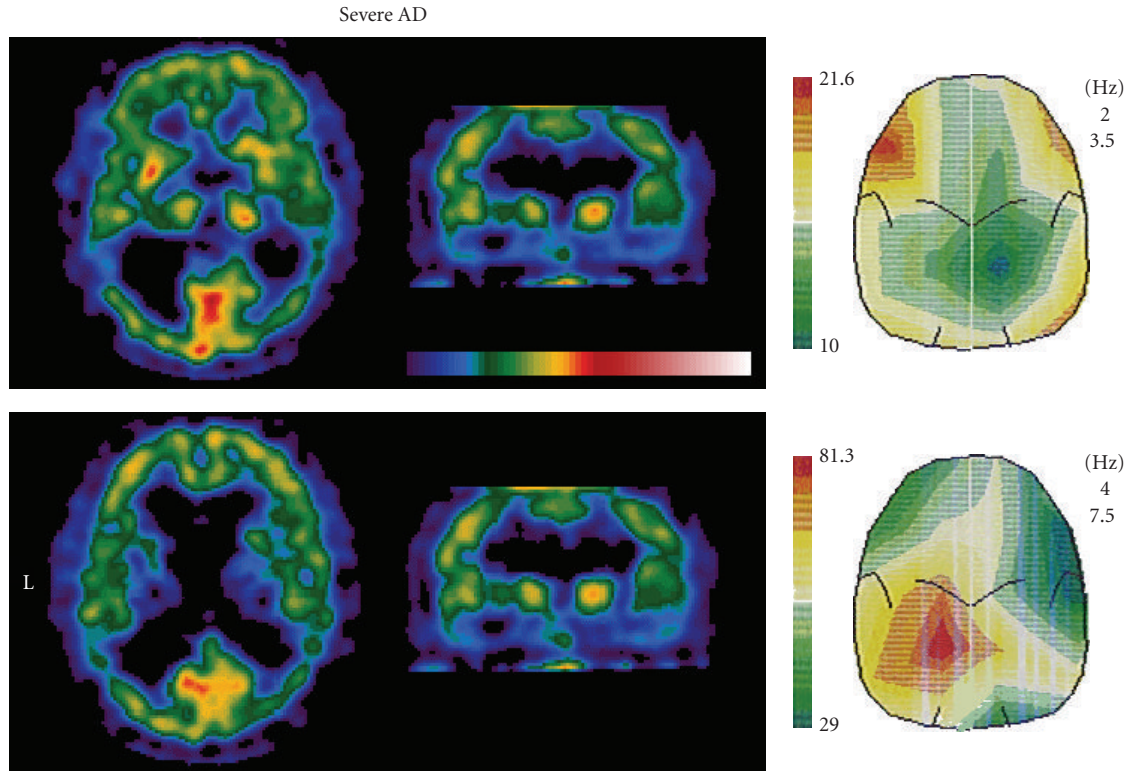
Severe AD

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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