REVIEW

Neurophysiological Markers of Alzheimer's Disease: Quantitative EEG Approach

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ABSTRACT

Currently established and employed biomarkers of Alzheimer's disease (AD) predominantly mirror AD-associated molecular and structural brain changes. While they are necessary for identifying disease-specific neuropathology, they lack a clear and robust relationship with the clinical presentation of dementia; they can be altered in healthy individuals, while they often inadequately mirror the degree of cognitive and functional deficits in affected subjects. There is growing evidence that synaptic loss and dysfunction are early events during the trajectory of AD pathogenesis that best correlate with the clinical symptoms, suggesting measures of brain functional deficits as candidate early markers of AD. Resting-state electroencephalography (EEG) is a widely available and noninvasive diagnostic method that provides direct insight into brain synaptic activity in real time. Quantitative EEG (qEEG) analysis additionally provides information on physiologically meaningful frequency components, dynamic alterations and topography of EEG signal generators, i.e. neuronal signaling. Numerous studies have shown that qEEG measures can detect disruptions in activity, topographical distribution and synchronization of neuronal (synaptic) activity such as generalized EEG slowing, reduced global synchronization and anteriorization of neuronal generators of fast-frequency resting-state EEG activity in patients along the AD continuum. Moreover, qEEG measures appear to correlate well with surrogate markers of AD neuropathology and discriminate between different types of dementia, making them promising low-cost and noninvasive markers of AD. Future large-scale longitudinal clinical studies are needed to elucidate the diagnostic and prognostic potential of qEEG measures as early functional markers of AD on an individual subject level.

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Key Summary Points

Quantitative EEG (qEEG) is a noninvasive method that mirrors synaptic (dys)function in real time.

Generalized EEG slowing, decreased EEG synchronization and frontal shift of neuronal generators of fast frequencies have been repeatedly reported across the clinical continuum of Alzheimer's disease (AD).

qEEG measures correlate with molecular and imaging AD biomarkers and discriminate between different types of dementia.

qEEG measures are potential early and noninvasive markers of synaptic dysfunction in AD patients.

Future large-scale longitudinal studies are needed to confirm diagnostic and prognostic potential of qEEG measures on an individual level.

INTRODUCTION

For more than a decade, massive efforts and investments in dementia drug discovery platforms have failed to yield a successful result [1]. Alzheimer's dementia is the most common form of dementia, whose pathophysiological mechanisms, early diagnostic markers and drug candidates have been particularly extensively investigated. Despite discouraging results from clinical drug trials, the field has come to an important realization: conventional markers of Alzheimer's disease (AD) used as diagnostic markers and/or secondary outcome measures do not sufficiently mirror clinically relevant effects, i.e. changes in cognitive functions in AD patients [2]. Moreover, patients with the same extent of AD neuropathological alterations in the brain, such as brain atrophy and/or amyloid accumulation, have been shown to exhibit

different levels of cognitive impairment, and vice versa. This notion, known as brain and cognitive reserve, is explained by the individual differences in resilience to AD-related neuropathology [3]. Together, these findings have motivated the pursuit of novel biomarkers that would help bridge the gap between the clinical symptomatology, disease pathology and individual vulnerability to the biological substrates of the disease. The gradual clinical manifestation of AD, from subjective (preclinical) through mild (early clinical) cognitive impairment (subjective cognitive decline [SCD] and mild cognitive impairment [MCI], respectively [4, 5]), has also driven the search for biomarkers towards the early stages of this insidious disease.

This review paper discusses the potential for quantitative electroencephalography (qEEG) to serve as an early and noninvasive marker of synaptic dysfunction in patients along the AD continuum.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

SYNAPTIC DYSFUNCTION IN ALZHEIMER'S DISEASE

Conventional markers of AD reflect amyloid and tau pathology, as the core neuropathological elements of the disease [6]. The histological features of abnormal accumulation of these two proteins, amyloid plaques and neurofibrillary tangles, have been first observed and described at the same time as the clinical symptoms of the disease itself [7]. However, the field has recently shifted its focus towards methods and markers that might reveal AD-associated disturbances in brain function rather than simply in structure. This was motivated by numerous studies that have shown that synaptic dysfunction and loss such as decreased synaptic density in neocortex and limbic regions, seem to be an early event in AD, present already in the pre-dementia (MCI) stage of the disease [8–11]. Moreover, assembly of amyloid β protein (Aβ) into oligomers, presumably the most toxic amyloid species in the brain, during the AD pathophysiological

process has been shown to disrupt synaptic function and structure, deplete synaptic number and consequently impair memory [12, 13]. In addition to the direct deleterious effect on synapses, recent findings provide evidence that Aβ oligomers have the potential to indirectly impair synaptic and neuronal activity by inducing AD-associated tau pathology, neuritic degeneration and neuroinflammation [12, 14–16]. Altogether, synaptic loss, being more extensive than neuronal loss when analyzed in the same brain regions, has been shown to be the best neuropathological correlate of cognitive impairment in patients along the AD continuum [8, 11, 17, 18].

SYNAPTIC MARKERS: EEG TAKES SPOTLIGHT

EEG reflects the real-time functioning of brain synapses. EEG oscillatory signals, recorded at the level of the scalp, mainly result from the summated excitatory and inhibitory postsynaptic potentials generated by the patches of pyramidal neurons in the brain gray matter. Pyramidal cells are spatially aligned and perpendicular to the cortical surface, which allows them to generate current flow that can be recorded by EEG as scalp potentials [19]. Eyes-closed resting-state EEG recordings are performed as standard procedure in the clinical setting. In addition to EEG, diagnostic methods such as functional magnetic resonance imaging (fMRI), fluorodeoxyglucose PET imaging (FDG-PET) or magnetoencephalography (MEG) are available for assessment of brain synaptic function. Functional MRI and FDG-PET are valuable research and clinical imaging methods, but have limited time resolution and resemble metabolic signals, i.e. indirect neuronal signaling only [19]. MEG shares many similarities with EEG; it measures the magnetic field perpendicular to the direction of the electrical current generated by neurons, but is currently used mainly in research settings [20]. Transcranial magnetic stimulation (TMS) has recently emerged as a noninvasive neurophysiological tool with the potential to detect disturbances in

long-term potentiation (LTP)-like cortical plasticity, and hence synaptic activity in AD patients [21]. However, TMS as a diagnostic tool has yet to be validated in the context of research and clinical dementia assessment. At the same time, increasing attention has been dedicated to the development of in vivo synaptic imaging methods, such as synaptic vesicle protein 2A (SV2A) PET imaging, which would provide invaluable spatial information on synaptic density and degeneration [22]. Even though decreased levels of SV2A in the brain tissue have already been described in AD patients [23], the exact function of the protein, its role in the disease and the properties of several available radioligands have yet to be elucidated [22].

Routine resting-state EEG recordings in the clinical setting are generally subjected to visual assessment and analysis, which is crucial for the investigation of certain neurophysiological phenomena. However, objective and reproducible investigation of complex EEG signals requires quantitative or computerized EEG analysis. qEGG analysis provides multi-perspective information on the EEG signal such as its frequency components (spectral analysis), dynamic alterations (time analysis) and spatial estimates of cortical sources (space domain analysis) (Fig. 1 and Table 1) [19]. In addition, qEEG provides reliable and quantifiable (numerical) results that can be further utilized in associative and correlative studies [24].

SPECTRAL EEG CHANGES ALONG THE AD CONTINUUM: FREQUENCY DOMAIN ANALYSIS

The most commonly used qEEG method is frequency domain analysis (Table 1), performed by fast Fourier transform (FFT) spectral analysis (Fig. 1). FFT-based spectral analysis quantifies the amplitude and power of the EEG oscillations averaged throughout a predefined recording period in various frequency bands. The genesis of the characteristic cortical rhythms, divided into conventional slow- and fast-frequency activity, has long been discussed, with thalamocortical circuits and cortex itself as the main
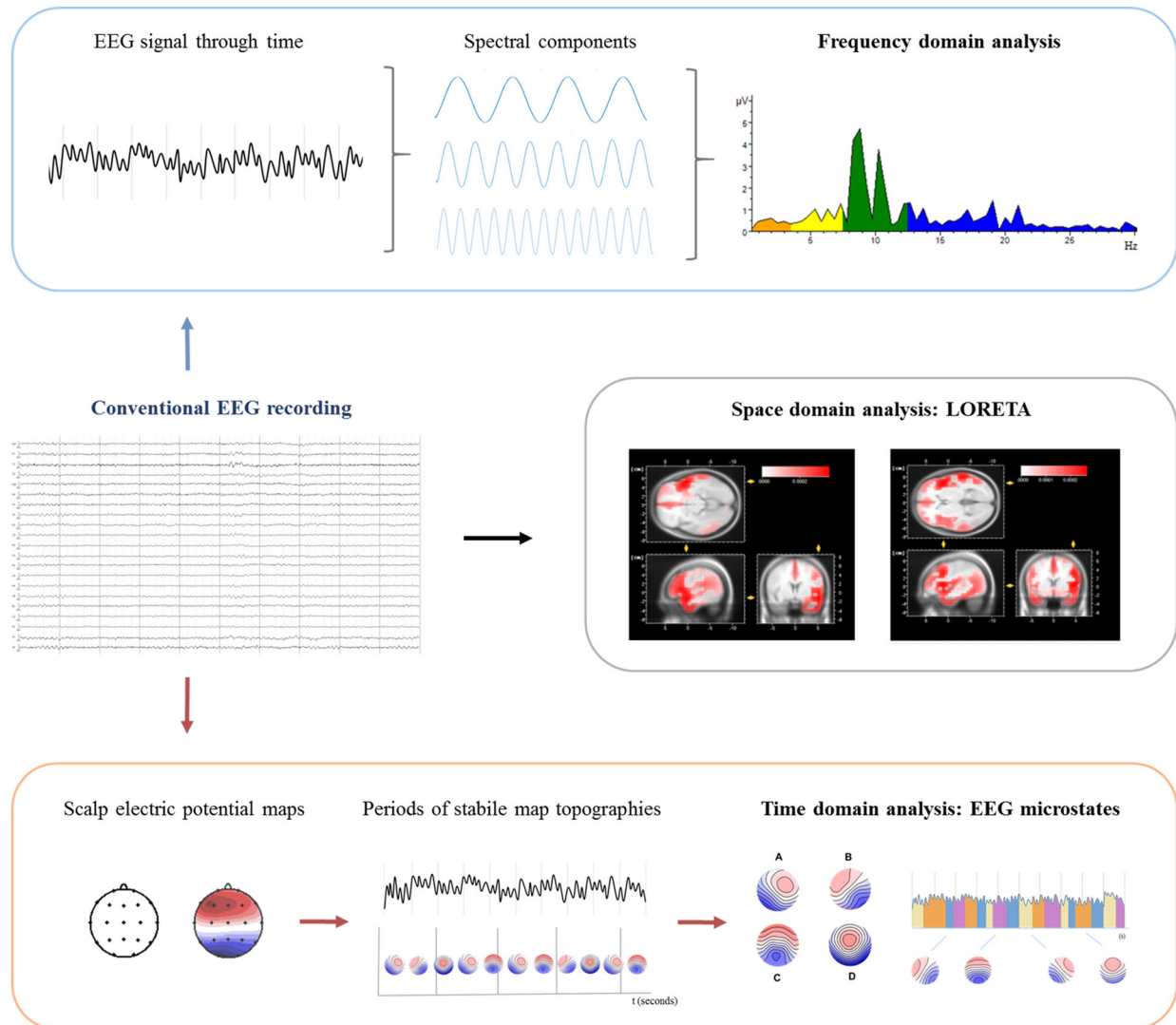
Fig. 1 Quantitative EEG analysis in frequency (FFT spectral analysis; blue square), time (EEG microstate analysis; orange square) and space domains (LORETA = low-resolution brain electromagnetic tomography analysis; gray square)

generators of this phenomenon [82]. Numerous qEEG studies have reported an increase in slow-frequency bands (delta and theta) and a decrease in fast-frequency (alpha and beta) amplitude and power, referred to as generalized EEG slowing in patients along the clinical AD continuum [26, 27, 29, 32, 49–51, 61]. These findings have been shown to correlate with and be predictive of neuropsychological performance, memory, attention, verbal deficits, frontal lobe function and ability to carry out everyday activities in cognitively impaired individuals [28, 29, 33, 36, 51]. Moreover, these changes seem to develop gradually, that is as an early increase in theta and decrease in beta, followed by a decrease in alpha and late increase in delta power, present in more severe stages of AD [25, 83]. A referenced temporal pattern of qEEG changes was substantiated by a prospective qEEG study that demonstrated a decrease in alpha and increase in delta power in AD patients at the 1-year follow-up compared with baseline [26]. In addition, Jelic et al. and Luckhaus et al. reported that combined alpha and theta power are the best predictors of future cognitive decline in MCI subjects [38, 47].

Table 1 Overview of qEEG studies in the context of dementia research including qEEG analyses in frequency, time and space domains

QEEG method	Parameters/classifiers	Study population (n = range)	References
Frequency domain analysis	Power spectral analysis	SCD (n = 20–210)	Coben et al. [25]
	Absolute and relative power and amplitude	MCI (n = 12–230)	Soininen et al. [26]
	Global field power (GFP)	AD (n = 14–320)	Prichep et al. [27]
	Global field synchronization (GFS)	FTD (n = 13–19)	Pozzi et al. [28]
	Coherence	Mixed (AD–VD) (n = 24)	Jelic et al. [29]
	Synchronization likelihood (SL)	DLB/PDD (n = 15–66)	Yener et al. [30]
	Phase lag index (PLI)		Chiaramonti et al. [31]
			Jelic et al. [32]
			Claus et al. [33]
			Jelic et al. [34]
			Rodriguez et al. [35]
			Nobili et al. [36]
			Huang et al. [37]
			Jelic et al. [38]
			Lehtovirta et al. [39]
			Adler et al. [40]
			Lindau et al. [41]
			Stam et al. [42]
			Mattia et al. [43]
			Koenig et al. [44]
			Park et al. [45]
			Schreiter Gasser et al. [46]
			Luckhaus et al. [47]
			Ommundsen et al. [48]
			Fonseca et al. [49]
			Anghinah et al. [50]
			Kim et al. [51]
			De Waal et al. [52]
			Ma et al. [53]
			Engels et al. [54]
			Engedal et al. [55]
			Dauwan et al. [56]
			Ferreira et al. [57]
			Gouw et al. [58]
			Smailovic et al. [59]
			Schjønning Nielsen et al. [60]
			Musaeus et al. [61]

Table 1 continued

QEEG method	Parameters/classifiers	Study population (*n* = range)	References
Time domain analysis	EEG microstates (topography and parameters)	SCD (*n* = 31)	Ihl et al. [62]
		MCI (*n* = 38)	Dierks et al. [63]
		AD (*n* = 8–64)	Strik et al. [64]
		FTD (*n* = 18)	Stevens and Kircher [65]
		SD (*n* = 8)	Nishida et al. [66]
		DLB (*n* = 42)	Grieder et al. [67]
			Schumacher et al. [68]
Space domain analysis	Dipole source localization	SMI (*n* = 1–53)	Dierks et al. [69]
	LORETA	MCI (*n* = 12–155)	Chiaramonti et al. [31]
		AD (*n* = 21–193)	Huang et al. [37]
		FTD (*n* = 19–39)	Dierks et al. [70]
			Babiloni et al. [71]
			Babiloni et al. [72]
			Gianotti et al. [73]
			Babiloni et al. [74]
			Babiloni et al. [75]
			Nishida et al. [76]
			Caso et al. [77]
			Kim et al. [51]
			Canuet et al. [78]
			Hatz et al. [79]
			Babiloni et al. [80]
			Lizio et al. [81]

AD Alzheimer's disease, *DLB* dementia with Lewy bodies, *FTD* frontotemporal dementia, *LORETA* low-resolution brain electromagnetic tomography, *MCI* mild cognitive impairment, *PDD* Parkinson's disease dementia, *SD* semantic dementia, *SCD* subjective cognitive decline, *SMI* subjective memory impairment, *VD* vascular dementia

In contrast to conventional FFT power spectral analysis, recent studies have investigated the single qEEG measure of global field power (GFP). GFP corresponds to the sum of all squared potential differences of all electrodes on the scalp, and therefore represents single and global measures of scalp potential field strength, i.e. generalized EEG amplitude [19]. Huang et al. reported increased delta and theta GFP and decreased alpha GFP in AD patients compared with healthy controls, and decreased alpha and beta GFP in AD compared with MCI patients. In addition, they demonstrated decreased GFP alpha in progressive MCI compared with stable MCI patients [37]. Significant differences in GFP delta, theta and alpha frequency bands have been confirmed in over 600 memory clinic patients diagnosed with SCD, MCI and AD [59], indicating the reproducibility and comparability of reference-independent and simplified measures of EEG power to the conventional multichannel FFT-spectral analysis.

The widespread AD neuropathology, neuronal and synaptic loss, and consequent

impairment in multiple cognitive domains have motivated the investigation of disturbances in the synchronization of large-scale neural circuits in patients along the AD continuum. EEG coherence has been introduced as a measure of altered brain connectivity and neurophysiological organization [84, 85], since it measures the phase consistency between two signals (at two different channels) in each frequency band [19, 85]. Studies on EEG coherence have shown that AD patients have decreased coherence in all frequency bands, with the most prominent finding being decreased coherence in the alpha band [29, 32, 40, 49, 50]. However, the measure of coherence is calculated between the channel pairs only and is contaminated by a volume conduction effect, which implies overall spreading of electrical currents through the biological tissue and can therefore overestimate interdependence between channels [19, 85]. Stam et al. introduced another measure of dynamic interdependence between the two channels (or a set of channels), referred to as synchronization likelihood (SL) [86], which has been shown to correlate with global cognitive status and to decrease across all frequency bands in cognitively impaired patients (MCI and AD) compared with healthy controls [42, 87–89].

The phase lag index (PLI) has been proposed as a new measure of EEG synchrony that overcomes the problem of volume conduction effect [90]. AD patients have been shown to have reduced PLI in alpha and beta bands [54, 90] which correlate with disease severity [54]. However, PLI as such reflects synchronization between pairs of signals and is blind to the true instantaneous interactions that might constitute a substantial amount of connectivity between brain regions. Koenig et al. introduced a method that reduces multichannel EEG analysis to the single global measure of brain functional connectivity across frequency bands. Global field synchronization (GFS) is therefore a reference-free method that measures the instantaneous phase-locked neural activity across the whole scalp, oblivious to differences in activity of a single or several sources oscillating at the same time, as it includes all electrodes simultaneously and makes no assumption about the location of the sources of brain activity [91]. Decreased GFS in fast frequencies (alpha and beta) with the more severe stage of cognitive impairment has been reported in three large databases comprising healthy controls and memory clinic patients [44, 59]. Moreover, Park et al. and Ma et al. highlighted that GFS alterations correlate with cognitive status in AD patients, assessed by the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating (CDR) Scale [45, 53].

Widespread disturbances in neural signaling in patients with preclinical and clinical AD have been confirmed with multiple qEEG measures of brain functional connectivity, suggesting qEEG as a valuable method for investigation of AD as a "global disconnection syndrome" [44, 92].

BRAIN NETWORK DYNAMICS IN AD: TIME DOMAIN ANALYSIS

Resting-state qEEG frequency domain analysis revealed AD-associated disturbances in brain synchronous activity in physiologically meaningful frequency ranges. However, when it comes to the investigation of neurocognitive networks, another aspect of interest involves the investigation of their intrinsic dynamic properties that might disintegrate in patients with impaired higher cortical functions, such as in patients along the AD continuum. Temporal organization of neuronal networks can be analyzed by investigating the momentary brain states with a high temporal resolution, in the millisecond range, allowed by EEG [19]. This led to the discovery of EEG microstates—periods of stable topographies of electric fields that are thought to reflect all momentary active neural networks [93]. These topographies of electric fields represent 2-D scalp maps of EEG electric potential values recorded at all electrode sites at a given moment in time. Spontaneous resting-state EEG recording can therefore be presented as a time series of alternating momentary brain states, i.e. functional microstates (Fig. 1). Microstates have several remarkable properties: their duration is compatible with the resolution of human information processing (60–120 ms),

they transition sharply from one to another topographical configuration, and only a limited number of microstate topographies can explain a great part of the variance in the resting-state EEG data across different subjects [93–95]. Most of the resting-state EEG microstate studies report four reproducible and analogous clusters of microstate topographies, referred to as maps A, B, C and D [94].

Several studies have reported changes in microstate dynamics and/or topographies in patients with dementia. Ihl et al. showed that AD patients have longer microstate duration than healthy controls [62]. On the other hand, three independent studies reported decreased EEG microstate duration, two of which showed anteriorization of the electric fields and correlation of microstate alterations with cognitive performance in AD patients [63–65]. However, a study that distinguished four conventional microstate maps by employing more advanced spatial cluster analysis revealed an increase in the duration of asymmetrical microstate maps (A and B) and a decrease in the duration of symmetrical maps (C and D) in patients with the more severe stage of cognitive impairment [96]. Conversely, Nishida et al. and Grieder et al. reported no changes in microstate dynamics or topographies; however, they included patients with other types of dementia and only a small number of patients with AD [66, 67]. More recently, Schumacher et al. showed that microstate topographies are indeed altered in AD patients for all microstate classes compared with controls and patients with Lewy body dementia [68].

Studies employing different functional imaging modalities have already reported disturbances of large-scale brain networks during rest in cognitively impaired patients [97]. Investigation of EEG microstate topographies and dynamics might therefore be a valuable tool for detecting fine disarrangements in activation and organization of large-scale resting-state networks in AD patients [93, 94]. Even though microstate analysis lacks straightforward topographical interpretation, its distinct temporal organization and across-subject reproducible topographical representation makes it a plausible marker candidate for future validation studies of brain functional impairment.

MAPPING BRAIN (DYS)FUNCTION USING QEEG: SPACE DOMAIN ANALYSIS

Some of the first attempts to directly assess topographical correlates of EEG-recorded brain activity included the dipole source localization method. It involved "fitting" of a single dipole in the three-dimensional (3-D) coordinating system that depicts the corresponding center of gravity and strength of the intracerebral activity [98]. Using the referenced technique, several studies have shown more anteriorly located centers of gravity of alpha and beta activity in AD patients compared with healthy controls and MCI subjects. The general anteriorization of fast-frequency activity was hypothesized to be associated with the early and more severe neuropathology in the posterior brain areas in patients along the AD continuum. In addition, the degree of shift was reported to be sensitive to disease activity and progression, as it correlated with the severity of cognitive impairment and was predictive of the development of AD in MCI patients [31, 37, 69]. Dipole source localization is a simple and user-friendly estimator of the electric gravity center, but does not portray a realistic location of the EEG generators, for two reasons: it calculates a single locus of activity, while the exact number of dipoles to be optimally fitted remains unknown [19].

Mapping the electrical generators in the brain that give rise to the electric field topographies at the level of the scalp is enabled by mathematical calculations of the EEG inverse solution. Low-resolution electromagnetic tomography (LORETA) is a functional neuroimaging method that estimates cortical sources of brain electrical activity in a 3-D human head model (Fig. 1) [99]. Decreased activity in parieto-occipital alpha sources and widespread increases in activity in delta and theta bands have been repeatedly reported in AD patients compared with healthy controls [51, 72, 73, 78, 80, 89]. Babiloni et al. showed that some of the referred disturbances in

cortical EEG rhythms occur already in subjects with memory complaints (SMC) and MCI patients, supporting the hypothesis of brain functional disturbances already in the pre-dementia stages of the disease [74]. In addition, introduced studies have shown that cortical sources of delta, theta and alpha activity correlate with neuropsychological test scores and are sensitive to disease progression, suggesting clinical implication for EEG-based imaging techniques in cognitively impaired individuals [51, 72, 73, 75, 80]. The LORETA method can also be utilized for regional assessment of brain functional connectivity. Canuet et al. reported decreased lagged phase synchronization between the medial frontal/parietal region and the left temporal and bilateral inferior parietal cortex in the alpha 2 frequency band and the most prominent increase in synchronization of low-frequency activity of the temporal lobe in 125 AD patients [78]. EEG neuroimaging methods can therefore be used for topographical investigation of resting-state disruptions of cortical activity and functional connectivity in AD patients.

BIOLOGICAL VALIDITY OF QEEG MEASURES: WHAT DOES QEEG ADD?

Studies employing multi-perspective qEEG analyses have demonstrated an association between qEEG measures and the cognitive status, disease activity and progression in subjects along the AD continuum; however, biological and clinical validation of the referred markers requires further investigation of their relationship to disease-specific neuropathology.

Conventional cerebrospinal fluid (CSF) markers of AD include decreased Aβ42 and increased total tau (t-tau) and phosphorylated tau (p-tau) protein levels as a result of amyloid and tau accumulation and pathology in the brain of AD patients [100]. The referred biomarker pattern has demonstrated good sensitivity, specificity and predictive value for future cognitive deterioration [101]. Jelic et al. showed that CSF tau levels correlate with the ratio of alpha and delta global power in AD patients.

Interestingly, this revealed a negative correlation between EEG slowing and CSF tau levels; however, the study involved a rather small population and only 14 AD patients [34]. A retrospective study including over 600 memory clinic patients diagnosed with SCD, MCI and AD reported a significant negative correlation between CSF Aβ42 levels and global power in slow and CSF p- and t-tau levels and global power in fast frequencies [59]. It suggested the pattern of AD-related changes in qEEG parameters: amyloid pathology might mediate slow-frequency disturbances through cholinergic dysfunction, while tau pathology resembles neuronal loss and degeneration that might particularly affect fast frequencies, presumably generated and propagated in the cortex itself. On the other hand, CSF biomarkers were associated with decreased global synchronization in fast frequencies only [59], which has already been shown to correlate with the degree of cognitive decline [45, 53, 102]. This notion was substantiated in a study by Babiloni et al., who demonstrated a correlation of the level of hippocampal and occipital gray matter volume and density with cortical alpha activity, estimated by LORETA imaging, in MCI and AD patients [103–105]. Conversely, Mattia et al. reported a lack of association between EEG power spectra and index of brain atrophy in a small-scale study, although they did not employ source imaging techniques. Yet the same study demonstrated a correlation between alpha and theta power and total level of brain hypoperfusion assessed by perfusion MRI, indicating a relationship between neurophysiological and hemodynamic changes in AD patients [43].

The topography of abnormal synaptic activity can be further assessed using FDG-PET to analyze brain glucose metabolism [106]. Many studies have shown that decreased glucose metabolism in temporoparietal regions is an early and consistent finding in AD and cognitively deteriorating MCI patients [107–110]. When it comes to the correlative FDG-PET–EEG studies, both Dierks et al. and Babiloni et al. reported an association between topographical estimates of EEG generators and patterns of brain glucose metabolism, employing dipole

and LORETA source localization techniques [70, 111].

The effect of the apolipoprotein ε4 (apoE ε4) genotype, a risk factor for the disease [112], on neurophysiological disturbances in AD patients is still open to discussion. Jelic. et al. reported an association between apoE ε4 and reduced alpha coherence in AD patients [32], while Lehtovirta et al. described more pronounced slow EEG activity in apoE ε4 carriers [39]. Conversely, a more recent large-scale study demonstrated that AD apoE ε4 noncarriers exhibited more severe EEG slowing than apoE ε4 carriers [52]. Topographical EEG analysis in a study by Canuet et al. reported an association between the apoE ε4 allele and decreased alpha activity in the left inferior parietal and temporo-occipital cortex and reduced alpha connectivity in the frontal and temporoparietal regions in AD patients [78]. While the relationship between apoE ε4 and the molecular neuropathology in AD patients has been thoroughly described [113–115], an unambiguous association with the disturbances in brain function remains to be demonstrated in future studies.

qEEG markers in the frequency and space domains have been shown to correlate with AD-associated molecular and neuroimaging markers; however, most of the latter will fail to reach pathological thresholds in the early, pre-dementia stages of the disease. Moreover, subjects in preclinical and early clinical stages of the disease show discordance between the severity of clinical symptoms and conventional biomarker abnormalities, in addition to considerable biological and clinical heterogeneity. This can be explained, at least in part, by the different levels of cognitive reserve in these patient groups and a lack of diagnostic markers that would directly indicate disturbances in brain function. Several studies have already shown that qEEG complements and improves the currently established diagnostic workup of patients along the AD continuum [57, 116, 117]. qEEG may therefore be a valuable add-on in dementia assessment, as an early marker of brain synaptic (functional) disturbances due to the AD molecular neuropathology.

QEEG IN DIFFERENTIAL DIAGNOSIS OF DEMENTIA

There is growing evidence that a considerable number of cognitively impaired patients with clinical presentation of AD have pathologically mixed or other types of dementia [118–121], some of them being just recently described [122]. Therefore, candidate markers of AD would ideally reflect both the clinical stage of the disease and the underlying disease-specific brain pathology.

It has been long known that EEG signals exhibit high interindividual variability [123], thus emphasizing the need for quantitative analyses that might provide a more objective approach to neurophysiological phenotyping. In addition, measures of EEG variability as a function of brain (dis)organization and inflexibility have appeared as a novel subject of interest [124–126]. Lehmann et al. reported that a set of qEEG features, including EEG measures of amplitude, power and synchronization, have overall sensitivity of up to 85% and 89% and specificity of 78% and 88% in differentiating mild and moderate AD, respectively, from healthy controls [127]. Many EEG studies have shown a plausible classification rate of qEEG measures in discriminating both MCI and AD patients from healthy controls [40, 55, 57, 81, 128].

When it comes to the neurophysiological potential to distinguish AD from other types of dementia, Lindau et al. demonstrated that patients with frontotemporal dementia (FTD) have a more severe decrease in fast-frequency and lack of increase in slow-frequency power compared with AD patients [41, 129]. In addition, FTD patients exhibit decreased global field synchronization in all frequency bands relative to both healthy controls and AD patients, suggesting GFS as a valuable differential diagnostic tool [129]. An EEG source localization study further unveiled the topographical pattern of observed changes: decreased alpha 1 activity in the orbitofrontal and temporal lobes in FTD patients versus controls, a widespread increase in delta activity in AD patients versus controls, and a more pronounced decrease in beta 1

activity in the parietal lobe and sensorimotor area in AD versus FTD patients [76]. EEG analysis in the time domain additionally revealed shorter microstate duration of asymmetric class C in FTD patients, indicating the sensitivity of microstate parameters to frontal lobe dysfunction [66].

In contrast, patients diagnosed with mixed dementia, i.e. vascular and Alzheimer's dementia, seem to exhibit a more pronounced increase in slow-frequency power and a lack of decrease in fast-frequency power compared with AD patients [46], indicating an opposite qEEG power spectral pattern to that observed in FTD patients. This notion was substantiated by the multicenter EEG LORETA study by Babiloni et al. that showed a distributed increase in theta activity in vascular dementia relative to healthy controls and AD patients [130].

One of the most common forms of dementia, following Alzheimer's disease, is dementia with Lewy bodies (DLB) [131]. Prominent EEG slowing in the posterior regions, more severe than that observed in patients along the AD continuum, is one of the main EEG findings in patients with DLB [132–134]. These EEG changes occur early during the disease course and correlate well with the clinically evident cognitive fluctuations [135]. In addition, disturbances in resting-state network connectivity and brain network dynamics, evidenced by EEG microstate and functional connectivity studies, have been repeatedly reported in DLB patients [68, 132, 136]. According to the latest DLB Consortium consensus report, EEG should be included as a supportive DLB diagnostic biomarker [135], as EEG features seem to exhibit particularly high potential in differentiating DLB from AD and other types of dementia [55–57, 126, 137].

Most of the studies that investigated the classification potential of qEEG methods in the context of dementia were based on group-level analyses. It is of interest for future validation studies to explore and validate qEEG as a diagnostic tool on the single-subject level, necessary for future clinical implementation.

CONCLUSIONS

There is an urgent need for novel functional biomarkers of AD for use in both clinical settings and drug trials. EEG is a noninvasive, low-cost and widely available diagnostic method that directly reflects synaptic activity, which is significantly affected early in the course of AD. In addition, applying objective and multi-perspective quantitative EEG analyses enables the investigation of physiologically meaningful frequency, time and space components of EEG signals. Since a number of prospective studies have reported promising diagnostic and prognostic potential for qEEG measures, there is a need to confirm a concordance of qEEG findings with the amyloid PET status and post-mortem disease-specific neuropathological changes in patients with preclinical and clinical AD. In addition, high between- and state-dependent within-subject variability in EEG signals suggests a combination, rather than just a single measure, of qEEG parameters as a plausible marker of AD dementia. Hence, future large-scale longitudinal studies that integrate analysis in different but complementary domains with novel and advanced topographical and temporal properties might help elucidate reliable and robust qEEG measures that could be utilized at the individual-level dementia assessment.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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