Electroencephalography and event-related potentials as biomarkers of mild cognitive impairment and mild Alzheimer’s disease

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Abstract

Background: Successful early detection of mild cognitive impairment (MCI) and Alzheimer’s disease demands the identification of biomarkers capable of distinguishing individuals with prodromal or early cognitive impairment from healthy aging adults. Many laboratories are engaged in the discovery and validation of a wide array of potential genetic, proteomic, cognitive, and other types of biomarkers.

Methods: This review focuses on the application of quantitative electroencephalography (qEEG) and event-related potential (ERP) technologies as markers of prodromal impairment and early disease progression. It is the aim of this review to critically assess where this field currently stands, as well as future directions for EEG biomarker development.

Results: As a neuroimaging tool that is relatively inexpensive, potentially portable, and capable of providing high-density spatial mapping, qEEG offers a noninvasive, rapid, and replicable method for assessing age-related and disease-related neurophysiologic change.

Conclusions: As different signature changes associated with particular stages of disease burden are identified and validated, we anticipate expanded application of qEEG as a reliable and sensitive biomarker(s) of MCI and early Alzheimer’s disease.

Keywords: Mild cognitive impairment; Alzheimer’s disease; EEG; ERP; Biomarker

1. Introduction

With a rapidly aging population in the United States and many other countries, the prevalence of cognitive impairment associated with aging continues to increase at a brisk pace [1]. Of the many causes for dementia in the elderly (e.g., vascular causes, tauopathologies, synucleinopathies), Alzheimer’s disease (AD) is most prevalent; in 2006 there were 26.6 million cases of AD worldwide. It is estimated that by 2050, the worldwide prevalence of individuals living with AD will be 1 in 85 persons or 106.8 million individuals [2]. Furthermore, the prevalence of AD doubles for each 5-year increase in age, such that 16.7% to 43% of the population, depending on geographic location, older than the age of 85 years meets criteria for AD [3].

Neural changes associated with AD include widespread neuronal cell loss and the development of neurofibrillary tangles and amyloid plaques in the hippocampus, entorhinal cortex, neocortex, and additional brain regions [4]. In addition, decreased cholinergic tone further intensifies the cognitive difficulties resulting from the neural damage [5]. Although amyloid plaques and neurofibrillary tangles are the most characteristic neural changes associated with AD, these symptoms have also been identified in nondemented individuals, suggesting that the neural changes associated with AD might develop before typical cognitive and behavioral changes are evident [6,7]. Although a conclusive diagnosis of AD is only obtained after postmortem autopsy, cognitive and behavioral changes (e.g., in episodic memory) are successfully used as proxy measures for assessing disease progression. For example, evidence of diminished episodic memory might be seen in nondemented individuals...
who ultimately convert to AD [8], and increasing impairments in executive functioning, attention, and praxis are also observed during the course of disease progression [9–11].

The potential to intervene with novel neuroprotective agents early in the course of the disease to protect quality of life is of great interest, because there is clearly a lengthy transitional state between healthy aging and AD. Individuals in this mild cognitive impairment (MCI) transitional state experience memory loss and other cognitive deficits similar to those seen in persons with AD; however, the severity of these deficits falls below the criteria necessary to meet National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD [12–16]. Individuals with MCI are at a substantially higher risk for conversion to AD; whereas annual AD conversion rates in typical aging populations ranges from 0.2% to 2.3% [15], and annual conversion rates for MCI range between 10% and 54% [14,17].

Concurrent with many exciting programs underway to discover neuroprotective therapies for MCI and early AD, there is heightened interest in developing reliable and sensitive biomarkers of early—and possibly prodromal—disease-related impairments. For example, the use of cognitive measures assessing episodic memory and working memory have been widely used, with mixed success, to identify individuals in the earliest stages of disease [18–25]. Other research efforts aimed at identifying quantifiable and objective markers of risk of very early disease progression and of treatment response have ranged broadly across technology platforms and approaches, with the common aims of improving early detection capabilities as well as accelerating drug discovery and development. Examples of such efforts include the discovery of novel cerebrospinal fluid proteins that are differentially expressed during the course of AD progression [26], the development of novel positron emission tomography ligands used to study neuropathologic correlates of disease progression [27], as well as the use of noninvasive home motor activity monitoring [28]. Certainly these are but a few examples of the expanding field of biomarker development and research [29–32].

Despite this recent flurry of research efforts, there remains a need to identify biomarker(s) with sufficiently high sensitivity and specificity for identifying early or prodromal AD in individual patients [33]. In fact, this special issue of Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association is being published in support of a symposium held December 2–4, 2007 in Las Vegas, Nevada to honor the life and seminal contributions of Dr Leon Thal. The focus of this symposium is on the identification of solutions for the variety of impediments to rapid drug discovery and development; with one major barrier being a need for sensitive biomarkers of early progression and treatment response. Most reviews of recent biomarker discovery efforts have focused on an array of genetic, proteomic, imaging, and cognitive performance–based approaches [34,35]. Comparative little attention has been paid to the application of quantitative electroencephalography (qEEG) and/or event-related potentials (ERPs) as useful clinical markers of early disease or progression, despite the fact that the literature on this topic extends back for nearly half a century. Nonetheless, during the past 10 years there has been an expansion in the exploration of qEEG and ERP biomarkers of AD, 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 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.

Compared with what was generally available even 5 years ago, the ability to collect electrophysiologic data simultaneously from up to 256 leads, to image such data topographically in 3-dimensions, and to perform source localization analyses, even for subcortical structures, is now far more affordable and less complicated to implement, allowing for the data processing for an individual patient to be completed in a matter of minutes. Consequently, qEEG and ERPs have gained renewed interest among those interested in discovering and developing novel therapies for several important reasons: (1) to establish central nervous system pharmacodynamic activity for novel compounds [36] and (2) to potentially yield noninvasive and relatively low-cost biomarkers for key diseases, including AD. As an example of the rapidly growing interest in this technology platform, Pfizer Inc just recently announced a Request for Proposals (RFP) to develop such qEEG markers in AD, attention deficit–hyperactivity disorder, and schizophrenia (www.pfizer.com/translationalmedicine). This review is intended to reevaluate the key findings culled from a literature on this topic that has been scattered across a disparate array of journals and fields of study (eg, electrical engineering, clinical neurophysiology, neuropsychology, psychiatry), with the goal of identifying promising candidate markers and future research and clinical directions.

1.1. Use of EEG as a biomarker for AD

The use of EEG as an early biomarker of cognitive impairment is not a novel idea, and yet until recently the technology itself failed to meet at least two of the three ideal characteristics for any new biomarker, as identified at a 1998 National Institute on Aging consensus conference on biomarker development. Specifically, the final communication from that conference noted that useful biomarkers would be relatively uncomplicated to use, simple in design and implementation, and inexpensive [37]. However, more recently, proponents of qEEG have touted these very characteristics as benefits, stating, “EEG may represent a cost-
effective, noninvasive brain imaging tool capable of identifying the earliest signs of brain dysfunction in subjects with evolving MCI or dementia” [38], and “In order to plan optimal therapeutic, organizational and rehabilitative interventions for MCI, a reliable prognostic indicator on the likelihood of progression to dementia would be required. Along this line electroencephalogram (EEG) would be an ideal candidate to this issue, since it is a widely diffused, non-invasive and low-cost procedure” [39]. In fact, a recent PubMed literature search for “Alzheimer’s and EEG” returned 829 articles published during the last 25 years on this topic. Despite this large number of publications on the topic, clinical researchers and practitioners remain uncertain how to apply this technology and which specific quantitative end points to rely on in daily practice. Research has spanned the spectrum from quantitative EEG methods, to ERP peaks, to coherence models. These varying approaches have, as expected, led to a fragmented literature, with multiple candidate qEEG markers having been nominated for wide use.

Unfortunately, a fragmented literature is not the only barrier that must be overcome before EEG might be widely used in the diagnosis and diagnosis of individuals with early cognitive impairment. Historically, obtaining a signal-to-noise ratio great enough to provide useful information has been a difficult task, a task that, when combined with labor-intensive signal processing, made the use of EEG in a clinical setting too time- and labor-intensive to be of practical value. However, recent years have seen the development of portable EEG systems and signal processing and filtering algorithms that have led to improved signal detection, while minimizing the time and effort required for data collection and analyses. These advances have in turn made qEEG more accessible and easier to use in clinical settings. With these welcome technological advances, it is now an opportune time to reevaluate the array of potential markers or end points that have been identified during the past 25 years. This article is intended as an initial step leading to a critical consideration of qEEG as a diagnostic and prognostic tool used in the assessment of individuals with cognitive impairment associated with MCI and early AD.

Reports describing the utility of EEG as a biomarker for MCI and/or AD have seen many advances during just the last 6 years, and hence this review will be limited to a consideration of literature published within the previous 6-year period. In addition, this review is further limited to studies applying qEEG while patients are awake and performing cognitive tasks. Although qEEG is routinely applied to collect electrophysiologic data during the resting state (eyes open or closed) and during sleep, this review will not focus on these behavioral states [40].

2. EEG markers of MCI

Multiple different qEEG components, as well as ERP activity, are altered during the transitional stage between healthy aging and AD. Specifically, low-frequency power spectra are particularly affected, namely both theta and delta power spectra are uniquely changed in individuals with MCI compared with healthy controls. Reduced delta power (1 ± 3.5 Hz) in MCI patients during resting EEG has been identified [41], with specific localization to the centrotemporal and posterior fields [42]. Furthermore, individuals with MCI showed a significant positive correlation between delta power and immediate memory recall [41]. Liddell et al [41] suggested that on the basis of these results, delta power might be associated with memory decline in MCI, and thus delta power might be used as a sensitive indicator of prodromal or early cognitive decline. In addition, theta differences (4 to 7 Hz) are also initially evident between healthy control participants and MCI patients [43], and increased theta activity is commensurate with impairment in MCI and AD [43,44].

Low-frequency waveform spectra are also differentially affected by MCI. Evidence of diminished alpha activity at the earliest AD stage (clinical dementia rating [CDR] = .5) is supported by research indicating that MCI patients show decreased alpha power (8 ± 11.5 Hz) when compared with elderly control participants without cognitive complaints [42]. Furthermore, a significantly smaller decrease in lower alpha band power (8 to 10.5 Hz) was identified in MCI patients, compared with healthy controls, during the completion of a picture memory task [45]. Reactivity in the lower alpha band is believed to be indicative of attentional processes; thus, an increase in lower alpha band power is suggestive of diminished memory performance, whereas decreased lower alpha band power is indicative of better performance. Therefore, the significantly smaller decrease in lower alpha band power in MCI patients reflects memory impairment that was also evident in behavioral measures [45].

Finally, the P600, an ERP measure of memory, particularly episodic memory encoding, is also impacted during the early stage of cognitive impairment. Because the P600 is a measure of episodic memory encoding, a specific cognitive ability that is diminished in individuals with MCI, it would be expected that the P600 peak would show differences in individuals with AD compared with healthy older adults. Such differences are evident in the decreased P600 response to word repetition in MCI patients [46] and patients in the early stages of AD [47]. In addition, there have been significant correlations between P600 repetition effect amplitude and multiple declarative verbal memory measures [47], which have also previously been reported in MCI patients [46].

Whereas the selection of EEG and ERP markers of early cognitive change is important in the identification of patients with MCI, it is also important to identify such end points that might predict which individuals will ultimately progress from MCI to AD. This would allow for the provision of novel therapeutic interventions targeted to those persons at greatest risk for conversion to AD.
3. EEG markers associated with the transition from MCI to AD

Overall, the sensitivity of qEEG in the detection of functional changes in mild AD ranges between 69% and 84% [48–50]. For example, Prichep et al [51] found that EEG theta power was increased in patients with MCI who converted to AD compared with patients with MCI who did not convert. Logistic regression identified an overall predictive accuracy of 90% when comparing baseline EEG and the likelihood of future decline. A related study further supports the role of EEG as a noninvasive tool used in the early identification of dementia by demonstrating the sensitivity of qEEG to the earliest subcortical and cortical changes, likely localized to the hippocampus, amygdala, parahippocampal gyrus, and parietotemporal cortex, associated with neural decline [38]. Furthermore, a separate study identified significantly stronger EEG sources for delta (temporal areas), theta (parietal, occipital, temporal areas), and alpha 1 (central, parietal, occipital, temporal, limbic areas) rhythms for patients with MCI who rapidly progress to AD in approximately 1 year [39]. Finally, P300 latency might also potentially prove to be a useful predictor of conversion to AD. In a study examining 94 individuals with subjective memory complaints by using ERP P300 latency at baseline and then again at 24-month follow-up, results indicated that P300 latency was delayed among individuals who were eventually diagnosed with AD [52].

Coherence is a linear measure of the correlations between two signals as a function of frequency. As such, analysis of levels of coherence provides information about the functional connections between different cortical regions; thus, it is not a surprise that coherence activity is decreased in individuals with dementia [53]. Differences in baseline frontoparietal coherence have been identified between individuals who converted from MCI to AD compared with individuals whose diagnosis of MCI remained stable. In addition, Cox regression modeling demonstrated that low temporal delta source and low gamma band coherence along the frontoparietal midline predicted around 10% of annual rate of conversion to AD [39].

4. EEG markers of mild AD

Although there is a substantial degree of overlap in the choice of qEEG and ERP end points that have been studied between patient groups with MCI and those who have converted to mild AD, there are also some differences in the choice and utility of these end points between these two clinically differentiable patient groups. For patients with both mild and more advanced stages of AD, one commonly reported finding is an increased power in both delta and theta bands [41,44,54,55]. In addition, there is a long history of literature supporting the frequently observed decreased alpha wave activity characteristic of early AD [56,57]. Specifically, decreased alpha2, alpha3, and beta power have been identified in individuals with mild AD [48,55].

With regard to the ERP literature, several interesting group differences have been reported for the N400 component. The N400 is elicited by deviations in congruency expectations (ie, incongruent pairs of words) and is reflective of semantic comprehension. Key N400 generators are believed to reside in the anterior fusiform gyrus, as well as adjacent structures in the medial temporal lobe such as the parahippocampal gyrus [58,59]. Abnormal N400 latency has been associated with AD [46]. In particular, the N400 in patients with mild AD was shown to be attenuated, with a less well-defined peak at posterior electrode sites, when compared with healthy controls. In addition, patients with mild AD demonstrated a decrease in N400 amplitude elicited by repeated incongruent target words compared with new incongruent target words [47]. Interestingly, the diminished N400 in response to repeated incongruent versus new incongruent target words, found in patients with mild AD, differs from previous findings in patients with amnesia or MCI [46]. The P300, an additional ERP whose change is associated with cognitive decline, also shows abnormal latency and amplitude in individuals with mild AD. Specifically, in an auditory oddball paradigm, individuals with mild AD had a longer latency of the auditory P300, whereas in a visual oddball paradigm, these individuals showed a smaller visual P300 amplitude when compared with healthy controls [60].

Finally, Yoshimura et al [61] have reported the use of a novel EEG analysis method that showed clear differences between individuals with mild AD versus healthy controls. Omega complexity reflects the synchronization between spatially distributed processes; greater omega complexity is indicative of less synchronization or the presence of a higher number of simultaneously active processes. EEG recordings from patients with mild AD revealed greater omega complexity as compared with age-matched control subjects [61], suggesting that mild AD patients present with diminished neocortical electrophysiologic synchronization in comparison to their matched healthy controls.

5. Conclusion

This review has summarized literature from the previous 6 years exploring the use of qEEG and ERP as biomarkers for early cognitive change associated with MCI and mild AD. Review of this recent literature has led to a “short list” of promising candidate EEG and ERP markers of disease progression in both MCI and AD populations. Although there is certainly overlap between common EEG and ERP signatures in MCI and AD populations, there are also several differences that might provide promising biomarker leads for these two stages of cognitive decline (Table 1). There are increasing numbers of published studies documenting the potential utility and reliability of qEEG and
ERP as methods for delivering sensitive biomarkers for MCI and early AD. This renewed interest in electrophysiology has been driven by recent technological and user-interface advances, resulting in substantial improvements in the ease with which data are acquired, processed, and prepared for analysis. Quantitative EEG provides viable and promising avenues for clinical investigation, with the aim of developing useful biomarker(s) of early cognitive decline.

This review has focused on the application of this technology to deliver markers of disease progression. The complementary role of this technology, as a means to monitor therapeutic response to pharmacologic interventions (eg, citicoline, ginkgo biloba, nicotine), has received comparatively less attention [62–64]. Still, within the last 6 years, approximately 20 studies exploring qEEG or ERP correlates of response to treatment with acetylcholinesterase inhibitors have been published [65–67], many of these with encouraging results. For example, Babiloni et al [66] recently reported that persons with mild AD who were clinically responding to treatment with donepezil also showed restored temporal and occipital alpha rhythms in comparison to treatment nonresponders. Although this literature is nonetheless smaller as a result of the currently limited range of marketed symptomatic therapies, there is no conceptual reason to suspect that one or more of the promising qEEG and/or ERP markers described above will not be sensitive to change (or a lack thereof), with novel and truly disease-modifying therapies yet to be discovered.

### References


