Event-Related Potentials in the Continuum of Alzheimer’s Disease: Would they Suit recent Guidelines for Preclinical Assessment?

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Abstract

There are theoretical and practical constraints associated with using molecular biomarkers in the diagnosis of Alzheimer’s disease (AD) during preclinical stages when patients are asymptomatic. Event-related potentials (ERPs) provide an affordable measure of neurological functioning and have been used extensively to measure the onset and progression of cognitive decline in AD. However, the traditional paradigms used to elicit ERPs in the context of AD are influenced by unwanted factors such as ageing, cultural background and education, as well as other neuropsychiatric conditions and comorbidities. We propose that a revision of the task domain is necessary to increase the sensitivity and specificity of ERP measurements. Performance on the short-term memory binding task (STMBT) is highly specific to AD and mirrors the trajectory of neurological pathology in preclinical samples. Theory-driven cognitive assessments, electrophysiology and the emergence of mobile neuroimaging systems may serve as a fundamental combination to overcome the challenges of diagnosing preclinical AD.

Keywords: Alzheimer’s disease; EEG; ERP; Preclinical diagnosis; Mild cognitive impairment; Subjective cognitive decline

Introduction

According to Alzheimer’s Disease International, just 25% of individuals that suffer from Alzheimer’s dementia (AD) are receiving a diagnosis (The World Alzheimer Report, 2015, www.alz.co.uk/research/). Recent guidelines suggest that the diagnosis of individuals with preclinical AD and individuals at risk of AD is contingent on the presence of one or more molecular AD biomarkers (beta amyloid or tau pathology; [1]). The steady growth in the numbers of AD sufferers due to the unstoppable ageing of the population makes identification of molecular pathology at preclinical stages economically and ethically inviable, so we are currently seeking alternatives. While low-cost neuroimaging methods relying on electroencephalography (EEG) have provided us with highly sensitive measures of cognitive decline and disease progression in AD, the specificity of these measures is still too low to promote them as a diagnostic tool. We propose that careful theory-based selection of assessment modality is imperative for maximising the specificity of task-driven EEG measurements. Here we consider the efficacy of event-related potentials (ERP) in the assessment, monitoring and prediction of AD-related pathological ageing. A reconceptualisation of ERP task modality in AD may be necessary to align researchers with current recommendations for clinical diagnostics [1].

Event-related potentials (ERPs) are electrophysiological responses elicited by specific sensory, motor or cognitive occurrences. In the context of AD, various ERP components have been investigated in attempts to assess and monitor the onset, progression and treatment of the disease [2]. Early sensory components such as the P1, N100 and P200 are deemed relatively stable in AD [2], although amplitude reductions in the N100 have been reported [3]. Undoubtedly, the most researched ERP component in the context of AD is the P300, a positive-going deflection peaking at around 300-500 ms post-stimulus. The P300 is usually elicited during an ‘oddball task’, where a low-probability stimulus must be discriminated from a high-probability stimulus. There is still no consensus about what specific cognitive function the P300 is attributed to, but seems to be implicated broadly in attention, context updating and information processing [4]. Early studies established that the latency of the P300 is prolonged and the amplitude reduced in AD patients compared to healthy age-matched controls [5,6]. P300 parameters tend to have high sensitivity for identifying AD patients, but specificity of the measure has varied across studies [7,8]. The N200 precedes the P300 in oddball tasks, and has a similarly elongated latency in AD patients [9,10]. In semantic categorisation tasks, AD patients have abnormal N400 [11-15] and P600/LPC components [12,16,17], whereby they do not exhibit a typical amplitude reduction in response to repeated stimuli.

Over the past two decades, AD has become viewed as a continuum ranging from healthy ageing to dementia [18]. Scientific research has
witnessed a drive towards identifying phenotypic markers in patients at preclinical and prodromal stages of AD, in order to prematurely identify individuals who are likely to develop AD and to maximise the efficacy of interventions [19]. Preclinical AD typically refers to presymptomatic individuals known to have an AD-related genetic biomarker (familial-AD) or the presence of two molecular biomarkers (beta amyloid and tau pathology [1]). Prodromal AD refers to symptomatic individuals who present with AD biomarkers. Due to economical and ethical constraints, biomarker status is not always confirmed, and studies have relied on neuropsychological constructs to stage the disease progression. Subjective cognitive decline (SCD) and mild cognitive impairment (MCI) are two classifications of ‘prodromal AD’ defined by symptom severity and neuropsychological performance [20,21], and have high rates of conversion to full AD [22-24].

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Table 1: Significant ERP effects in selected studies comparing preclinical and prodromal AD to healthy controls. MCI = mild cognitive impairment; SCD = subjective cognitive decline; fAD = familial Alzheimer’s Disease; FH = Family History of AD; STMBT = Short-Term Memory Binding Task; SW = Slow Wave; TB = Temporo-Basal; TS = Temporo-Superior

In line with these calls for research, ERPs have been investigated in these pre-AD groups, leading to extensive cross-sectional findings (Table 1: for a selection of findings and interpretations). In the traditional oddball task, presymptomatic genetic fAD carriers exhibited increased latency of the N100, P200, N200 and P300 components, and reduced amplitude of a late slow wave from 400-550 ms, compared to non-carrier controls [25]. The P200 wave correctly classified 87% of presymptomatic carriers, and 64% of controls in this small sample [25]. Even when the genetic link is unestablished, next generation relatives of AD patients have reduced amplitude and increased latency of the P300 [26,27]. Amplitude and latency of the N400 during semantic categorisation are estimated to be unaffected by presymptomatic fAD [28]. However, using source localisation techniques, Bobes et al. demonstrated that presymptomatic fAD carriers had a reduction in the power of the N400 generator, which experienced a topographical shift in the same direction as fully symptomatic fAD patients [28]. Component-free, data-driven approaches have also been utilised in this population. Quiroz and colleagues demonstrated that compared to controls, presymptomatic fAD patients had a reduced positive ERP in left posterior sites between 200-300 ms during long term memory retrieval, which correctly classified 73% of patients and 82% of controls [29]. Although encouraging, this evidence is difficult to generalize as it is drawn from rare cases of AD which account for less than 5% of all affected individuals [1].

An interesting definition is SCD, one that aims to identify the earliest time window into the most common form of AD, the sporadic variant [30]. SCD describes any asymptomatic individuals that report memory impairment occurring over the previous year, so memory problems in SCD groups may be due to extraneous factors [30]. Unsurprisingly, few published studies have demonstrated ERP abnormalities in SCD compared to healthy controls, but some have demonstrated significant findings. A large group of individuals with...
SCD (n=189) demonstrated significantly longer P300 latencies than two separate groups of control participants [31]. Elsewhere, a SCD group had equivalent mean, but increased variability of P300 latency (SD=27.7 ms) to MCI patients (SD=10 ms; [32]), highlighting the heterogeneity of SCD groups. This evidence is promising as together with behavioural studies [30], it indicates that SCD may indeed offer a gateway into the preclinical detection of AD. For instance patients with SCD are more likely to progress to MCI than asymptomatic elderly people [30].

P300 latency in MCI patients tend to fall between that of healthy controls and AD patients [32-35] although this likely depends on the sample characteristics [7]. The combination of P300 latency measures with neuropsychological assessments has been shown to boost sensitivity for detecting MCI [33]. P300 latency has high accuracy for distinguishing non-amnestic MCI patients from single and multi-domain amnestic variants (81-90%; [36]). The N200 was more predictive of MCI status than AD, with 90% sensitivity and 70% specificity [8]. In a recent study, the P50 component had increased amplitude in MCI patients, and successfully predicted the level of amyloid burden in MCI patients [37]. The amplitude of the N400 repetition effect is also reduced in MCI patients [17]. In summary, ERPs have been used extensively to measure AD progression in its preclinical and prodromal stages. In summary, robust differences between MCI and controls are found mainly in the oddball N200, P200 and P300 parameters, and in the absence of a N400/P600 word repetition effect.

ERP measurements of preclinical AD: Limitations

As evident from this brief review, ERP anomalies in AD and pre-AD stages are by enlarge restricted to oddball and semantic categorisation paradigms. Despite these robust effects, the paradigms are limited in terms of their theoretical specificity to the trajectory of cognitive decline in AD.

The oddball paradigm specifically measures reaction times to an attentional stimulus evaluation process, which declines behaviourally with typical ageing [3,38], depression in the elderly [39,40] and other age-related disorders [41,42]. Accordingly, parameters of the N200 [42] and P300 [4,38,43] are contingent on the age of the participant. Abnormal P300 latencies have been observed in depressed elderly groups [45-47], and accuracy is extremely poor (~ 13%) when classifying AD patients against depressed and healthy controls [46]. In addition to MCI, N200 latency is delayed in individuals with vascular cognitive impairment [47,48] suggesting it is unspecific to AD processes.

Similarly, the N400 repetition effect relies on long term recognition, which is unspecific to AD pathology in the elderly [49,50]. Reduction of the N400 repetition effect is seen in healthy agers [13,51,52] and Parkinson’s disease [53,54] while it is not yet established in depression or other dementias. Clearly, ERPs elicited during non-AD specific tasks have value in classifying full onset AD amongst healthy controls, and the processes that govern these ERPs are indeed affected during AD. However, specificity rates for distinguishing preclinical and prodromal stages of AD from healthy controls are either substandard (e.g. [8]), or unreported, calling into question the ability of these measures to classify individuals on the AD trajectory.

Logie, Parra and Salla recently proposed a selection of features that a high quality assessment for Alzheimer’s disease should incorporate [54]. Some key features the authors mentioned are that the assessment should not show effects of healthy ageing, should be sensitive and specific to the very early stages of AD, not show improvement solely as a result of repeated testing, be useable in primary care and in intervention trials, be targeted at cognitive impairments shown in AD but not in other disorders, be non-invasive with minimal discomfort to the patient, and should be insensitive to the cultural background and literacy levels of those assessed. A new generation of cognitive tests for the detection of preclinical AD is quickly developing [55]. This offers a unique opportunity to capitalise on these methodologies to enhance the efficacy of ERP assessments.

Theory-based ERP assessments in the AD trajectory

Ultimately, there is a discrepancy between the tasks used to elicit ERP anomalies in preclinical AD and current models of the AD continuum. It is important to take a multimodal approach when developing assessments, taking into consideration findings from molecular, structural and functional neuroimaging, as well as stereotypical AD symptomatology. Cognitive and behavioural tasks designed to assess preclinical stages of AD need to fall in line with these specific findings [54]. ERPs recorded during more specific tasks should in turn be more specific in the detection of preclinical AD, and unequivocally inform about the disease severity and progression. Many tasks that fall in line with this idea [55,56] have already been investigated in the electrophysiological context.

AD symptoms are primarily classified by impairments in episodic memory functions of the hippocampus, and this is a promising domain in which to base AD assessments. For example, the Name Associate Memory Exam (FNAME) assesses cross-modal associations of names and faces, and has been associated with hippocampal grey matter decline and beta amyloid deposition in asymptomatic healthy elderly [57,58]. ERP indices of such a task are well established in healthy young adults [59,60], and could easily be investigated in the context of the AD trajectory. Similarly, the Behavioural Pattern Separation-Object test (BPS-O; [59]) has specific ERP signatures [60], and has been cited as a promising assessment for MCI and AD [55].

However useful hippocampal assessments may be during prodromal stages when patients are symptomatic, opinions have recently changed about which functions are the first to decline with the onset of preclinical AD. Probing hippocampal deficits (i.e. in long-term and associative episodic memory) is a redundant contribution to the detection of preclinical AD [61]. This reasoning is constructed from neuroimaging evidence that the hippocampus is associated with significant grey matter decline during the healthy ageing process [62-64]. Subsequently, performance in associative memory tasks [58, 65-67] is negatively correlated with age [68-71]. Conversely, there is well established evidence for AD-specific degeneration in anterior subhippocampal regions incorporating the Entorhinal Cortex (EC) and Perirhinal Cortex (PRC). Unlike the hippocampus, grey matter volume in the EC/PRC does not degenerate with increasing age [70]. Critically, grey matter in the EC/PRC does degenerate in early AD [72-74] and the EC/PRC are initiatory sites in the development of AD-related tau pathology [75,76]. These areas receive information from the ventral visual stream (the “what” stream) and are associated with context-free object memory and intra-object associations [61].

Deficits in cognitive functions that rely on the EC/PRC may well map the molecular pathway of neural degeneration, and thus inform about which ERP paradigms may be most useful in preclinical AD. One example that fits this criterion is the Short-Term Memory Binding
task (STMBT; [75]). The STMBT requires participants to memorise and retrieve shape-colour feature conjunctions in a change detection paradigm. Relative to healthy controls, STMBT deficits have been identified in presymptomatic fAD [75], mirroring the timeline of significant beta-amyloid accumulation in this group [76]. STMBT deficits are also evident in full-onset sporadic AD [77], SCD and MCI [78]. Furthermore, STMBT performance is uninfluenced by healthy ageing [79], depression [80] and other dementias [81]. A recent study documented reduced amplitude in early ERPs (N1 and P2) in presymptomatic fAD and MCI individuals compared to controls [82], which may indicate neural deficits in ventral visual processing leading to impaired memory performance. STMBT-related ERPs have potential to map the progression of AD pathology into later stages, as the task can be titrated with regards to the number of stimuli used in the task [75]. The STMBT, or other context-free memory tasks that rely solely on memory functions of the EC/PRC, may therefore be the most theoretically driven tasks available to researchers who wish to investigate ERPs in preclinical AD.

Monitoring disease progression and response to treatment using ERPs

Oddball ERP’s have been used to measure longitudinal changes in the brain when tracking AD progression and evaluating pharmacological interventions. During prodromal stages, component parameters tend to mirror the trajectory of cognitive decline. Oddball N200 amplitude is sensitive to longitudinal cognitive changes at early prodromal stages, whereas P300 latency is more sensitive at later stages [32,83]. Over a 3-year period, MCI patients with N400/P600 abnormalities were three times as likely to convert to full AD than patients with preserved components [84]. Changes in morphology of the PNWM working memory component were observed in progressive compared to stable MCI patients over a 12-month period [85]. ERP parameters have been linked to the deposition of hallmark AD biomarkers in the brain. The P50 component, in conjunction with level of education, has successfully predicted the quantity of beta-amyloid (Aβ42) in the brains of MCI patients [37]. The inclusion of P300 amplitude and latency with Aβ42 status strengthened the classification of 5 MCI-AD converters from 48 non-converters [86]. In the same sample, N200 latency correlated with Aβ42 levels, and both measures in combination predicted MCI-AD conversion with 100% sensitivity and specificity [87]. Although the number of MCI-AD converters in these samples was low, the results seem to indicate that the ERPs can increase the accuracy of molecular biomarkers for tracking the progression from prodromal to full onset AD. If this classification rate is stable across larger samples, the dual approach could be a better indicator for MCI-AD conversion than what is typically reported for molecular biomarkers alone [88].

ERPs have been used as neural outcome measures to the effects of pharmacological treatments in AD. While a shortening of the P300 latency was evident in some cases [88,89], the effects seem to be specific to moderate/severe cases of AD [90,91]. Where effects are found, the findings suggest improvements in attentional mechanisms in response to drug treatment at late stages of the disease. In the preclinical context, using oddball ERP latencies as longitudinal outcome measures would likely be meaningless. A revision of the ERP task modality to test functions that are sensitive to preclinical cognitive and neurological changes would be more sensitive in mapping neural degeneration or plasticity over time.

Network connectivity approaches

Aside from ERPs, EEG connectivity analysis has been heavily explored in AD and prodromal stages, predominantly in the resting state modality. Graph theory principles applied to EEG sensors have revealed a host of connectivity abnormalities in AD and its related stages, including reductions in long-range connectivity [92], loss of small-world connectivity [93,94] and a posterior-anterior shift in network centrality, indicating a redundancy in the connectivity between posterior brain regions in AD [95,96]. Resting state measures have several advantages. They are unaffected by discrepancies between task parameters at different recording sites, allowing for multi-site research. The participant is not required to exert mental effort or perform well in a task that may be beyond their capabilities, thus reducing the likelihood of omitting data based on task performance. Relatively little data is needed to carry out connectivity analysis, with reports that four 8-second trials give reliable connectivity estimates [96]. Although EEG network connectivity is a thriving research area, the sensitivity and specificity of resting state connectivity for detecting AD are currently poor in comparison to ERPs [94,95].

For the same reasons as described for ERPs, task-related connectivity may prove more specific than the resting state method when the AD continuum is considered in the selection of the task. Combination of the STMBT with connectivity analysis may uncover novel networks in which to assess and monitor disease progression in preclinical and prodromal AD [97-99]. Recent efforts using novel connectivity approaches [100] have detected specific connectivity patterns of the STMBT [101] in healthy adults. The application of this analysis to individuals with preclinical AD is currently underway.

Mobile EEG tools in AD

Advances in technology mean that mobile EEG systems are becoming increasingly viable. In light of the numbers of current AD sufferers (44 million people worldwide; The World Alzheimer’s Report, 2015), mobile systems are incredibly desirable tools. Remote EEG recordings would ensure data to be acquired by multiple patients simultaneously, from the comfort of their own homes. It would facilitate longitudinal studies and likely maximise adherence to follow-up sessions. Recent studies have shown that systems with 35 sensors may be adequate to collect reliable data that can still be treated for movement artefacts using independent component analysis [102]. Combined stimulus delivery and mobile EEG systems would enable tasks like the STMBT to be administered to large numbers of older adults over a given time period, and could be used as a screening tool for preclinical AD.

Cecchi and colleagues recently demonstrated the feasibility of this approach. Using COGNITION®, an EEG/ERP system that relies just on a few sensors, the authors recorded clinically meaningful electrophysiological data which reliably differentiated between AD patients and healthy controls [3]. Such a portable technology would offer an ideal solution to address the need of Mobile Brain Imaging Tools [102]. Future efforts will need to integrate complex computational algorithms to identify the best combination of electrophysiological, clinical and cognitive variables that can achieve a clinically acceptable classification [102,103].

Overcoming barriers and providing clinical solutions

According to recent guidelines, biological markers are required to properly classify the onset of AD and disease progression;
asymptomatic individuals at risk of AD can be identified by the confirmation of either amyloidopathy (A+) or tauopathy (T+), while the presence of both leads to a preclinical classification [1]. The detection of such biomarkers relies on Positron Emission Tomography (PET) imaging or Cerebrospinal Fluid (CSF) analysis. A number of economical and ethical factors such as expense, the need for specialist training and equipment, and invasiveness, are implicated with biomarker acquisition at early stages of AD [54]. PET and MRI methodologies identify several mechanisms related to AD, but their use is limited by availability only in specialised clinics normally located in major cities, costs, and invasiveness due to radiation exposure (e.g., PET, CT scan). These techniques would unlikely be available for screening purposes. Similarly, CSF analysis requires an invasively lumbar puncture which needs to be carried out by a trained professional and can lead to unpleasant side effects.

CSF and PET analysis have several limitations not only due to their availability and cost, but also the lack of standardisation. Particularly for CSF biomarkers, as mentioned by Dubois et al., each laboratory has to establish their own internally validated cut-off values and a rigorous analytical quality control system, including certified procedures, methodologies, and bridging of batches, to guarantee longitudinal stability in its measurements [1]. Even in developed countries, the cost of most if not all of these tests must be partially or totally supported by governments or through research. Limitations are not only linked to the few centres where techniques such as PET scan are available but also to the high cost of the radio-ligands used in the procedure which often poses a major logistic issue. Furthermore, biomarkers have been detected in the brains of cognitively normal individuals, and the specificity of these measures to AD other dementias is still somewhat limited [104].

Logie, Parra and Dela Salla [54] propose that specific cognitive markers like the STMBT, in combination with biomarkers, may provide the sensitivity and specificity necessary to monitor AD progression from its earliest stages. In line with current recommendations for assessment [1], we propose that the simultaneous recording of EEG with the cognitive task can serve as a multimodal assessment when biomarkers are unattainable. EEG is a low-cost and non-invasive methodology for clinical applications. EEG recording has a high temporal resolution offering opportunities to extract cognitive related events occurring in the order of milliseconds, something that available neuroimaging techniques cannot achieve. This property makes EEG/ERP the most suitable tool to investigate brain physiology [105,106]. Methods applied to EEG data have developed enormously over the last decade to the extent that they can yield information about brain function in a way akin to neuroimaging [102-114]. The EEG has been used for many decades and is considered a completely safe procedure, with no risks or side effects. EEG procedures are widely available in any country and they can be repeated over time without habituation effects. It is a procedure that is usually well-tolerated by patients and is not affected by the task difficulty [112].

**Conclusions and Recommendations**

Due to the technological advances in the last few decades it is now possible to propose novel EEG-based biomarkers for AD. In this regard, ERP methods are promising tools. However, the tasks traditionally used to obtain ERPs are not specific to AD. For instance, the continuous performance task used in odd-ball paradigms traditionally developed to record P300 reveals abnormal patterns of brain activity in several neuropsychiatric disorders, and in healthy ageing. Additionally, sensitivity and specificity statistics are rarely reported in prodromal studies, implying a lack of classification ability. These criticisms hold for most of the available ERP methodologies. Efforts should be directed towards linking ERP recordings with cognitive tests that have high sensitivity and specificity for the AD continuum [54]. A new generation of neuropsychological tests which can inform about the preclinical stages of AD is becoming available [55]. One such a test is the STMBT which appears to meet the aforementioned criteria. Such a test has already been combined with EEG recording to elicit ERPs [82] and continuous EEG patterns [101]. Future efforts should address the development of mobile tools which can be detached from hospital facilities and used in community settings to screen for dementia in populations that are at risk of AD.

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