

P300-tracking of changes in information processing / working memory in preclinical alzheimer's and mild cognitive impairments (MCI)

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Abstract

Alzheimer's disease (AD) is a presently incurable disease with a significant health burden, with a prevalence of 5.8 million Americans as of 2019. Prognosis as well as more effective treatment regimens could be greatly augmented by reliable means of diagnosis in the earlier stages of development. Efforts to characterize impairments in memory in pre Clinical AD and mild cognitive impairment (MCI) range from the domain involved (episodic, semantic, working, perceptual, or visuospatial), to storage (sensory, long-term, short-term, explicit, implicit, autobiographical and morpheus), to memory processing including working memory or information processing (encoding, storage, and retrieval). An emerging area of research aims to determine whether detectable impairments in encoding, storage or retrieval have the ability to serve as hallmarks of pre Clinical Alzheimer's and early MCI giving both clinicians and patients a window of opportunity to halt or reverse progression to AD via early treatment options. For the identification of event related potential (ERP) markers, the P300 has shown promise as a state-of-the-art new device. While prolonged P300 latency recorded via electroencephalograph's (EEG) like BrainView NeuralScan is seen in normal aging, individuals with AD exhibit more prolonged P300 latencies and frontal-dominant P300 distribution when compared to normal individuals of the same age. Key questions now remaining include whether identification of these EEG hallmarks identified with the assistance of devices such as the P300 may provide us with an earlier timeframe in the diagnosis, prognosis and early treatment for AD, as well as providing crucial insights into mechanisms of its early pathogenesis.

Introduction

Predicting the pre-clinical risk of Alzheimer's disease (AD) years in advance of the onset of symptoms would present patients and clinicians with a greatly extended window of opportunity to introduce lifestyle modifications or applicable treatments with a potential to ameliorate or delay the onset of the disease [1-3]. This comes in the wake of findings that primary prevention of AD is possible as among the risk factors for AD, 1/3rd are modifiable and include metabolic syndrome and cardiovascular risk factors, lifestyle risk factors (physical inactivity, smoking), demographic factors like low education levels and depression [4-14]. "Pre-clinical AD" includes the *presymptomatic individual who carries an autosomal dominant monogenic mutation* and the "asymptomatic at risk state" includes the *individual without the onset of clinical symptoms with the presence of any one of the current known biomarkers of AD like amyloidosis in the brain with or without neurodegeneration* [2,4,15,16].

In terms of neurocognitive markers of AD, episodic memory, psychomotor speed, and verbal fluency decline 5–8 years while others like concept formation show changes 10-17 years prior to the onset of dementia [17-19]. However, these neurocognitive markers are still considered relatively non-specific as they are also seen in depression, drug abuse, and Parkinson's disease [20-23]. Subjective cognitive decline (SCD), another candidate marker of pre-clinical AD had its own hiccups with only 16% of individuals with SCD progressing to clinical AD in the AMSTERDAM study, 7%–37% in the Mayo Clinic Study on Aging (MCSA) and 2.33% annual progression in Mitchell *et al.*'s study with a low relative risk of 2.07 [24-28]. Two other factors chipping away at its candidacy are that a) majority of individuals with

SCD are >60 years and b) <30% of individuals with SCD test biomarker positive [29-34].

In 2019 a study inferred that the P300 an event related potential (ERP) marker was able to differentiate with 100% accuracy between individuals with new-onset Alzheimer's disease (AD) and normal subjects [35]. The study also suggested that the P300 elicited using the task-drive odd-ball paradigm recorded using electroencephalography (EEG) machines like BrainView NeuralScan could be potentially used to detect AD in the pre-clinical stage [35]. In 2019 it was estimated that 5.8 million Americans had AD [36]. In general, **normal aging** exhibits "decline in" – recall, episodic memory, processing speed and divided attention, while implicit memory and recognition remains "stable" with semantic memory, crystallized IQ and emotional reasoning improving till ≈60 years of age [37-39]. Beginning with "loss of memory" (inability to encode or retrieve recent memories) individuals with **Alzheimer's disease (AD)** subsequently complain of difficulty with attention, planning, semantic memory, and abstract thinking. Further progression of AD results in greater memory loss, language difficulties, failure to recognize close family and friends, emotional instability and finally loss of control over bodily functions [37-39].

The present article will describe the changes in working memory (WM) and information processing in pre-clinical AD and MCI

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captured via the P300. The benefit of state-of-the-art EEG machines like BrainView NeuralScan (Figure 1) is that in addition to ERP-based (i.e. P300) identification of preclinical AD, brain mapping using quantitative electroencephalogram (qEEG), and source localization using low resolution brain electromagnetic tomography (sLORETA) imaging to identify Brodmann areas (BA) affected is possible. Thus the clinician can micro-monitor progression and titer treatments using ERPs like the P300 and at the same time be able to identify areas of the cortex that are involved which in turn allows them to anticipate which cortical functions might be compromised in the future.

Working memory and Information processing

Deficit in episodic memory is a key impairment seen in early AD. Working memory (WM) defined as “the capacity to hold information that is absent in mind for brief periods of time” [35,36]. The model consists of the central executive that controls and regulates the function of the phonological loop (articulatory loop and acoustic store), the episodic buffer and the visuospatial sketchpad; allocating attention

to current relevant tasks and block out irrelevant tasks. In the WM model the three processes in memory formation include: information encoding, maintenance, and retrieval. Long-term memories are formed when information is transferred from short-term to permanent episodic representation by rehearsal [35,36]. Early AD memory complaints revolve around encoding, maintenance, and retrieval of information, deficits in the acquisition of new information (encoding) and retention or retrieval deficit in early AD remains equivocal [37-50],

P300 and Theories on P300

Neurocognitive functional connectivity markers like the P300 that use EEG/MEG/event related potentials) in combination with resting state or goal-driven oddball paradigms (tasks/attention/visual/auditory/response inhibition Go/NoGo) to elicit and study brain function are sensitive [35-41,51-57]. They have the potential to demonstrate abnormal diffuse slowing, delay and suppression of responses to sensory and cognitive stimuli, identify pre-clinical AD, in treatment evaluation be it medication (eg.: effect of acetylcholinesterase inhibitors on AD

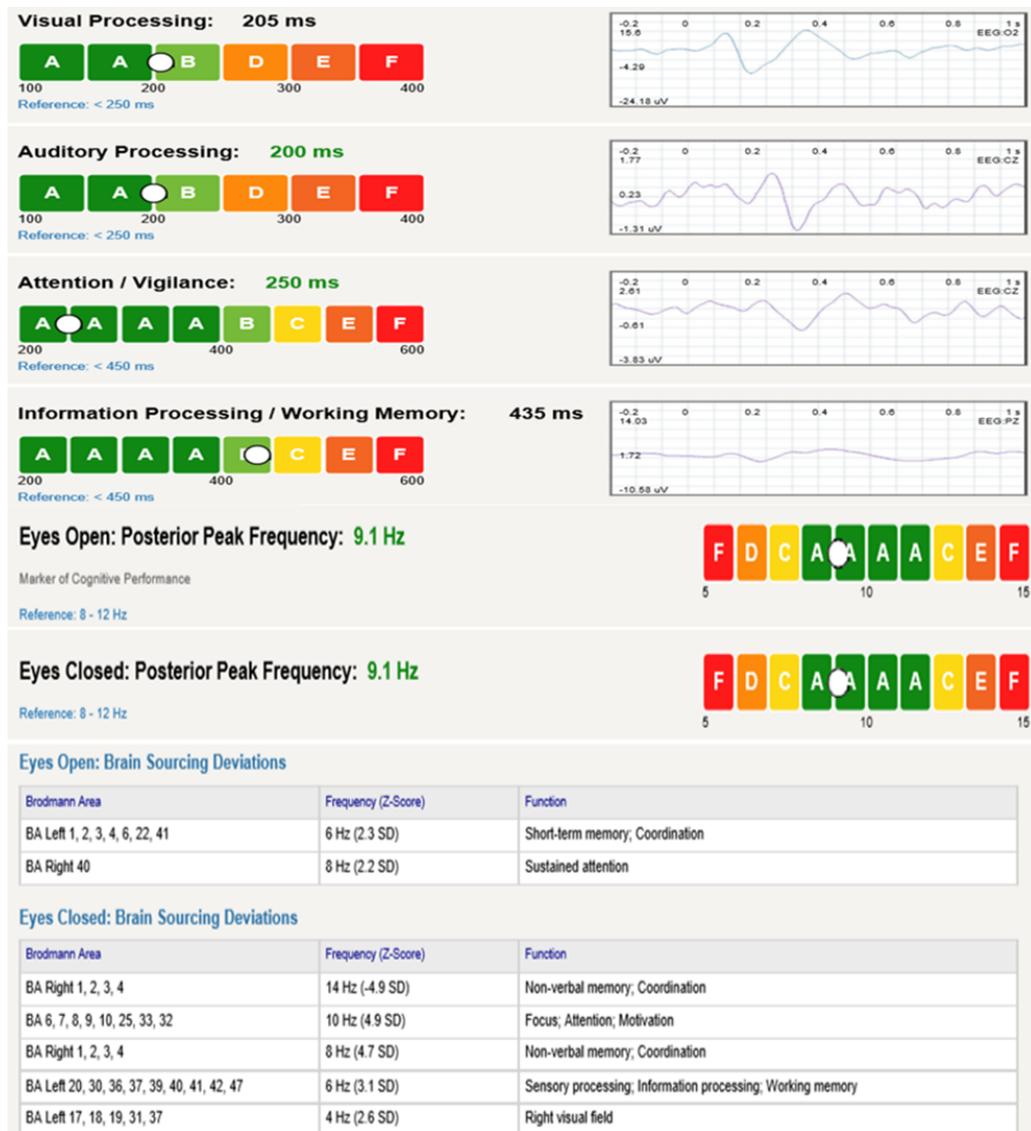


Figure 1. Report summarizing the results of visual and auditory processing, attention, working memory/information processing evaluated using the P300 and resting EEG (eyes open and eyes closed) using BrainView NeuralScan by Medeia

patients), neurofeedback or neurotherapy [35-47,51-63]. Among them, the P300 recorded using EEG machines like BrainView NeuralScan by Medeia (Figure 1) captures information processing memory, attention, executive function with the dopamine-mediated P300a playing a key role in frontal working memory (WM) function while medial temporal lobe generated P300b component, is norepinephrine-mediated [48,49]. P3a reflects orientation to a nontarget deviant stimulus, focal attention, engagement of attention, processing novelty executive function [50-53,62-65]. Decline in P3a amplitude has been shown to correspond to decreased attention and executive function in mild AD indicative of its potential as a preclinical marker of AD and aiding clinicians in arriving at a more objective diagnosis and treatment titration [50-53,62-65].

Theories on P300 include i) stimulus evaluation hypothesis subsequently refuted [66-68], ii) Sokolov's context-updating hypothesis environment i.e. updating occurs when relevant stimuli are presented [60,69-71], iii). context-closure hypothesis namely; first consolidation of stimuli is carried out to achieve a meaningful context and when this is followed by background stimuli i.e. the meaningful event is over. closure is initiated [70,72-74]. Other trivia to keep in mind include; P300 latencies and larger amplitudes reflect superior information processing with the converse indicating decline in cognitive function [60,70,74-78]. 60% of P300 morphology observed is individual specific and stable showing little variation over recording sessions/trials and with morphology, reaction times (RTs), 75% of speed and errors positively correlated with age [79-88]. Individual variations in P300 mediated by arousal levels are guided by an individual's traits, state (natural and biological eg. body temperature, sleep quality, exercise, food intake, drugs) and physiological properties (anatomical features of the corpus callosum or skull thickness) [86-88].

Systematic and meta-analytic reviews on P300

Figure 2 illustrates the relationship between the auditory P300 and age based on both a systematic and meta-analytic review of 75 studies (n=2811) [89]. Age-related degenerative effects include increase in P300 latencies and decline in amplitude [90,91]. This coupled with changes in white matter integrity influence executive dysfunction in the elderly [90,92,93]. To compensate for this decline older adults recruit other neural networks mediated in the prefrontal cortices to help meet the task as hand however once a particular threshold is crossed this is no longer possible and decline in cognitive performance can be seen ('CRUNCH' model) [85,94-108]. In a clinical trial on 103 with mild AD and 101 healthy controls (HC) between 60 and 90 years of age Cecchi et al. evaluated suitable ERP markers of mild AD. **P3a amplitude (μV)** differed significantly between **healthy controls (HC, n=101) 5.88 ± 0.19** and those with mild AD (**n=103**) **$3.63\pm 0.20^{**}$** following a distractor (white noise) stimulus. **Latency (ms)** did not appear to be significantly different between HC **417.3 ± 2.4** and those with AD **419.8 ± 3.0** [70]. Both **P3b amplitude (μV)** differed significantly between **healthy controls (HC) 6.03 ± 0.20** and those with AD **$4.42\pm 0.20^{**}$** following a target (2000 Hz) stimulus as well as **latency (ms) HC 396.0 ± 2.8 , AD $419.6\pm 3.3^*$** [109]. Pedroso et al. carried out a systematic review of 8 studies (Caravaglios et al., O'Mahony et al., Lai et al., Yamaguchi et al., Golob & Starr, Bennys et al., Juckel et al. and Frodl et al.) that examined the auditory P300 amplitude and latency in AD [110-118]. Findings were that while P300 consistently showed an increase in latency in the elderly with AD, amplitude showed no such consistent pattern [110-118]. One reason could be was a lack of standardization in the method used to elicit and capture the P300 [110-118]. However, another meta-

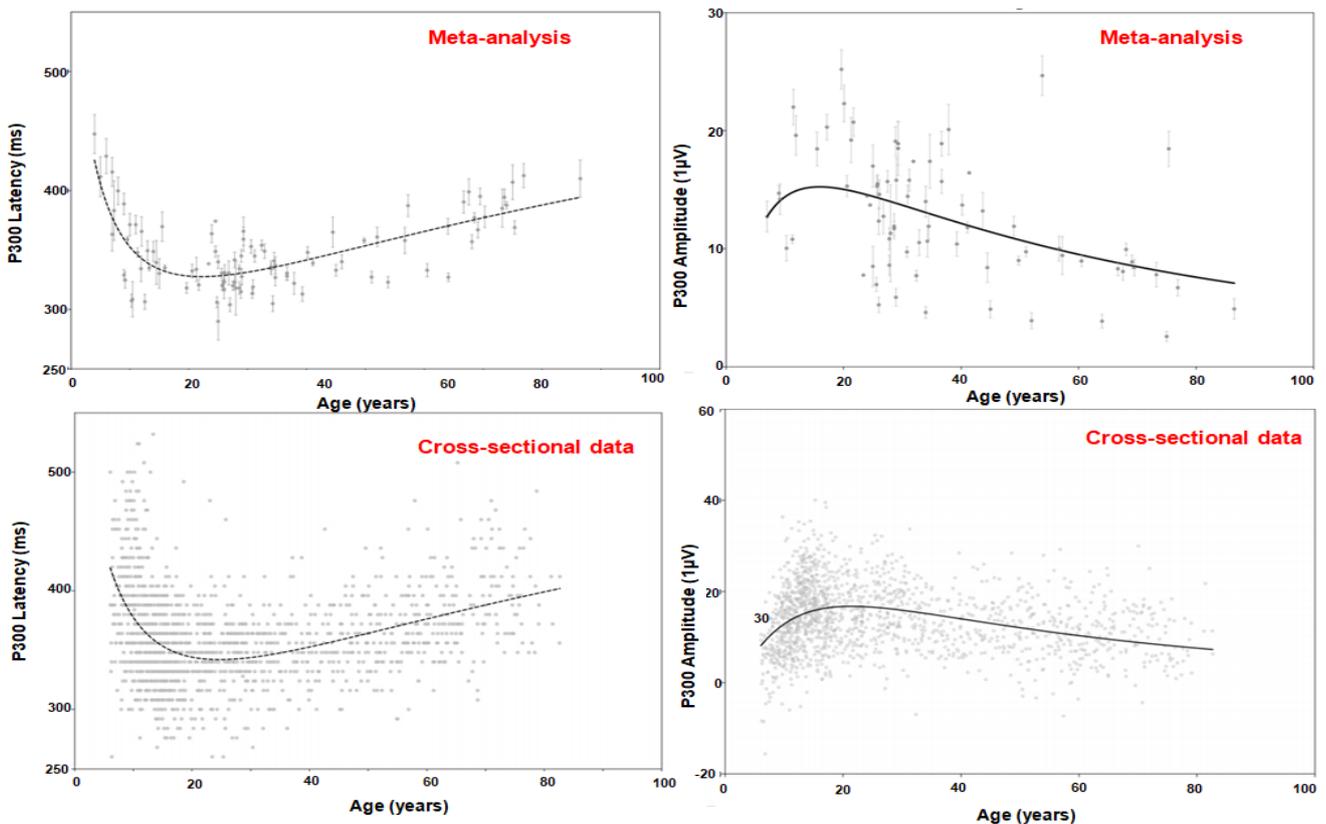


Figure 2. P300 and age [89]

analysis and meta-regression carried out by Hedges *et al.* found P300 amplitude was smaller in those with AD [24].

P300 and recording electrode

Among studies comparing healthy elderly and those with AD three found lower P300 amplitude and two, higher P300 latency differentiated healthy elderly versus those at risk of AD while another found amplitude and latency were better in individuals without subjective memory complaints than those with complaints [119-126]. One study found that parietal electrodes were best at identifying changes in P300 patterns between controls, MCI and AD [125-128].

P300 and treatment (Rx) tracking

In six studies, three on allopathic medication, another on ayurvedic medication and two on exercise, the P300 was able to capture the influence of the respective therapeutic regimen on the cognitive function of elderly [129-134]. The elderly in the clinical trial compared to the placebo/ control group showed improvements in amplitude and latency during the respective treatments and return to baseline values once they were taken off them. Figure 3a illustrates the usefulness of the P300 in treatment tracking from a study carried out by Vaitkevicius A. 22 consecutive treatment-naïve AD subjects, 22 AD on donepezil (10 mg/day) [135], and 50 healthy controls were tested using neuropsychological testing and the auditory P300 was recorded at Fz, Cz and Pz. While P300 latency and amplitude improved in the AD on treatment (Rx) group. While comparison of mean P300 latencies ($p < 0.001$) via the ANOVA was significant, both treatment-naïve AD and AD on Rx differed from control group ($p < 0.001$), however when treatment-naïve AD and AD on Rx were compared there was no

significant difference seen ($p = 0.49$). Predictors of P300 latency via linear regression were age ($p = 0.019$) and AD Rx status ($p < 0.001$).

P300 and AD-related cognitive function

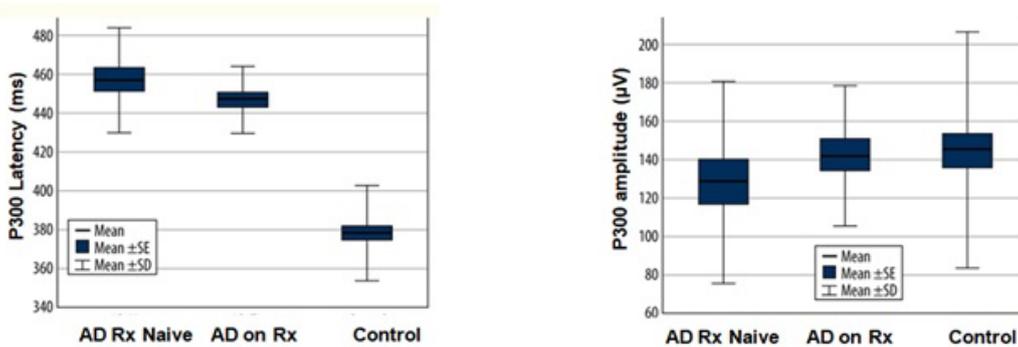
Lee *et al.* in a study of 31 HC and 31 with AD found that while P300 amplitudes were lower the two study groups did not differ by latency [121]. They found the EEG recorded from the medial electrodes Cz and Pz correlated with performance levels on word list recognition, constructional praxis, and word fluency neuropsychological tests. Findings indicate that deterioration in memory, language and executive functions due to AD can be captured via the P300. Wang *et al.*'s study illustrated the use of the auditory P300 in the differential diagnosis of AD ($n = 27$) and behavioral variant of frontotemporal dementia (bvFTD, $n = 30$) with those with by FTD having significantly longer P300 latency (Figure 3b) [136].

Auditory post-processing was found to be deficient in individuals with AD when compared to elderly controls. While this deficiency could not be explained by sensory gating, aging in general and auditory perception dysfunction; short-term memory (STM) capacity and executive control tasks instead point at possible deficits in memory encoding and/or cognitive control [137].

Visually-evoked (VEP) P300

Kuba M *et al.* looked at visually-evoked (VEP) P300 in electrophysiological studies that examined the effect of aging on visual cognitive processes [84]. Visual information processing was evaluated in the primary cortical visual areas and the secondary extrastriate motion processing visual cortex while cognitive function was examined

a) As marker of Donepezil (10 mg/day) /cholinesterase inhibitor (ChEI) treatment (Rx)-dependent cognitive functions



b) For differential diagnosis of AD and bvFTD

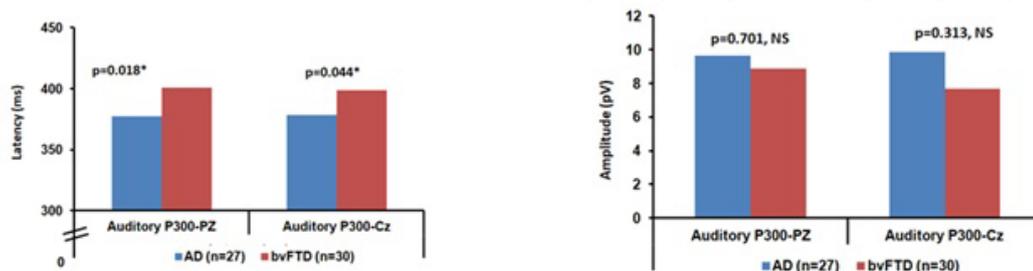


Figure 3. Comparison of mean P300 amplitude (pV) and latency (ms) [133,136]

in the centroparietal and frontal brain cortex to be able to understand visual processing in the elderly. 150 volunteers, 15 to 85 years of age, male%=46% with fairly good visual acuity in at least one eye were included in the study. Pattern-reversal (black/white checkerboard) and motion related VEP (translating unidirectional linear motion and radial centrifugal or centripetal motion (“expansion/contraction”) were recorded from Oz, Pz, Cz and Fz and from OL and OR monocularly. Table 1 presents the results of the linear regression carried out to derive the equation predicting visual P300 amplitude (μV) and latency (ms) [84].

P300, AD, working memory and attention

Another study on mild dementia of the Alzheimer's type (DAT, n=10) and age-matched controls (n=10) found no difference in P1, N1, and P2 (ERPs) however P300 amplitudes were significantly reduced, reaction time retarded, and increased behavioral errors were observed [138]. The inference was in mild DAT early sensory processing including pattern recognition is intact while higher-level processing is compromised.

The P300 signature of cognitive processes such as attention and working memory is positively correlated with the amount of attentional resources assigned to a given task and its latency is negatively correlated with latencies associated with superior cognitive performance [139]. It reflects cortical activity during incoming information when it is contextually processed and incorporated. While the P300 is a measure of stimulus evaluation time it is unrelated to both response selection processes and behavioral reaction time. P300 latency increases as cognitive capability decreases from dementing illness.

Changes in the latency, amplitude, and topography of the P300 correlate with cognitive impairment in AD. AD and MCI patients have increased P300 latency and decreased P300 amplitude compared to elderly indicating that it has the potential to identify preclinical changes

in participants with and without a genetic predisposition to AD and who will convert to AD as well as to help evaluate of cholinesterase inhibitors treatment in dementia. P3a a frontocentrally maximal positive ERP marker of the attentional switching is generated by the prefrontal, cingulate, temporo-parietal, and hippocampal regions. AD patients have longer P3a latency and exhibit delayed orientation to deviant stimuli and the P3a is different in AD compared to vascular dementia.

In a study on 200 middle-aged construction workers Portin *et al.* linked P300 with attentional performance (with low rather than effortful working memory demands and updating), retrieval from memory stores and or MCI [140]. Li BY *et al.* carried out a study on 24 subjects with MCI and 22 normal controls (Figure 4). Neuropsychological tests, delayed match to sample task (DMS task), visual P300 at O1, O1, and Pz, and standard low-resolution tomography analysis (s-LORETA) were measured. P300 amplitude differed significantly ($p = 0.025$ and $p=0.038$) for the retrieval epoch [141]. Positive correlation was found between P300 amplitude and memory load, language fluency and visual-spatial ability. Findings suggest that P300 might represent general cognitive ability, while P2 correlated with attention allocation via sLORETA and early AD/MCI are marked by retrieval deficit.

Table 1. Linear regression co-ordinates predicting Visual Evoked P300 potential (VEP) [84]

n	Visual P300 (y-axis)	Intercept (c), Slope (m), R ² , p-value
Whole Group (n=150)	Latency (ms)	324.5, 2.005, 0.601, p=0.001
	Amplitude (μV)	21.9, -0.161, 0.255, p=0.001
Males (n=69)	Latency (ms)	336.9, 1.600, 0.515, p=0.001
	Amplitude (μV)	22.3, -0.175, 0.263, p=0.001
Female (n=81)	Latency (ms)	314.7, 2.336, 0.676, p=0.001
	Amplitude (μV)	21.7, - 0.151, 0.250, p=0.001

a) P300 in Encoding and Retrieval epochs

Parameters		MCI (n = 24)	Normal control (n = 22)	p*
Encoding epoch	Number of valid trials	1643	1637	0.889
	Latency (ms)	317.69±46.51	312.64±45.17	0.711
	Amplitude (μV)	4.37±2.66	4.50±2.88	0.803
Retrieval epoch	Number of valid trials	1642	1604	0.634
	Latency (ms)	296.67±37.75	306.54±34.80	0.363
	Amplitude (μV)	3.72±2.31	5.45±3.14	0.038*

b) sLORETA images showing positive differences between aMCI and controls (in yellow)
(3D-view, slice-view, P200 time-range; Montreal Neurological Institute (MNI) coordinates x, y, z = 25, 45, -10)

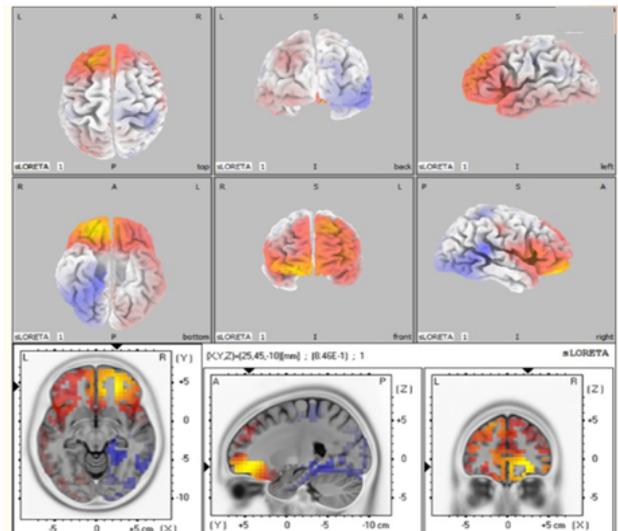


Figure 4. Early MCI: P300 and sLORETA images at P200 of aMCI versus controls illustrate central-executive-based on medial frontal gyrus retrieval deficit [141]

Conclusion

The criteria delineating the stages of progression from pre clinical to clinical AD remain to be fully characterized and defined, and earlier identification i.e. at the stage of early MCI would greatly augment the implementation of earlier and potentially more efficacious treatment, delay or even prevention of AD. More recent advancements in the field have led to a refocusing of efforts to emphasize identifying individuals at risk for AD development. The present article explored the utility of state-of-the-art new innovations including EEG machines such as the BrainView NeuralScan in identifying individuals at preclinical risk of AD, citing their unique capability to identify key hallmarks through such measure's oddball paradigm elicited P300 morphology, amplitude and latency recording. While the ability of the P300 to aid in identifying those at risk of preclinical AD or MCI is well-documented, there remains a need to standardize paradigms used to elicit the P300, and while there are many studies on the auditory as well as the visual P300, a more comprehensive identification of P300 changes correlating to specific symptoms will need to be established within the context of a preclinical AD to maximize these devices' full potential for diagnostic, prognostic and therapeutic-guidance benefit.

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