JBR Journal of Clinical Diagnosis and Research

Scally et al., J Clin Diagn Res 2016, 4:1
DOI: 10.4172/2376-0311.1000126

Review Open Access

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

Scally B [*], **Calderon PL**[2], **Anghinah R**[3] **and Parra MA**[4-8]

[1]*School of Psychology, University of Leeds, UK*

[2]*Department of Neurology, Chu Brugmann, Brussels, Belgium*

[3]*Department of Neurology, University of São Paulo Medical School, São Paulo, Brazil*

[4]*Department of Psychology, University Heriot-Watt, UK*

[5]*Scottish Dementia Clinical Research Network, NHS Scotland, UK*

[6]*Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, UK*

[7]*Diego Portales University, Psychology, Chile*

[8]*Universidad Autónoma del Caribe, Colombia*

[*]**Corresponding author:** Brian Scally, School of Psychology, Faculty of Medicine and Health, University of Leeds, LS2 9JT, UK, Tel: +441133439197; E-mail: b.scally@leeds.ac.uk

Received date: May 23, 2016; **Accepted date:** June 24, 2016; **Published date:** July 1, 2016

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].

Study	Sample	Task	ERP	Effect	Sens/Spec	Interpretation
Preclinical studies						
Ally et al. [26]	FH (n=20)	Auditory oddball	P300	Reduced amplitude	_	Reduction in attentional control
				Increased latency	_	Delayed attentional/context processing
Green and Levy [27]	fAD (n=9)	Auditory oddball	P300	Increased latency	_	Delayed attentional/context processing
			N200	Increased latency	_	Delayed stimulus detection/response selection
	FH (n=8)		P300	Increased latency	_	Delayed attentional/context processing
Golob et al. [25]	pre-fAD (n=15)	Auditory oddball	N100	Increased latency	_	Delayed visual processing
			N200	Increased latency	87/64%	Delayed stimulus detection/response selection
			P200	Increased latency	_	Delayed auditory/memory processing
			P300	Increased latency	_	Delayed attentional/context processing
			Slow wave	Reduced amplitude	_	Reduction in attentional control
Bobes et al. [28]	pre-fAD (n=24)	Semantic categorisation	N400	Reduced generator strength	_	Long-term recognition memory deficit
Quiroz et al. [29]	pre-fAD (n=24)	Recognition memory	200-300 ms	Increased amplitude in occipital sites	73/82%	Over-reliance on occipital areas in memory tasks
Pietto et al. [82]	MCI-fAD (n=10)	STMBT	N1	Reduced amplitude	_	Reduced visual processing
			P200	Reduced amplitude	_	Delayed auditory/memory processing
Reduced visual processing						
Braverman and Blum [31]	SCD (n=189)	Auditory oddball	P300	Increased latency	_	Delayed attentional/context processing
Golob et al. [25]	MCI-AD converters (n=15)	Auditory oddball	N100	Increased amplitude	_	Delayed visual processing
			P300	Increased latency	_	Delayed attentional/context processing
			P50	Increased amplitude	_	Impaired inhibition/sensory gating
	MCI stable (n=16)		P50	Increased amplitude	_	Impaired inhibition/sensory gating
Bennys et al. [8]	MCI (n=20)	Auditory oddball	N200	Increased latency	90/70%	Delayed stimulus detection/response selection
			N300	Increased latency	80/73%	Delayed attentional/context processing
Parra et al. [75]	MCI (n=30)	Auditory oddball	P300	Increased latency	80/100%	Delayed attentional/context processing
Frodl et al. [7]	MCI	Auditory oddball	TB-P300	No effect	_	_

	(n=26)					
		Auditory oddball	TS-P300	No effect	_	_
Papaliagkas, Kimiskidis, Tsolaki and Anogianakis [83]	MCI (n=22)	Auditory oddball	N200	Increased latency	_	Delayed stimulus detection/response selection
			N200	Reduced amplitude	_	Reduced stimulus detection/response selection
			SW	Increased latency	_	Delayed stimulus evaluation
Papaliagkas et al. [106]	MCI (n = 91)	Auditory oddball	N200	Increased amplitude	_	Reduced stimulus detection/response selection
				Increased latency	_	Delayed stimulus detection/response selection
			P300	Increased latency	_	Delayed attentional/context processing
			SW	Increased latency	_	Delayed stimulus evaluation
Lai, Lin, Liou and Liu [107]	MCI (n=18)	Auditory oddball	P300	Increased latency	_	Delayed attentional/context processing
van Deursen et al. [108]	MCI (n=20)	Auditory oddball	P300	Increased latency	_	Delayed attentional/context processing
				Reduced amplitude	_	Reduction in attentional control
Gozke et al. [109]	MCI (n=20)	Visual Oddball	N200	Increased latency	_	Delayed stimulus detection/response selection
			P300	Increased latency	_	Delayed attentional/context processing
Olichney et al. [110]	MCI (n=14)	Semantic categorisation	N400	Reduced priming effect	_	Long-term recognition memory deficit
			P600	Reduced priming effect	_	Long-term recognition memory deficit
Galli et al. [111]	MCI (n=17)	Recognition memory	N400	Reduced priming effect	_	Long-term recognition memory deficit

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 with 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 offers 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 symptomology. 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 Face Name Associative 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 ERP's 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 enable 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 COGNISION®, 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 economic 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 invasive 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 over 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.

Acknowledgements

MAP work is supported by Alzheimer's Society (Grant # Grants AS-R42303 and AS-SF-14-008). MAP and RA are currently supported by FAPESP/University of Edinburgh Grant (FAPESP Grant # 2014/50203-8).

References

1. Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, et al. (2016) Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimers Dement 12: 292-323.
2. Olichney JM, Yang JC, Taylor J, Kutas M (2011) Cognitive event-related potentials: biomarkers of synaptic dysfunction across the stages of Alzheimer's disease. J Alzheimers Dis 26 Suppl 3: 215-228.
3. Cecchi M, Moore DK, Sadowsky CH, Solomon PR, Doraiswamy PM, et al. (2015) A clinical trial to validate event-related potential markers of Alzheimer's disease in outpatient settings. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 1: 387–394.
4. van Dinteren R, Arns M, Jongsma ML, Kessels RP (2014) P300 development across the lifespan: a systematic review and meta-analysis. PLoS One 9: e87347.
5. Polich J, Corey-Bloom J (2005) Alzheimer's disease and P300: review and evaluation of task and modality. Alzheimer Res 2: 515-525.
6. Polich J, Ladish C, Bloom FE (1990) P300 assessment of early Alzheimer's disease. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 77: 179–189.
7. Frodl T, Hampel H, Juckel G, Bürger K, Padberg F, et al. (2002) Value of event-related P300 subcomponents in the clinical diagnosis of mild cognitive impairment and Alzheimer's Disease. Psychophysiology 39: 175-181.
8. Bennys K, Portet F, Touchon J, Rondouin G (2007) Diagnostic value of event-related evoked potentials N200 and P300 subcomponents in early diagnosis of Alzheimer's disease and mild cognitive impairment. J Clin Neurophysiol 24: 405–412.
9. Yokoyama Y, Nakashima K, Shimoyama R, Urakami K, Takahashi K (1995) Distribution of event-related potentials in patients with dementia. Electromyogr Clin Neurophysiol 35: 431-437.
10. Goodin DS, Aminoff MJ (1986) Electrophysiological differences between subtypes of dementia. Brain 109: 1103-1113.
11. Ford JM, Woodward SH, Sullivan EV, Isaacks BG, Tinklenberg JR, et al. (1996) N400 evidence of abnormal responses to speech in Alzheimer's disease. Electroencephalogr Clin Neurophysiol 99: 235-246.
12. Olichney JM, Iragui VJ, Salmon DP, Riggins BR, Morris SK, et al. (2006) Absent event-related potential (ERP) word repetition effects in mild Alzheimer's disease. Clin Neurophysiol 117: 1319–1330.
13. Iragui V, Kutas M, Salmon D (1996) Event-related brain potentials during semantic categorization in normal aging and senile dementia of the Alzheimer's type. Electroencephalogr Clin Neurophysiol 100: 392–406.

14. Schwartz TJ, Kutas M, Butters N, Paulsen JS, Salmon DP (1996) Electrophysiological insights into the nature of the semantic deficit in Alzheimer's disease. Neuropsychologia 34: 827-841.
15. Castañeda M, Ostrosky-Solis F, Pérez M, Bobes MA, Rangel LE (1997) ERP assessment of semantic memory in Alzheimer's disease. Int J Psychophysiol 27: 201-214.
16. Tendolkar I, Schoenfeld A, Golz G, Fernandez G, Kuhl KP, et al. (1999) Neural correlates of recognition memory with and without recollection in patients with Alzheimer's disease and healthy controls. Neuroscience Letters 263: 45–48.
17. Olichney JM, Riggins BR, Morris SK, Salmon DP, Kutas M (2002) Reduced effects of word repetition on the n400 and lpc event-related potentials are common in mild Alzheimers disease and mild cognitive impairment converters. Neurology, 58: A217–A218.
18. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, et al. (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7: 280-292.
19. Sperling RA, Karlawish J, Johnson KA (2013) Preclinical Alzheimer disease-the challenges ahead. Nat Rev Neurol 9: 54-58.
20. Petersen RC, Smith GE, Waring SC, Ivnik RJ, et al. (1999) Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56: 303-308.
21. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, et al. (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's and Dementia 7: 270–279
22. Tabert MH, Manly JJ, Liu X, Pelton GH, Rosenblum S, et al. (2006) Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. Archives of General Psychiatry 63: 916–24.
23. Schofield PW, Marder K, Dooneief G, Jacobs DM, Sano M, et al. (1997) Association of subjective memory complaints with subsequent cognitive decline in community-dwelling elderly individuals with baseline cognitive impairment. American Journal of Psychiatry 154: 609–615.
24. Wang L, Van Belle G, Crane PK, Kukull WA, Bowen JD, et al. (2004) Subjective memory deterioration and future dementia in people aged 65 and older. Journal of the American Geriatrics Society 52: 2045–2051.
25. Golob EJ, Ringman JM, Irimajiri R, Bright S, Schaffer B, et al. (2009) Cortical event-related potentials in preclinical familial Alzheimer disease. Neurology, 73: 1649–1655.
26. Ally BA, Jones GE, Cole JA, Budson AE (2006) The P300 component in patients with Alzheimer's disease and their biological children. Biol Psychol 72: 180-187.
27. Green J, Levey AI (1999) Event-related potential changes in groups at increased risk for Alzheimer disease. Arch Neurol 56: 1398-1403.
28. Bobes MA, Garcí YF, Lopera F, Quiroz YT, Galán L, et al. (2010) ERP generator anomalies in presymptomatic carriers of the alzheimer's disease E280A PS-1 mutation. Human Brain Mapping 31: 247–265.
29. Quiroz YT, Ally BA, Celone K, McKeever J, Ruiz-Rizzo AL, et al. (2011) Event-Related potential markers of brain changes in preclinical familial Alzheimer disease. Neurology 77: 469–475.
30. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, et al. (2014) A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement 10: 844-852.
31. Braverman ER, Blum K (2003) P300 (latency) event-related potential: an accurate predictor of memory impairment. Clin Electroencephalogr 34: 124-139.
32. Gironell A, García-Sánchez C, Estévez-González A, Boltes A, Kulisevsky J (2005) Usefulness of p300 in subjective memory complaints: a prospective study. J Clin Neurophysiol 22: 279-284.
33. Parra MA, Ascencio LL, Urquina HF, Manes F, Ibáñez AM (2012) P300 and neuropsychological assessment in mild cognitive impairment and Alzheimer dementia. Front Neurol 3: 172.
34. Howe AS, Bani-Fatemi A, De Luca V (2014) The clinical utility of the auditory P300 latency subcomponent event-related potential in preclinical diagnosis of patients with mild cognitive impairment and Alzheimer's disease. Brain and Cognition 86: 64–74.
35. Jiang S, Qu C, Wang F, Liu Y, Qiao Z, et al. (2015) Using event-related potential P300 as an electrophysiological marker for differential diagnosis and to predict the progression of mild cognitive impairment: a meta-analysis. Neurological Sciences 7: 1105-1112.
36. Golob EJ, Irimajiri R, Starr A (2007) Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia. Brain 130: 740-752.
37. Green DL, Payne L, Polikar R, Moberg PJ, Wolk DA, et al. (2015) P50: A candidate ERP biomarker of prodromal Alzheimer's disease. Brain Res 1624: 390-397.
38. Iragui VJ, Kutas M, Mitchiner MR, Hillyard SA (1993) Effects of aging on event-related brain potentials and reaction times in an auditory oddball task. Psychophysiology 30: 10-22.
39. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Kalayam B, Katz R, et al. (2007) Event-related potentials in an emotional go/no-go task and remission of geriatric depression. Neuroreport 18: 217-221.
40. Cooper JA, Sagar HJ, Tidswell P, Jordan N (1994) Slowed central processing in simple and go/no-go reaction time tasks in Parkinson's disease. Brain 117 : 517-529.
41. Jiménez-Escrig A, Fernandez-Lorente J, Herrero A, Baron M, Lousa M, et al. (2002). Event-related evoked potential p300 in frontotemporal dementia. Dementia and Geriatric Cognitive Disorders 13: 27–32.
42. Enoki H, Sanada S, Yoshinaga H, Oka E, Ohtahara S (1993) The effects of age on the N200 component of the auditory event-related potentials. Brain Res Cogn Brain Res 1: 161-167.
43. Polich J (1996) Meta-analysis of P300 normative aging studies. Psychophysiology 33: 334-353.
44. Kindermann SS, Kalayam B, Brown G G, Burdick KE, Alexopoulos GS, et al. (2000) Executive functions and P300 latency in elderly depressed patients and control subjects. The American Journal of Geriatric Psychiatry 8: 57–65.
45. Brown WS, Marsh JT, LaRue A (1982) Event-related potentials in psychiatry: differentiating depression and dementia in the elderly. Bulletin of the Los Angeles Neurological Societies 47: 91–107.
46. Patterson JV, Michalewski HJ, Starr A (1988) Latency variability of the components of auditory event-related potentials to infrequent stimuli in aging, Alzheimer-type dementia, and depression. Electroencephalography and Clinical Neurophysiology 71: 450–460.
47. Van Harten B, Laman DM, Van Duijn H, Knol DL, Stam CJ, et al. (2006) The auditory oddball paradigm in patients with vascular cognitive impairment: A prolonged latency of the N2 complex. Dementia and Geriatric Cognitive Disorders 21: 322–327.
48. Mansoor Y, Jastrzab L, Dutt S, Miller BL, Seeley WW, et al. (2015) Memory Profiles in Pathology or Biomarker Confirmed Alzheimer Disease and Frontotemporal Dementia.. Alzheimer Disease and Associated Disorders 29: 135-140.
49. McDermott LM, Ebmeier KP (2009) A meta-analysis of depression severity and cognitive function. J Affect Disord 119: 1-8.
50. Kutas M, Iragui V (1998) The N400 in a semantic categorization task across 6 decades. Electroencephalogr Clin Neurophysiol 108: 456-471.
51. Karayanidis F, Andrews S, Ward PB, McConaghy N (1993) Event-related potentials and repetition priming in young, middle-aged and elderly normal subjects. Brain Res Cogn Brain Res 1: 123-134.
52. Minamoto H, Tachibana H, Sugita M, Okita T (2001) Recognition memory in normal aging and Parkinson's disease: Behavioral and electrophysiologic measures. Cognitive Brain Research 11: 23–32.

53. Tachibana H, Miyata Y, Takeda M, Sugita M, Okita T (1999) Event-related potentials reveal memory deficits in Parkinson's disease. Cognitive Brain Research 8: 165–172.
54. Logie RH, Parra MA, Della SS (2015) From Cognitive Science to Dementia Assessment. Policy Insights from the Behavioral and Brain Sciences 2: 81–91.
55. Rentz DM, Parra Rodriguez MA, Amariglio R, Stern Y, Sperling R, et al. (2013) Promising developments in neuropsychological approaches for the detection of preclinical Alzheimer's disease: a selective review. Alzheimer's Research & Therapy 5: 58.
56. Rentz DM, Amariglio RE, Becker JA, Frey M, Olson LE, et al. (2011) Face-name associative memory performance is related to amyloid burden in normal elderly. Neuropsychologia 49: 2776-2783.
57. MacKenzie G, Donaldson DI (2009) Examining the neural basis of episodic memory: ERP evidence that faces are recollected differently from names. Neuropsychologia 47: 2756–2765.
58. Guo C, Voss JL, Paller KA (2005). Electrophysiological correlates of forming memories for faces, names, and face-name associations. Cognitive Brain Research 22: 153–164.
59. Stark SM, Yassa MA, Stark CEL (2010) Individual differences in spatial pattern separation performance associated with healthy aging in humans. Learning & Memory 17: 284–288.
60. Morcom AM (2015) Resisting false recognition: An ERP study of lure discrimination. Brain Res 1624: 336-348.
61. Didic M, Barbeau EJ, Felician O, Tramoni E, Guedj E, et al. (2011) Which memory system is impaired first in Alzheimer's disease? J Alzheimers Dis 27: 11-22.
62. Yang X, Goh A, Chen SH, Qiu A (2013) Evolution of hippocampal shapes across the human lifespan. Hum Brain Mapp 34: 3075-3085.
63. Qin S, Rijpkema M, Tendolkar I, Piekema C, Hermans EJ, et al. (2009) Dissecting medial temporal lobe contributions to item and associative memory formation. Neuroimage 46: 874-881.
64. Staresina BP, Davachi L (2010) Object unitization and associative memory formation are supported by distinct brain regions. J Neurosci 30: 9890-9897.
65. Mayes A, Montaldi D, Migo E (2007) Associative memory and the medial temporal lobes. Trends Cogn Sci 11: 126-135.
66. de Jager CA, Milwain E, Budge M (2002) Early detection of isolated memory deficits in the elderly: the need for more sensitive neuropsychological tests. Psychological Medicine 32: 483–491.
67. De Jager C, Blackwell AD, Budge MM, Sahakian BJ (2005) Predicting cognitive decline in healthy older adults. Am J Geriatr Psychiatry 13: 735-740.
68. Naveh-Benjamin M, Guez J, Kilb A, Reedy S (2004) The associative memory deficit of older adults: further support using face-name associations. Psychology and Aging 19: 541–546.
69. Naveh-Benjamin M, Hussain Z, Guez J, Bar-On M (2003) Adult age differences in episodic memory: further support for an associative-deficit hypothesis. Journal of Experimental Psychology: Learning, Memory, and Cognition 29: 826–837.
70. Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, et al. (1998) MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. In American Journal of Neuroradiology 19: 659–671
71. Zhou M, Zhang F, Zhao L, Qian J, Dong C (2016) Entorhinal cortex: a good biomarker of mild cognitive impairment and mild Alzheimer's disease. Rev Neurosci 27: 185-195.
72. Juottonen K, Laakso MP, Insausti R, Lehtovirta M, Pitkänen A, et al. (1998) Volumes of the entorhinal and perirhinal cortices in Alzheimer's disease. Neurobiol Aging 19: 15-22.
73. Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82: 239-259.
74. Braak H, Thal DR, Ghebremedhin E, Del Tredici K (2011) Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol 70: 960-969.
75. Parra MA, Abrahams S, Logie RH, Méndez LG, Lopera F, et al. (2010) Visual short-term memory binding deficits in familial Alzheimer's disease. Brain 133: 2702-2713.
76. Fleisher AS, Chen K, Quiroz YT, Jakimovich LJ, Gomez MG, et al. (2012) Florbetapir PET analysis of amyloid-Î² deposition in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: a cross-sectional study. Lancet Neurol 11: 1057-1065.
77. Parra MA, Abrahams S, Fabi K, Logie R, Luzzi S, et al. (2009) Short-term memory binding deficits in Alzheimer's disease. Brain 132: 1057-1066.
78. Koppara A, Frommann I, Polcher A, Parra MA, Maier W, et al. (2015) Feature Binding Deficits in Subjective Cognitive Decline and in Mild Cognitive Impairment. Journal of Alzheimer's Disease 48: S161–70.
79. Brockmole JR, Parra MA, Della SS, Logie RH (2008) Do binding deficits account for age-related decline in visual working memory? Psychon Bull Rev 15: 543-547.
80. Parra MA, Abrahams S, Logie RH, Della Sala S (2010) Visual short-term memory binding in Alzheimer's disease and depression. J Neurol 257: 1160-1169.
81. Della SS, Parra MA, Fabi K, Luzzi S, Abrahams S (2012) Short-term memory binding is impaired in AD but not in non-AD dementias. Neuropsychologia 50: 833-840.
82. Pietto M, Parra MA, Trujillo N, Flores F, Garcia AM, et al. (2016) Behavioral and electrophysiological correlates of memory binding deficits in patients at different risk levels for Alzheimer's disease. Journal of Alzheimer's Disease.
83. Papaliagkas VT, Kimiskidis VK, Tsolaki MN, Anogianakis G (2011) Cognitive event-related potentials: Longitudinal changes in mild cognitive impairment. Clinical Neurophysiology 122: 1322–1326.
84. Olichney JM, Taylor JR, Gatherwright J, Salmon DP, Bressler AJ, et al. (2008) Patients with MCI and N400 or P600 abnormalities are at very high risk for conversion to dementia. Neurology 70: 1763-1770.
85. Missonnier P, Gold G, Fazio-Costa L, Michel JP, Mulligan R, et al. (2005) Early event-related potential changes during working memory activation predict rapid decline in mild cognitive impairment. J Gerontol A Biol Sci Med Sci 60: 660–6.
86. Papaliagkas VTT, Anogianakis G, Tsolaki MNN, Koliakos G, Kimiskidis VKK (2010) Combination of P300 and CSF ß-Amyloid(1-42) Assays May Provide a Potential Tool in the Early Diagnosis of Alzheimers Disease. Curr Alzheimer Res 7: 295–299.
87. Papaliagkas VT, Anogianakis G, Tsolaki MN, Koliakos G, Kimiskidis VK (2009) Progression of mild cognitive impairment to Alzheimer's disease: improved diagnostic value of the combined use of N200 latency and beta-amyloid(1-42) levels. Dement Geriatr Cogn Disord 28: 30-35.
88. Diniz BSO, Pinto Júnior JA, Forlenza OV (2008) Do CSF total tau, phosphorylated tau, and beta-amyloid 42 help to predict progression of mild cognitive impairment to Alzheimer's disease? A systematic review and meta-analysis of the literature. World J Biol Psychiatry 9: 172–82.
89. Saletu B, Paulus E, Linzmayer L, Anderer P, Semlitsch HV, et al. (1995) Nicergoline in senile dementia of alzheimer type and multi-infarct dementia: a double-blind, placebo-controlled, clinical and EEG/ERP mapping study. Psychopharmacology 117: 385–395.
90. Thomas A, Iacono D, Bonanni L, Andreamatteo GD, Onofrj M (2001) Donepezil, rivastigmine, and vitamin E in Alzheimer disease: a combined P300 event-related potentials/neuropsychologic evaluation over 6 months. Clinical Neuropharmacology 24: 31–42.
91. Onofrj M, Thomas A, Luciano AL, Iacono D, Di Rollo A, et al. (2002) Donepezil versus vitamin E in Alzheimer's disease: Part 2: mild versus moderate-severe Alzheimer's disease. Clinical Neuropharmacology 25: 207–215.
92. KubovÃ¡ Z, KremlÃ¡Äek J, ValiÅ¡ M, Szanyi J, LangrovÃ¡ J, et al. (2010) Effect of memantine in Alzheimer's disease evaluated by visual-evoked potentials to pattern-reversal, motion-onset, and cognitive stimuli. J Clin Neurophysiol 27: 334-340.
93. Stam CJ, Jones BF, Manshanden I, van Cappellen van Walsum AM, Montez T, et al. (2006) Magnetoencephalographic evaluation of resting-

state functional connectivity in Alzheimer's disease. NeuroImage 32: 1335–1344.

94. Miraglia F, Vecchio F, Bramanti P, Rossini PM (2016) EEG characteristics in "eyes-open" versus "eyes-closed" conditions: Small-world network architecture in healthy aging and age-related brain degeneration. Clinical Neurophysiology 127: 1261–8.
95. Supekar K, Menon V, Rubin D, Musen M, Greicius MD (2008) Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. PLoS Comput Biol 4: e1000100.
96. Engels MM, Stam CJ, van der Flier WM, Scheltens P, de Waal H et al. (2015) Declining functional connectivity and changing hub locations in Alzheimer's disease: an EEG study. BMC Neurol 15: 145.
97. Jelic V, Kowalski J (2009) Evidence-based evaluation of diagnostic accuracy of resting EEG in dementia and mild cognitive impairment. Clin EEG Neurosci 40: 129–142.
98. Jackson CE, Snyder PJ (2008) Electroencephalography and event-related potentials as biomarkers of mild cognitive impairment and mild Alzheimer's disease. Alzheimers Dement 4: S137-143.
99. Ibanez A, Parra MA (2014) Mapping memory binding onto the connectome's temporal dynamics: toward a combined biomarker for Alzheimer's disease. Front Hum Neurosci 8: 237.
100. Smith K, Azami H, Parra MA, Starr JM, Escudero J (2015) Cluster-span threshold: An unbiased threshold for binarising weighted complete networks in functional connectivity analysis. Annual International Conference of the IEEE Engineering in Medicine and Biology Society 2840–3.
101. Smith K, Azami H, Escudero J, Parra MA, Starr JM (2015) Comparison of network analysis approaches on EEG connectivity in beta during Visual Short-term Memory binding tasks. Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2207–10.
102. Lau TM, Gwin JT, Ferris DP (2012) How Many Electrodes Are Really Needed for EEG-Based Mobile Brain Imaging? Journal of Behavioral and Brain Science 02: 387–393.
103. Trambaiolli LR, Lorena AC, Fraga FJ, Kanda PA, Anghinah R, et al. (2011) Improving Alzheimer's disease diagnosis with machine learning techniques. Clin EEG Neurosci 42: 160-165.
104. Lehmann C, Koenig T, Jelic V, Prichep L, John RE, et al. (2007) Application and comparison of classification algorithms for recognition of Alzheimer's disease in electrical brain activity (EEG). J Neurosci Methods 161: 342-350.
105. Sperling R, Johnson K (2013) Biomarkers of Alzheimer disease: current and future applications to diagnostic criteria. Continuum (Minneap Minn) 19: 325-338.
106. Papaliagkas V, Kimiskidis V, Tsolaki M, Anogianakis G (2008) Usefulness of event-related potentials in the assessment of mild cognitive impairment. BMC Neurosci 9: 107.
107. Lai CLC, Lin RTR, Liou LML, Liu CKC (2010) The role of event-related potentials in cognitive decline in Alzheimer's disease. Clinical Neurophysiology 121: 194–199.
108. van Deursen JA, Vuurman EF, Smits LL, Verhey FR, Riedel WJ (2009) Response speed, contingent negative variation and P300 in Alzheimer's disease and MCI. Brain Cogn 69: 592-599.
109. Gozke E, Tomrukcu S, Erdal N (2013) Visual Event-Related Potentials in Patients with Mild Cognitive Impairment. International Journal of Gerontology.
110. Olichney JM, Morris SK, Ochoa C, Salmon DP, Thal LJ, et al. (2002) Abnormal verbal event related potentials in mild cognitive impairment and incipient Alzheimer's disease. Journal of Neurology, Neurosurgery, and Psychiatry 73: 377–384.
111. Galli G, Ragazzoni A, Viggiano MP (2010) Atypical event-related potentials in patients with mild cognitive impairment: An identification-priming study. Alzheimers Dement 6: 351-358.
112. Babiloni C, Triggiani AI, Lizio R, Cordone S, Tattoli G, et al. (2016) Classification of Single Normal and Alzheimer's Disease Individuals from Cortical Sources of Resting State EEG Rhythms. Front Neurosci 10: 47.
113. Schroeter ML, Stein T, Maslowski N, Neumann J (2009) Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. Neuroimage 47: 1196-1206.
114. Richiardi J, Achard S, Bunke H, Van De Ville D (2013) Machine learning with brain graphs: Predictive modeling approaches for functional imaging in systems neuroscience. IEEE Signal Processing Magazine 30: 58–70.