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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

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ABSTRACT

The present meta-analysis investigated the clinical utility of the auditory P300 latency event-related potential in differentiating patients with Alzheimer's disease (AD), patients with mild cognitive impairment (MCI), and unaffected controls. Effect size estimates were computed from mean P300 latency measurements at midline electrodes between patients and unaffected controls using the random effects restricted maximum likelihood model. The effects of clinical and ERP/EEG methological variables were assessed in a moderator analysis. P300 latency was found to be significantly prolonged in patients with AD (and MCI) compared to unaffected controls. Shortened P300 latencies were observed when comparing patients with MCI to patients with AD. Clinically relevant differences in P300 latency effect sizes were associated with mean age, interstimulus interval, stimulus difference, target frequency, reference electrode, and sampling rate. The meta-analytic findings provide robust statistical evidence for the use of the auditory P300 latency subcomponent as a biological marker of prodromal AD.

1. Introduction

The cognitive deterioration seen in Alzheimer's disease (AD) pathology has been characterized by the P300 event-related potential for the past 35 years. The first report to suggest and provide evidence of the clinical utility of the auditory P300 latency subcomponent in dementia was Goodin, Squires, and Starr (1978). During this time, event-related potentials were considered as a specific and sensitive measure of afferent function in neurologic patients. The NINCDS–ADRDA working group also commented on the use of event-related potentials for diagnosis of Alzheimer's disease in research settings (McKhann et al., 1984). However, the current view of the P300 waveform for clinical and diagnostic use of AD in research settings has drastically changed over the past 35 years. Since initial reports (Blackwood, St Clair, Blackburn, & Tyrer, 1987; Brown, Marsh, & LaRue, 1982; Goodin, Squires, Starr, et al., 1978; Goodin, Starr, Chippendale, & Squires, 1983; Ortiz, Martin Loeches, Miguel, Abdad, & Puente, 1994; Patterson, Michalewski, & Starr, 1988; Pfefferbaum, Wenegrat, Ford, Roth, & Kopell, 1984; Slaets & Fortgens, 1984; St Clair, Blackwood, & Christie, 1985), there has been an accumulation of ERP studies reporting non-significant differences between patients and unaffected controls (Ashford, Coburn, Rose, & Bayley, 2011; Boller et al., 2002; Caravaglios, Costanzo, Palermo, & Muscoso, 2008; Gironell, García-Sánchez, Estévez-González, Boltes, & Kulisevsky, 2005; Gungor et al., 2005; Juckel et al., 2008; Lai, Lin, Liou, & Liu, 2010; Lee et al., 2013; Van Deursen, Vuurman, Smits, Veryhey, & Riedel, 2009), and large variability in P300 measurement between AD patients (Ally, Jones, Cole, & Budson, 2006; Boller et al., 2002; Gironell et al., 2005; Hirata et al., 2000; Holt et al., 1995; Mochizuki, Oishi, & Takasu, 2001; Taguchi et al., 2003; Williams, Jones, Briscoe, Thomas, & Cronin, 1991; Yamaguchi, Tsuchiya, Yamagata, Toyoda, & Kobayashi, 2000). In addition, the use of ERPs as a clinical research biomarker in diagnosis of AD was not addressed in the recent publication of the NINCDS–ADRDA guidelines for clinical diagnosis of AD (McKhann et al., 2011). Therefore, a quantitative analysis is needed to amalgamate the literature, and provide an increased sample size to draw stronger inferences on the effectiveness of using auditory P300 latency measurements in clinical research settings (Goodin, 1986).

The auditory P300 ERP appears when the patient is unexpectedly presented with an incongruent stimulus (or target stimulus) during a stimulus discrimination task (Pfefferbaum, Ford, Wenegrat, Roth, & Kopell, 1984; Pfefferbaum, Wenegrat, et al., 1984; Polich, 2007). This task generally requires the patient to actively

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attend to the stimuli to produce a time-locked deflection that is associated with cognitive processing in the brain (Donchin, 1987). The deflection to the incongruent stimulus is subsequently measured by single/multi channel electrode analysis (Donchin, 1987; Picton & Hillyard, 1974, Picton, Stuss, Champagne, & Nelson, 1984). The most commonly used stimulus discrimination task is the auditory oddball. The conventional two-tone auditory oddball task requires the patient to identify the infrequent high pitch tones (target stimulus) while ignoring the frequent low pitch tones (standard stimulus) (Donchin, 1987; Pfefferbaum, Ford, et al., 1984; Pfefferbaum, Wenegrat, et al., 1984; Picton & Hillyard, 1974; Picton et al., 1984; Polich, 2007). Generally, the target stimulus is presented 20% of the time, while the standard stimulus is presented 80% of the time (Polich, 2007). The P300 component is a large positive ERP deflection that occurs ~300–500 ms post-stimulus (Goodin et al., 1983; Polich, 2007). The P300 component is commonly elicited by the two-tone auditory oddball task and measured at the Pz electrode where it has been shown to produce the strongest P300 differences between patients and unaffected controls (Kakigi, Neshige, Matsuda, & Kuroda, 1994; Polich, Ehlers, Otis, Mandell, & Bloom, 1986). The P300 wave is analyzed by the size of the deflection (amplitude) and the time elapsed post-stimulus before activation (latency). However, the P300 latency is the most common aspect of the P300 wave analyzed in studies of dementia and cognitive decline. P300 latency is thought to reflect post-stimulus information processing (Goodin, Squires, Starr, et al., 1978; Pfefferbaum, Ford, et al., 1984; Pfefferbaum, Wenegrat, et al., 1984; Polich, 2007) and executive function (memory, attention, integration of complex stimuli) (Bennys, Portet, Touchon, & Rondouin, 2007; Donchin, 1987; Johnson, Pfefferbaum, & Kopell, 1985). The P300 wave has also been classified into two subcomponents known as P3a and P3b, but the relationship of the P3a to the P300 wave has not been fully elucidated (Polich, 2007; Squires, Squires, & Hillyard, 1975; Squires, Wickens, Squires, & Donchin, 1976). P3a appears to reflect orientation to an incongruent stimulus while P3b reflects the discrimination of a congruent and incongruent tone (Polich, 2007).

Prolongation of the P300 latency has been hypothesized to be associated with the subtle, but progressive cognitive decline seen in AD (Lee et al., 2013). However, the major issue affecting the validity of the P300 latency as a clinical assay of preclinical AD is the variability in sensitivity and specificity for patients with AD (Bennys et al., 2007; Juckel et al., 2008). The sensitivity and specificity of P300 latency measurements in AD has been shown to range from 20% to 95% in the literature when compared to other dementias, mild cognitive impairment (MCI), and unaffected controls (Bennys et al., 2007; Brown, Marsh, & LaRue, 1983; Filipovic & Kostic, 1995; Gironell et al., 2005; Goodin & Aminoff, 1986; Goodin, Squires, Starr, et al., 1978; Gordon, Kraiuhin, Harris, Meares, & Howson, 1986; Hanafusa, Motomura, & Fukai, 1991; Ito, Yamao, Fukuda, Mimori, & Nakamura, 1990; Kraiuhin et al., 1990; Neshige, Barrett, & Shibasaki, 1988; Patterson et al., 1988; Pfefferbaum, Wenegrat, et al., 1984; Polich et al., 1986; Sumi, Nan'no, Fujimoto, Ohta, & Takeda, 2000; Swanwick et al., 1996; Syndulko et al., 1982; Tachibana, Kawabata, Takeda, & Sugita, 1993; Takeda et al., 2005). However, recent clinical ERP studies with more sophisticated approaches (dipole source analysis, topographical maps) have reported improved sensitivity (>80%) and specificity (>80%) compared to the conventional single/multi channel ERP averaging (AD compared to unaffected controls) (Bonanni et al., 2010; Frodl et al., 2002; Juckel et al., 2008). It is also important to note that most of the earlier reports did not differentiate between P3a and P3b latencies. In some studies, the P3a latency was more prolonged than the P3b latency in patients with AD (Ford et al., 1997; Goodin, Squires, Henderson, & Starr, 1978; Juckel et al., 2008; Pfefferbaum, Wenegrat, et al., 1984).

Numerous clinical ERP studies have reported significant P300 latency differences between patients with AD and unaffected controls. More specifically, patients with AD exhibit a prolongation of the P300 latency compared to age-matched unaffected controls. P300 latency has also been reported to be associated with several clinical variables in AD: family history of AD/genetic mutations (APOE) (Ally et al., 2006; Golob et al., 2009; Irimajiri, Golob, & Starr, 2010), cholinesterase inhibitors (Ally et al., 2006; Golob & Starr, 2000; Katada, Sato, Ojika, & Ueda, 2004; Onofrj et al., 2002; Reeves, Struve, Patrick, Booker, & Nave, 1999; Thomas, Iacono, Bonanni, D'Andreamatteo, & Onofrj, 2001; Werber, Klein, & Rabey, 2001), language and acoustic-motor ability (Blackwood et al., 1987), attention (Boller et al., 2002; Neshige et al., 1988; Picton & Hillyard, 1974), severity of cognitive deficits (Ball, Marsh, Schubarth, Brown, & Strandburg, 1989; Gungor et al., 2005; Lai et al., 2010; Lee et al., 2013; Pfefferbaum, Wenegrat, et al., 1984; Pokryszko-Dragan, Sfoltwinski, & Podemski, 2003; Polich & Pitzer, 1999; Polich et al., 1986; Syndulko et al., 1982; Szelies, Mielke, Grond, & Heiss, 1995; Tanaka, Kachi, Yamada, & Sobue, 1998; Van Deursen et al., 2009; Wright, Scott, Richardson, Rai, & Exton-Smith, 1988), delayed motor response (Kraiuhin et al., 1990; Van Deursen et al., 2009; Williams et al., 1991), CSF concentrations of monoamines (5-HIAA) (Ito et al., 1990) and neurotransmitters (Mochizuki et al., 2001), hypometabolism in parietal lobe (Marsh et al., 1990; Szelies et al., 1995) executive function (Lee et al., 2013), decreased cerebral blood flow (precuneus, frontal lobe) (Gungor et al., 2005). However, some studies have disconfirming evidence for these associations: memory (Blackwood et al., 1987; Boller et al., 2002), attention (Pfefferbaum, Wenegrat, et al., 1984), decreased cerebral blood flow (Mochizuki et al., 2001), age (Muscoso et al., 2006), severity of early stage cognitive deficits (Muscoso et al., 2006), differentiating subcortical and cortical dementias (Tachibana et al., 1993; Tachibana et al., 1996). Some studies have also suggested that P300 latency prolongation may be linked to neurodegeneration of cortical areas in the temporo-parietal lobe (Frodl et al., 2002; Gungor et al., 2005; Jiménez-Escrig et al., 2002; Juckel et al., 2012; Muscoso et al., 2006).

Recently, the NINCA-ADRAS working group has suggested that accumulated amyloid-β deposition begins the pathophysiological process and cognitive/behavioral deficits are further implicated as a result of this accumulation (Sperling et al., 2011). According to this criteria, the early cognitive deficits observed in patients are more likely to be indicative of the later asymptomatic AD phase (Sperling et al., 2011). Therefore, studying pathophysiological differences in patients with MCI may provide an effective model of the later stages of prodromal AD (Albert et al., 2011). There has been a few clinical auditory ERP studies investigating the P300 latency in patients with MCI compared to unaffected controls (Bennys, Rondouin, Benattar, Gabelle, & Touchon, 2011; Bennys et al., 2007; Frodl et al., 2002; Gironell et al., 2005; Golob, Irimajiri, & Starr, 2007; Golob, Johnson, & Starr, 2002; Lai et al., 2010; Medvidovic, Titlic, & Maras-Simunic, 2013; Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2008, 2010, 2011; Van Deursen et al., 2009) and to patients with AD (Bennys et al., 2007; Frodl et al., 2002; Gironell et al., 2005; Lai et al., 2010; Van Deursen et al., 2009). Most of these studies have reported longer prolongations of the P300 latency in patients with MCI compared to unaffected controls, and shortened P300 latencies when compared to patients with AD. However. quantifying these results for support of ERPs as useful clinical assays still remains to be a question that has not been fully answered (Bennys et al., 2011; Juckel et al., 2012).

Therefore, a quantitative meta-analysis is required to ascertain the potential of the P300 latency as an accurate assay of the cognitive dysfunction observed in the late preclinical stages of AD (Polich & Corey-Bloom, 2005). The primary goal of the present