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P50: A candidate ERP biomarker of prodromal Alzheimer's disease

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ABSTRACT

Introduction: Reductions of cerebrospinal fluid (CSF) amyloid-beta (Aβ42) and elevated phosphorylated-tau (p-Tau) reflect in vivo Alzheimer's disease (AD) pathology and show utility in predicting conversion from mild cognitive impairment (MCI) to dementia. We investigated the P50 event-related potential component as a noninvasive biomarker of AD pathology in non-demented elderly.

Methods: 36 MCI patients were stratified into amyloid positive (MCI-AD, $n=17$) and negative (MCI-Other, $n=19$) groups using CSF levels of Aβ42. All amyloid positive patients were also p-Tau positive. P50s were elicited with an auditory oddball paradigm.

Results: MCI-AD patients yielded larger P50s than MCI-Other. The best amyloid-status predictor model showed 94.7% sensitivity, 94.1% specificity and 94.4% total accuracy.

Discussion: P50 predicted amyloid status in MCI patients, thereby showing a relationship with AD pathology versus MCI from another etiology. The P50 may have clinical utility for inexpensive pre-screening and assessment of Alzheimer's pathology.

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1. Introduction

Cerebrospinal fluid (CSF) levels of amyloid-beta (Aβ42) and phosphorylated tau (p-Tau) are thought to reflect in vivo Alzheimer's disease (AD) pathology and have shown promise for identifying patients early in the disease course prior to the onset of dementia. Reductions in CSF Aβ42 correspond with the presence of amyloid plaques in the brain, with CSF levels

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approximately 50% lower in AD patients than in controls (Blennow et al., 2015). MCI patients also show AD-like reductions in CSF Aβ42, with baseline levels predicting conversion to AD dementia almost 5 years later (Hertze et al., 2010).

In contrast to CSF biomarkers, measurement of event-related potentials (ERP) is noninvasive, inexpensive, and more widely available. ERPs can reveal abnormalities in brain activity that reflect underlying disease-related changes in the brain. Abnormal ERPs have been documented in AD patients and in patients with mild cognitive impairment (MCI) (Goodin et al., 1978). In particular, recent studies have shown that the P50 differentiates mild AD patients from age-matched controls, and may have utility in predicting MCI conversion to dementia (Golob et al., 2002, 2007).

The P50 is a positive-going wave peaking approximately 50 ms after the onset of an auditory stimulus. It is produced in primary and secondary auditory cortices, though its amplitude is modulated by frontal brain regions and is typically maximal at the vertex electrode (Korzyukov et al., 2007). P50 amplitude is influenced primarily by exogenous factors, such as the physical features of a stimulus, rather than by endogenous cognitive factors, such as expectations and evaluation of the environment (Picton et al., 1974). P50 amplitude also reflects the inhibition of irrelevant or distracting stimuli, a process known as *sensory gating* when taking place at an early sensory stage of processing (Boutros and Belger, 1999).

One standard technique for investigating the filtering out of task-irrelevant information is the *oddball paradigm* in which participants are asked to identify infrequent targets embedded in a series of frequently occurring distractor stimuli (Golob et al., 2007). Successful inhibition of irrelevant information, indicating normal cognitive functioning, is reflected by larger amplitude responses to targets relative to distractors. Individuals with a large P50 response to distractors show impaired inhibition.

Using an oddball paradigm, Golob and Starr (2000) found larger P50 amplitude in response to distractors in mild-AD patients relative to age-matched controls. More recently, the M50, the magnetic counterpart of the P50, was found to be larger in mild-AD patients relative to young and older controls (Cheng et al., 2012). Methodological differences complicate comparison across studies; however, studies that failed to show significantly larger P50 amplitudes in AD patients relative to those from age-matched controls have included a more severe cohort in the mild-to-moderate AD range (e.g., MMSE=13.2±5.4) (Golob et al., 2007) than in the very mild range (e.g, MMSE=23±0.9)(Cheng et al., 2012; Golob and Starr, 2000). In contrast, P50 latency has been comparable between clinical groups and age-matched controls (Cheng et al., 2012; Golob and Starr, 2000; Golob et al., 2007; Irimajiri et al., 2005, 2010) in all but one study that found longer latencies in MCI patients and a correlation between larger amplitude and longer latency P50 response to distractor tones (Golob et al., 2002).

P50 amplitude increases with normal aging (Amenedo and Díaz, 1999; Azumi et al., 1995; Golob et al., 2007), but greater amplitude increase is observed in MCI patients relative to age-matched controls (Golob et al., 2002, 2007; Irimajiri et al., 2005). Amnestic MCI patients with deficits in multiple cognitive domains, who have the highest risk of conversion to AD, show larger P50 amplitudes than single-domain amnestic MCI (Golob et al., 2007). In small samples, MCI to AD converters have also shown baseline P50 amplitudes greater than their stable counterparts (Golob et al., 2002, 2007).

Overall, the literature suggests that P50 amplitude first increases during early stage AD and then decreases back to relatively normal levels with disease progression, possibly because the disease first attacks inhibitory mechanisms that restrain the P50 and only later does it impair the sensory cortical areas primarily responsible for generating the P50, consistent with the progression of underlying AD neuropathology (Arnold et al., 1991; Golubic et al., 2014). While this relationship between P50 and disease severity would be problematic for using P50 in differential diagnosis, when amplitudes may be going up or coming down and indistinguishable from controls, it may have utility as a prescreening tool during prodromal and asymptomatic stages, when inhibitory mechanisms, but not the neural generators of P50, are compromised.

2. Results

2.1. Demographic and clinical comparisons

The MCI-AD and MCI-Other groups were comparable in age, $t(34)=1.09$, $p=0.49$, and gender, $\chi^2(1, 36)=0.34$, $p=0.56$ (Table 1). The MCI-AD group was more highly educated than the MCI-Other group, $U(36)=246.00$, $p<0.01$. The MCI-AD group was comprised mostly of Non-Latino Caucasians whereas the MCI-Other group was largely split between Non-Latino Caucasians and self-identified, Multiracial Latinos, χ^2 (3, 36)=10.53, $p=0.02$.

Clinically, the groups did not differ in symptom severity as measured by the MMSE, $U(36)=143.50$, $p=0.57$, $r=0.09$. The

Table 1 – Demographic and clinical information.

	MCI-AD	MCI-Other
N	19	17
M/F	5/14	6/11
Age *M*(*SD*)	70.95 (6.72)	68.09 (8.93)
Age symptom onset *M*(*SD*)	66.58 (6.64)	65.44 (8.18)
Symptom duration *Mdn* (range) years *	3 (1–13)	2 (1–8)
Education *Mdn* (range) years *	16 (11–20)	12 (4–18)
MMSE *M* (*SD*)	25.89 (2.81)	26.41 (2.83)

* $p<0.05$.