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The P300 component in patients with Alzheimer's disease and their biological children

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Abstract

Objective: There are few studies examining P300 in the biological children of patients with Alzheimer's disease (AD). In addition to examining P300 in patients with AD, the current study examined the utility of P300 as a preclinical marker in the offspring of AD patients.
Methods: P300 was elicited from an AD group, their biological children, and two age- and gender-matched control groups using the auditory oddball paradigm. Each group consisted of 20 subjects each. ERPs recorded from sites Fz, Cz, and Pz were analysed using analysis of variance.
Results: Amplitudes were significantly smaller in the AD group when compared to controls. Both amplitude and latency values in the FH+ group were significantly impaired when compared to its control group.
Conclusion: These findings replicate previous P300 amplitude abnormalities found in patients with AD. Further, participants with a family history of AD demonstrate possible preclinical evidence at the electrophysiological level. Comparisons with other findings and theoretical implications are discussed.

Keywords: Event-related potential; P300; Alzheimer's disease; Risk for AD

1. Introduction

Alzheimer's disease (AD) is a progressive form of dementia affecting parts of the brain that control memory, language, and executive abilities, and is, currently, the most commonly diagnosed form of dementia. AD is becoming highly prevalent in the increasingly aged population of the United States. Because of the devastating impact of AD on patients and caregivers' lives, and on the infrastructure of the healthcare system, the clinical characteristics, pathology, and risk factors associated with this disease have received well-deserved attention over the last 25 years. Finding preclinical markers and additional risk factors of AD can, prospectively, lead to a more accurate identification of individuals who will ultimately develop the disease, allowing treatments to be initiated earlier. Early treatment will become increasingly more important as disease modifying therapies that are now in clinical trials become available. The subsequent treatment of these individuals can help reduce the near $ 100 billion annual cost to care for patients with AD, prolonging their independence and allowing them to live in the home for longer periods of time (Solomon and Budson, 2003).

Studies have shown that individuals with AD show altered cortical activity (spontaneous and elicited brainwaves) when compared to age-matched peers undergoing healthy aging (Holschneider and Leuchter, 1995). More specifically, systematic changes have been noted in various cortical event-related potentials with the development of Alzheimer's disease (Polich et al., 1990). One of the more commonly explored neurophysiological measures in AD assessment has been the auditory P300 event-related potential (ERP). P300 is a cognitive event-related potential with a distinct amplitude and latency. It is widely speculated that P300 amplitude is an index of brain processes elicited from tasks required in the

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maintenance of working memory (Donchin, 1981; Donchin and Coles, 1988). Research investigating ERPs and mnemonic processes has demonstrated that larger P300 amplitudes are associated with greater memory performance in normal participants (Fabiani et al., 1990; Noldy et al., 1990). Earlier investigations indicated that P300 amplitude is proportional to the amount of attentional resources that is employed in a given task (Kramer and Strayer, 1988; Polich, 1987b). This led Polich and Kok (1995) to suggest that P300 ''can be considered as a manifestation of CNS activity involved with the processing of new information when attention is engaged to update memory representations.'' Early evidence revealed that P300 amplitudes are disrupted during the dementing processes (Goodin et al., 1978; Polich et al., 1990). A plausible explanation for these P300 abnormalities that accompany AD is that P300 has neural generators in the temporoparietal cortex (Frodl-Bauch et al., 1999; Yamaguchi and Knight, 1991), an area that is known to have significant synaptic loss in AD. Early PET studies reveal that individuals with mild AD are characterized by metabolic declines in the temporoparietal association neocortex (Benson et al., 1983; Frackowiak et al., 1981).

Investigations involving P300 latency suggest that shorter latency times are related to greater cognitive performance, particularly on neuropsychological tests that assess the speed at which participants allocate and maintain attentional resources (Polich and Kok, 1995). This interpretation appears consistent with the finding that P300 latency times increase systematically as cognitive capability decreases in individuals with dementing illnesses (Brown et al., 1982; Homberg et al., 1986; O'Donnell et al., 1987; Polich et al., 1986). However, due to variable findings in latency differences, the clinical utility of P300 in the assessment of dementia is not yet clear (Polich and Herbst, 2000). One possibility for these variable findings may reflect evidence linking P300 with the chemicals in the brain discovered to be diminished in AD. It has been postulated that acetylcholine, whether alone or in combination with serotonin, produces a modulating effect on the long-latency component (Frodl-Bauch et al., 1999; Meador et al., 1989, 1995). Werber et al. (2003) hypothesize that the limbic system is involved in P300 generation, reflecting activity associated with attention and encoding information into working memory. The authors completed a study examining the effects of cholinesterase inhibitors on P300 in patients with dementia (Werber et al., 2003). It was found that after taking cholinesterase inhibitors for 26 weeks, patients with AD demonstrated significantly faster P300 latency times than at baseline, suggesting cognitive improvement when taking the drug. P300 amplitudes in the AD patients were not significantly affected by cholinesterase inhibitors (Werber et al., 2003). Drugs that modulate the cholinergic system improve attention (Perry et al., 1999), leading Werber and colleagues to suggest that the shortened latency times found after 26 weeks reflect a cholinesterase inhibitor-induced improvement in attention.

There is very little data on electrophysiological changes in individuals at higher risk for AD because of a direct genetic link to someone with the disease. It has been estimated that the cumulative risk in first-degree relatives ranges from 23 to 67% (Martin et al., 1988; Sadovnick et al., 1989), making the identification of such individuals critically important. In one of two studies involving subjects at relatively high risk for AD, Boutros et al. (1995) found that a ''definite at risk'' group (parent identified through autopsy) had P300 peak amplitudes that were twice as large at electrode sites more parietal and centrally located on the head (sites Pz and Cz) than control participants. P300 latency times did not differ between groups. Boutros et al. (1995) hypothesized that P300 amplitudes may be increased in the definite at risk participants because this reflects a compensatory mechanism (enhanced neuronal excitability) of an ''as yet non-debilitated cognitive system''.

Green and Levey (1999) used a methodologically different paradigm to elicit the N2 and P3 components in patients with a family history of the disease. In addition, the authors further subdivided groups based on apolipoprotein E [epsilon] 4-allele status. They found that participants with a family history of the disease had no neuropsychological deficits, but demonstrated delayed P300 latency times when compared with age and gender-matched controls, but showed no amplitude differences. The APOE 4 + group with a family history of the disease did not differ from the APOE 4 − group. Green and Levey reported that their findings support the mounting evidence that there is a 'pre-clinical' phase of AD that may manifest in early electrophysiological changes, and encouraged more research using P300 and N200.

Identification of the individuals who may eventually develop Alzheimer's disease is needed in order to initiate disease-modifying therapy when it becomes available, perhaps even preventing this disease at some point in the future. Electrophysiological measures have the potential to contribute to a growing list of risk factors such as APOE 4, or early preclinical markers such as extensive cognitive testing. The overarching aim of the current study is to evaluate the utility of P300 as a preclinical marker in the adult biological children of patients with AD who are not currently demonstrating cognitive deficits. The current study also intends to replicate findings of abnormal P300 amplitude and latency times in patients with AD when compared to age and gender-matched controls (Polich et al., 1990). Finally, we hope that this investigation can elucidate the conflicting findings reported by Boutros et al. (1995) and Green and Levey (1999).

2. Methods

2.1. Participants

Eighty community-dwelling participants were recruited for one of four experimental groups: an Alzheimer's disease group (AD), an age- and gender-matched healthy older adult control group (older controls), a first generation AD offspring group (positive family history, FH+), and an age- and gender-matched control group for the FH+ group (no family history, FH−). The FH+ group was recruited in pairs with their parents, establishing a true genetic link between AD patient and their offspring. Families were recruited to only participate as AD patient/adult child pairs, and to control for cumulative risk, FH+ participants had only one parent diagnosed with the disease.

Each of the four groups contained 20 participants. The AD group, which was recruited by local neurology services, contained individuals with both an NINCDS-ADRDA diagnosis of AD, and an MMSE (Mini Mental State

Examination, Folstein et al., 1975) score between 16 and 26. Age ranged from 64 to 87 years (mean of 76.20; S.D. = 5.34). There were 11 female and 9 male AD patients, with MMSE scores ranging from 18 to 25 (mean = 21.65; S.D. = 2.11). Participants in the AD control group (older controls) ranged in age from 61 to 89 with a mean of 75.35 (S.D. = 6.02) years. There were 9 females and 11 males, with MMSE scores ranging from 28 to 30 (mean = 28.65; S.D. = .81). The FH+ group was composed of 20 asymptomatic healthy adults ranging in age from 41 to 62 years (mean = 54.35 years; S.D. = 4.75) and composed of 13 females and 7 males, with MMSE scores ranging from 29 to 30 (mean = 29.77; S.D. = .74). Finally, FH− group was composed of healthy adults ranging in age from 39 to 63 years of age, with a mean age of 53.85 (S.D. = 5.70). There were 13 females and 7 males, all with MMSE scores of 30. Each participant in the study read and signed IRB approved consent forms before participating.

A complete interview of all participants was conducted to screen for individuals with a history of psychiatric or neurological disorders (e.g., Parkinson's disease, depression, schizophrenia, bipolar disorder, multiple sclerosis), or past cerebrovascular accidents or transient ischemic attacks. Screening for excessive alcohol and current use of psychotropic medications was also completed prior to laboratory assessment. Participants with a significant psychiatric history or diagnosed neurological disease, and those taking narcotics, benzodiazepines, or neuroleptic medications were also excluded from the study due to the possible effect of these conditions on the P300 waveform. The MMSE assessment of control participants was completed immediately preceding the laboratory session.

2.2. Stimuli and procedures

ERPs were recorded from three electrode sites located frontally, centrally, and parietally on the head (electrode sites Fz, Cz, and Pz of the International 10–20 system of electrode placement). The scalp was lightly abraded and Grass Instruments silver cup EEG electrodes were attached to the head. Electrodes were referenced to linked mastoid EEG electrodes. Electrode–skin impedances were held below 5 kΩ. Silver/silver chloride Sensormedics mini-biopotential electrodes were placed above each participant's left eyebrow, and directly below the left eye to record the EOG. Any oddball trial with EOG artifact activity +/−75 μV was excluded from the participant's average.

The auditory oddball task included presentation of a series of standard and target tones. Each tone was presented at 80 db SPL above subject threshold for 50 milliseconds (ms), and had rise and fall times of 5 ms. Standard tones were presented at a frequency of 1000 Hz, while 'odd-ball' target stimulus tones were presented at a frequency of 2000 Hz. Standard and target tones were presented in a predetermined quasi-random order such that no two target tones occurred consecutively, and each subject was presented with the same sequence of tones. Eighty five percent of the tones were standard tones and 15% were target (oddball) tones. The inter-stimulus interval was approximately 1.5 s. Participants were asked to keep a mental running count of how many target tones were presented to ensure proper attention to the task. The first 40 artifact-free responses to the target tones were used in each participant's grand average. Each oddball stimulus started a new sampling epoch. EEG data was collected over an 850 ms sampling epoch (100 ms pre-stimulus plus 750 ms post-stimulus), and was digitized by a Keithley Metrabyte laboratory interface board within a PC. The A/D board maintained a sampling rate of 100 samples/s. EEG was recorded using Grass Instruments 7P511J wideband AC pre-amplifiers, with a frequency bandwidth of .3–30 Hz (−6 db octave). EOG was recorded with a Grass 7P5B Wide Band AC preamplifier. The A/D process, all presentation of stimuli, and all data collection were programmed in Visual Basic 4.0 and Keithley Metrabyte VTX.

2.3. P300 identification

Pre-tone EEG activity was sampled for 100 ms immediately prior to the onset of each target tone, and was averaged to zero center all sampling epochs. This pre-stimulus average was then subtracted from each data point in the subsequent sampling epoch (750 ms duration). The baseline-adjusted data points were, then, averaged over the 40 target tone sampling epochs for each subject, producing the subject grand average. P300 identification was completed blind to the participants' group. The amplitude of P300 was defined as the greatest positive voltage measured from baseline, occurring between 300 and 650 ms post stimulus onset. The latency of P300 at each of the electrode sites was defined as the time from stimulus onset to the point of maximum positive amplitude occurring between 300 and 650 ms post stimulus onset. Amplitude and latency data was recorded and stored for each electrode site individually.

3. Results

Event-related potential data were analyzed using analysis of variance (ANOVA). When appropriate, the Greenhouse-Geisser correction was used to control for sphericity. When the correction is used, the adjusted p value is reported. Fifteen of the 20 AD participants reported mental counts of the target tones within 90% accuracy. Of the remaining 5 participants, 3 reported mental counts greater or less than 10 targets from the true number of target tones. A Pearson's correlation between MMSE score and target tone accuracy was performed. MMSE score was significantly correlated with target tone accuracy [$r = .226$ ($p = .044$)]. The implications of this will be discussed below. In the other three groups, all participants reported mental counts within 90% of the true number of total target tones. Figs. 1 through 6 show the group grand averaged event-related potentials in microvolts at each electrode site.

3.1. P300 amplitude

A 4 (Group) × 3 (Site) analysis of variance (ANOVA) with repeated measures on the second factor (Site) was performed on the P300 amplitude data, followed by a Tukey's Honestly Significant Difference (H.S.D.) analysis. Inspection of the amplitude data revealed a significant main effect of Group [$F(3, 76) = 9.878$, $p = .001$], and a significant Group × Site interaction [$F(6, 152) = 3.284$, $p = .009$]. See Table 1 for group P300 amplitude means and standard deviations.

A test of simple main effects of Group revealed that the Alzheimer's disease (AD) group displayed significantly smaller P300 peak amplitudes than the older control group [$F(1, 38) = 7.611$, $p = .009$]. Notably, 16 of the 20 AD participants (80%) had P300 peak amplitudes that were at least one standard

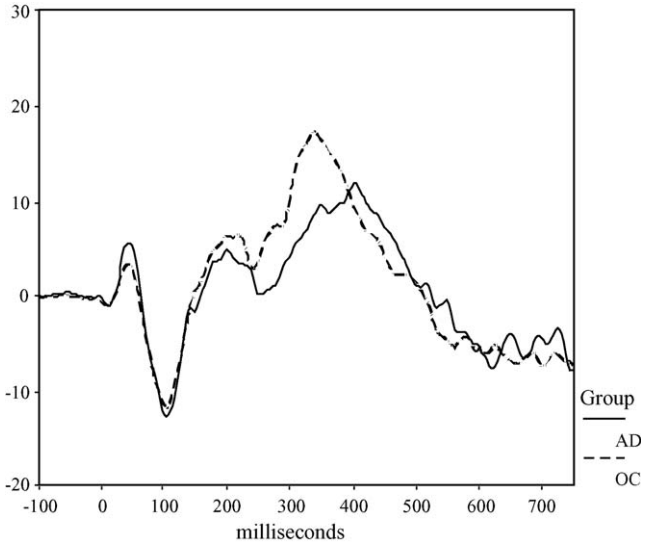

Fig. 1. ERP waveforms for the AD and older control groups at Site Fz.

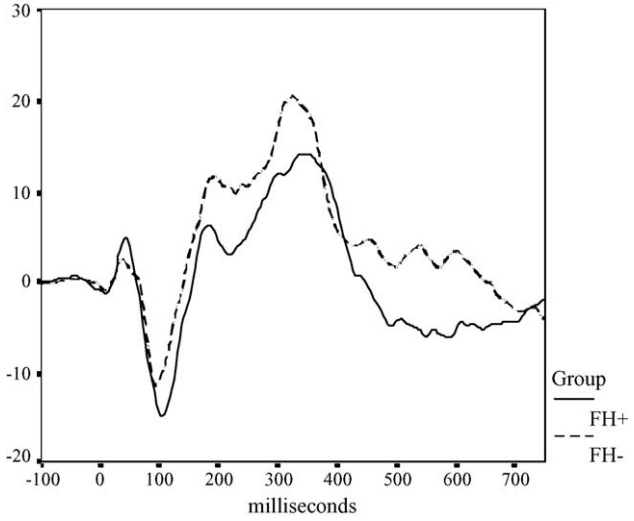

Fig. 2. ERP waveforms for the FH+ and FH− groups at Site Fz.

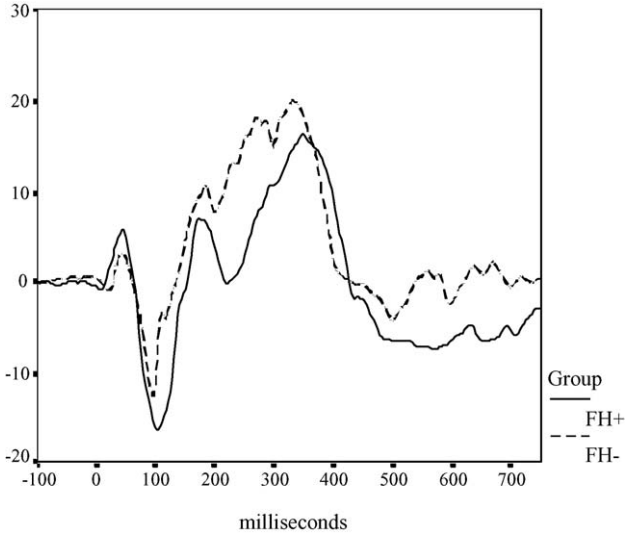

Fig. 4. ERP waveforms for the FH+ and FH− groups at Site Cz.

deviation from the older control group mean. The AD group also demonstrated smaller P300 peak amplitudes than the positive family history group (FH+) [$F(1, 38) = 5.871$, $p = .020$] and the younger control group (FH−) [$F(1, 38) = 26.732$, $p = .001$]. Interestingly, the older control group did not differ significantly from the FH+ group [$F(1, 38) = .081$, $p = .777$], but did differ significantly from the FH− group [$F(1, 38) = 7.777$, $p = .008$], indicating that the younger 'at risk' FH+ group demonstrated similar P300 amplitude responses as the older control group, 21 years their elder. Finally, the FH+ group mean was significantly smaller when compared to its control group, FH− [$F(1, 38) = 8.768$, $p = .005$]. Eleven of the 20 FH+ group members (55%) showed P300 peak amplitudes that were at least one standard deviation from the control group mean.

In addition to the significant main effect of Group, there was significant Group × Site interaction. A Tukey's HSD analysis was performed on the P300 amplitude data for all groups. Initial inspection of the data began at Site Pz. The AD group produced significantly smaller P300 peak amplitudes than the older control group ($p = .01$), the FH+ group ($p < .01$), and the FH− group ($p < .01$). Also, the older control group showed smaller peak amplitudes than the FH+ group ($p < .01$) and the FH+ showed significantly smaller peak amplitudes than the FH− group ($p = .047$). At Site Cz, the AD group showed smaller peak amplitudes than the older control group ($p = .02$), the FH+ group ($p = .02$), and the FH− group ($p < .01$). The older control group also demonstrated smaller peak amplitude than the FH− group ($p = .046$), and the FH+ showed smaller peak amplitudes than the FH− group ($p = .045$). Finally, at Site Fz, the AD group showed smaller peak amplitude than the older control group ($p = .037$) and the FH− group ($p < .01$), and the FH+ group demonstrated smaller peak amplitudes than the FH− group ($p = .013$).

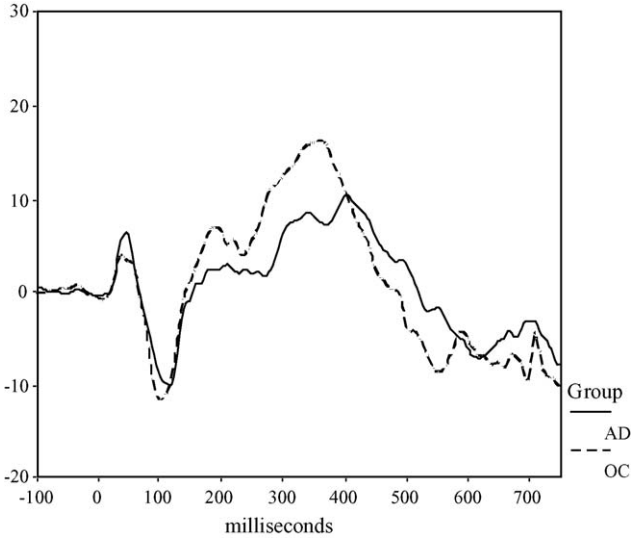

Fig. 3. ERP waveforms for the AD and older control groups at Site Cz.

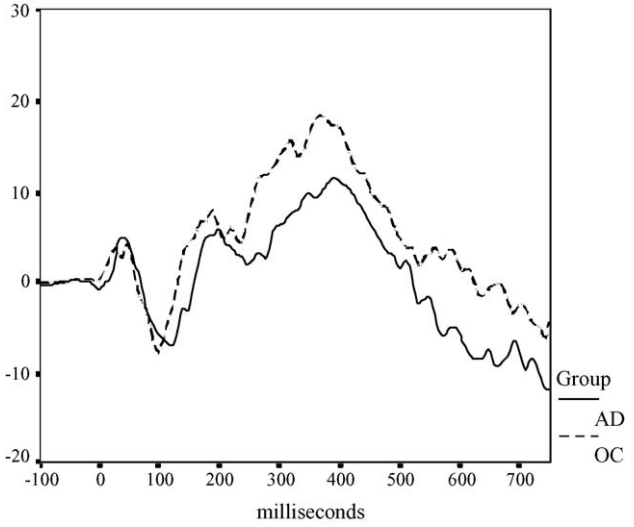

Fig. 5. ERP waveforms for the AD and older control groups at Site Pz.

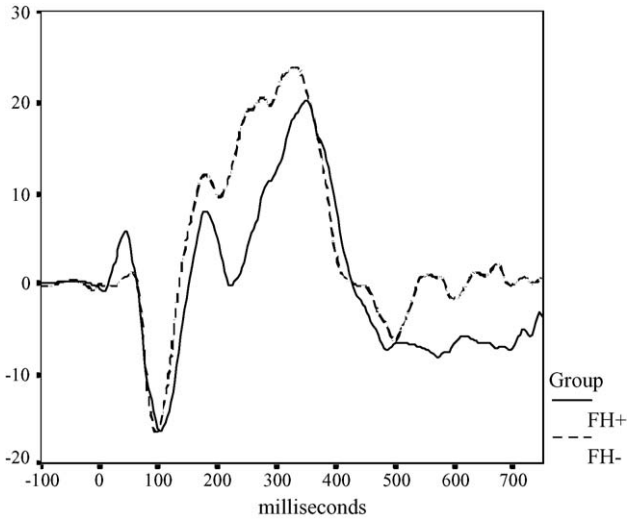

Fig. 6. ERP waveforms for the FH+ and FH− groups at Site Pz.

Table 1
P300 peak amplitude means and standard deviations for all groups (microvolts)

	Fz		Cz		Pz	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
AD	11.87	9.01	10.39	9.74	11.48	8.14
OC	17.28	6.62	16.28	8.93	18.47	6.69
FH+	14.01	7.64	16.27	6.97	20.03	9.01
FH−	20.43	9.23	21.24	5.88	24.67	7.54

3.2. P300 latency

As with the amplitude data, a 4 (Group) × 3 (Site) ANOVA with repeated measures on Site was performed on the P300 latency data. The analysis included a test of simple main effects of Group. Inspection of the latency data revealed a significant main effect of Group [$F(3, 76) = 9.446$, $p = .001$]. There was no significant Group × Site interaction [$F(6, 152) = 1.111$, $p = .359$]. See Table 2 for group latency means and standard deviations.

The analysis showed that the AD group produced significantly longer P300 latency times than the FH+ group [$F(1, 38) = 8.688$, $p = .005$] and the FH− group [$F(1, 38) = 16.729$, $p = .000$]. The AD group only demonstrated a trend towards longer latency times when compared to the older control group [$F(1, 38) = 3.148$, $p = .084$]. Only 4 of the 20 AD participants (20%) showed P300 latency times at least one standard deviation from the older control group mean. The older control group in turn demonstrated significantly longer latency times than the FH+ group [$F(1, 38) = 4.067$, $p = .051$] and the FH− group [$F(1, 38) = 18.727$, $p = .001$]. Perhaps the most interesting finding pertaining to the latency data, the FH+ group demonstrated significantly longer P300 latency times when compared to the FH− group [$F(1, 38) = 10.075$, $p = .003$]. Eight of the 20 FH+ group participants (40%) showed P300 latency times that were at least one standard deviation from the control group mean.

Table 2
P300 latency means and standard deviations for all groups (milliseconds)

	Fz		Cz		Pz	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
AD	404.5	79.3	399.5	82.4	395.0	80.6
OC	363.0	55.5	368.5	59.7	369.0	24.4
FH+	344.0	23.0	346.0	24.8	355.0	35.0
FH−	342.5	33.2	323.5	15.3	323.0	20.6

4. Discussion

The current investigation examined the event-related potential P300 in individuals with Alzheimer's disease and their adult biological children. The overarching aim of the study was to determine the utility of P300 as a preclinical marker in individuals with a family history of AD. In addition to investigating individuals at risk for the disease, the current study attempted to substantiate previous findings of smaller P300 amplitudes and delayed P300 latency times in patients with AD (Polich et al., 1990). The results of our investigation suggest that P300 peak amplitudes are significantly smaller in patients with Alzheimer's disease when compared to an age- and gender-matched control group. Eighty percent (80%) of the AD participants were identified as having P300 peak amplitudes that were at least one standard deviation smaller than their controls.

However, our results showed that the majority of AD participants did not display P300 latency times that were significantly different or delayed from to their age- and gender-matched controls, only approaching significance as a group. Twenty percent (20%) of patients with AD had P300 latency times that were greater than one standard deviation from the control group mean. Although amplitudes were found to be significantly smaller, the lack of significant latency findings may reflect the impact of cholinesterase inhibitors on P300 and cognitive performance (Werber et al., 2003). Eighteen of the 20 participants with AD in the current study were taking a cholinesterase inhibitor (15 of the patients were taking donepezil and 3 were taking galantamine). It was beyond the scope of this investigation to determine the exact impact of cholinesterase inhibitors on P300 performance, and for ethical reasons patients were not asked to halt the use of their medication for the purposes of this study. Although there has been clear evidence of cholinesterase inhibitors affecting event-related potential waveforms, particularly P300, this relationship needs further investigation (Onofrj et al., 2003; Werber et al., 2003).

One possible explanation of the significance of cholinesterase inhibitors in the current study may reflect the contributions of the medial temporal lobe and the temporoparietal association cortex in generating a P300 response. Research has suggested that structures such as the diagonal band of Broca and the medial septal nuclei in the medial temporal lobe provide a major cholinergic input to the hippocampus and to the neocortex via the nucleus basalis of Meynart (Frodl-Bauch

et al., 1999). These medial temporal structures, using acetylcholine as the primary neurotransmitter, may initiate the P300 and signal the temporoparietal association cortex. The neurons in the temporoparietal association cortex may then produce the actual response. Because patients with AD have pathology in two these regions, P300 studies of these patients who are not taking cholinesterase inhibitors have found both prolonged latencies and diminished amplitudes. As discussed above however, cholinesterase inhibitors may correct the latency of P300 without affecting amplitude. Additional studies using patients with AD who are and are not taking cholinesterase inhibitors are needed to confirm this hypothesis.

Newer to the literature is the examination of whether P300 peak amplitudes and latency times of the biological adult children of patients with AD differ from an age- and gender-matched control group. Results of this study found that P300 amplitudes for the biological adult children (FH+) group were significantly smaller than their age- and gender-matched controls. Fifty-five percent (55%) of the FH+ group demonstrated significantly smaller P300 peak amplitudes that fell beyond one standard deviation from the control group mean. Our results differ from both those of Green and Levey (1999), who found latency but not amplitude differences, and those of Boutros et al. (1995), who found that children of autopsy-identified AD patients displayed significantly *larger* P300 amplitudes compared to age-matched controls. Boutros et al. suggested that their results reflected a compensatory mechanism (enhanced neuronal excitability) of an 'as yet non-debilitated cognitive system'. Possible reasons for the differing results between our study and that of Boutros et al. may be attributable to methodological differences between the two studies. Boutros et al. presented stimuli to participants at a greater volume than the current investigation, which could be eliciting a different response. The current study presented tones at 80 db SPL where as Boutros and colleagues presented tones at 95 db SPL, possibly eliciting a startle response.

Reliable differences were also found in P300 latency times in the FH+ group and their controls, which supports previous findings of prolonged latencies in participants with a family history of AD (Green and Levey, 1999). Forty percent (40%) of the FH+ group was identified as having P300 latency times that were one standard deviation slower than their controls. The results of the latency data support those found by Green and Levey in 1999, and given Polich's assertion that P300 latency times can be used as a ''motor-free measure of cognitive function'' (Polich, 2004), these participants may have preclinical levels of cognitive dysfunction evident at the neurophysiological level. Although participants in the FH+ group appeared to have no cognitive deficits as measured by the MMSE, perhaps more sophisticated and in-depth neuropsychological testing would have identified subtle differences on measures associated with P300 latency, such as attention and working memory. The exact relevance of this finding is unclear at the present time. Further, it must be taken into account that for the most part, the FH+ group had parents in the 70–80-year-old range. Estimates of prevalence of AD suggest that the rate nearly triples when individuals reach the age of 85. Some of the participants in the FH+ may have a second parent develop AD in the coming years, increasing their cumulative risk. It has been estimated that the cumulative risk in first-degree relatives with one parent with AD ranges from 23 to 67% (Martin et al., 1988; Sadovnick et al., 1989), which is generally consistent with the percentage of at risk individuals in the current study identified as having P300 peak amplitude and latency values that were one standard deviation from the control group mean. Following these participants longitudinally would be ideal in identifying which of the participants with a family history of the disease and abnormal P300 responses ultimately develop the disease. The long-latency potential may be able to help researchers understand and identify the disrupted neurophysiological processes associated with the development of the disease or with increased risk. Research is currently focusing on changes in P300 amplitude and latency times due to the loss of certain chemicals in the brain associated with AD, such as acetylcholine. At some point in the future, perhaps ERP abnormalities will be identified as a preclinical marker of AD. Taken together, our results and the studies of Boutros et al. (1995) and Green and Levey (1999) reveal disruption in P300 amplitude and latency in the biological children of patients with AD, supporting a possible pre-clinical phase of the disease more than 20 years prior to its clinical presentation.

As briefly mentioned above, another interesting finding of this study is that the FH+ group demonstrated similar P300 amplitudes to the older control group. That is, P300 amplitude in participants with a family history of AD and a mean age of 54 is comparable to participants with a mean age of 75 and no family history of the disease. This similarity in P300 amplitude may lead one to draw the hypothesis that participants with a family history of AD are prematurely aging, however additional studies are needed to completely examine this relationship.

The present data also provide several interesting observations in scoring and interpretation. Consistent with the literature, P300 peak amplitude and latency values for each subject in this study were calculated by identifying the most positive voltage peak occurring in the grand average between 300 and 600 ms. The range of scored latency values in the current study ranged from 310 to 580 ms for individual participants. However, when reviewing individual grand averages, problems were quickly encountered when identifying P300 in 5 of the 20 AD participants. Although there were clear early ERP components in these participants, the exact peak of the P300 was unclear because the waveform formed a relatively straight line with small and apparently random peaks and valleys during the scoring interval. In contrast, the vast majority of the AD participants demonstrated clearly evident P300 responses somewhere between 300 and 600 ms. For the five AD participants that P300 was difficult to identify, the determination of the P300 peak was far more arbitrary. This scoring problem brings up a variation of a common debate in the literature: Does a P300 exist in all patients with Alzheimer's disease? It is possible the P300 does not exist in response to novel stimuli in some individuals with AD as suggested by Kraiuhin et al. (1990) and Phillips et al. (1997). Support for this concern is strengthened by the data variance, which was

substantially larger in the AD group than the other groups. A close examination of the data reveals that potentially the most debilitated patients with AD do not show a clear P300. The 3 participants with inaccurate mental counts of the target tones greater or less than 10 from the total number of target tones were included in the group of 5 participants with lack of clear identifiable P300s, and all had MMSE scores below 22. Perhaps, as suggested by Jocoy et al. (1998), P300 in these participants was nonexistent due to inattention. After the completion of all standard analyses, the P300 data were re-analyzed excluding the 5 AD participants with P300 that were difficult to define. The ANOVA comparing the AD group and older control group collapsed across Site showed that the fundamental pattern of the amplitude results did not change [$F(1, 38) = 5.870$, $p = .021$].

In conclusion, the present study suggests that the amplitude, but not the latency, of the cognitive event-related potential P300 differs between patients with AD who are taking cholinesterase inhibitors and healthy older control participants. The most important finding of the current investigation, however, suggests that P300 may identify preclinical changes in participants who are at relatively high risk for the disease because of genetic predisposition. P300 is associated with attention and working memory processes, particularly in tasks of sustained attention demanding vigilance (Portin et al., 2000). Recent research involving patients with AD, also link alterations in acetylcholine with impaired attention and working memory processes (Bohnen et al., 2005; Cummings, 2000). The results of the current investigation may suggest possible early 'precursor' changes in these cognitive abilities for biological children of patients with AD. These at risk participants with abnormal P300 amplitude and latency times may not yet show deficits in cognitive abilities measured by the MMSE. Clinical evidence of the disease may first be evident in very mild deficits in sustained attention and vigilance, leading to future memory impairment. Perhaps future investigations can identify subtle neuropsychological underpinnings of P300 associated with attention and working memory in participants at risk for AD.

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References

Benson, D.F., Kuhl, D.E., Hawkins, R.A., Phelps, M.E., Cummings, J.L., Tsai, S.Y., 1983. The fluorodeoxyglucose 18F scan in Alzheimer's disease and multi-infarct dementia. Archives of Neurology 40 (12), 711–714.

Bohnen, N.I., Kaufer, D.I., Hendrickson, R., Ivanco, L.S., Lopresti, B., Davis, J.G., Constantine, G., Mathis, C.A., Moore, R.Y., DeKosky, S.T., 2005. Cognitive correlates of alterations in acetylcholinesterase in Alzheimer's disease. Neuroscience Letters 380, 127–132.

Boutros, N., Torello, M.W., Burns, E.M., Wu, S., Nasrallah, H.A., 1995. Evoked potentials in participants at risk for Alzheimer's Disease. Psychiatry Research 57, 57–63.

Brown, W.S., Marsh, J.T., LaRue, A., 1982. Event-related potentials in psychiatry: differentiating depression and dementia in the elderly. Bulletin of the Los Angeles Neurological Society 47, 91–107.

Cummings, J.L., 2000. Cholinesterase inhibitors: a new class of psychotropic compounds. American Journal of Psychiatry 157, 4–15.

Donchin, E., 1981. Surprise! ... Surprise? Psychophysiology 18, 493–513.

Donchin, E., Coles, M.G.H., 1988. Is the P300 component a manifestation of context updating? Behavioral and Brain Sciences II, 357–374.

Fabiani, M., Karis, D., Donchin, E., 1990. Effects of mneumonic strategy manipulation in a von Restorff paradigm. Electroencephalography and Clinical Neurophysiology 75, 22–35.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-Mental State: A practical method for grading the state of patients for the clinician. Journal of Psychiatric Research 72, 189–198.

Frackowiak, R.S., Pozzilli, C., Legg, N.J., Du Boulay, G.H., Marshall, J., Lenzi, G.L., Jones, T., 1981. Regional cerebral oxygen supply and utilization in dementia. A clinical and physiological study with oxygen-15 and positron tomography. Brain 104 (4), 753–778.

Frodl-Bauch, T., Bottlender, R., Hegerl, U., 1999. Neurochemical substrates and neuroanatomical generators of the event-related P300. Neuropsychobiology 40, 86–94.

Goodin, D.S., Squires, K.C., Starr, A., 1978. Long latency event related components of the auditory evoked potential in dementia. Brain 101, 635–648.

Green, J., Levey, A., 1999. Event-related potential changes in groups at increased risk for Alzheimer's Disease. Archives of Neurology 56, 1398–1403.

Holschneider, D.P., Leuchter, A.F., 1995. Beta activity in aging and dementia. Brain Topography 8 (2), 169–180.

Homberg, V., Hefter, H., Granseyer, G., Strauss, W., Lange, H., Hennerici, M., 1986. Event-related potentials in patients with Huntington's disease and relatives at risk in relation to detailed psychometry. Electroencephalography and Clinical Neurophysiology 63, 552–569.

Jocoy, E.L., Arruda, J.E., Estes, K.M., Yagi, Y., Coburn, K.L., 1998. Concurrent visual task effects on evoked and emitted auditory P300 in adolescents. International Journal of Psychophysiology 30 (3), 319–328.

Kraiuhin, C., Gordon, E., Coyle, S., Sara, G., Rennie, C., Howson, A., Landau, P., Meares, R., 1990. Normal latency of the P300 event-related potential in mild-to-moderate Alzheimer's disease and depression. Biological Psychiatry 28, 372–386.

Kramer, A.F., Strayer, D.L., 1988. Assessing the development of automatic processing: an application of dual-track and event-related brain potential methodologies. Biological Psychology 26, 231–267.

Martin, R.L., Gerteis, G., Gabrielli Jr., W.F., 1988. A family-genetic study of dementia of Alzheimer type. Archives of General Psychiatry 45 (10), 894–900.

Meador, K.J., Loring, D.W., Davis, H.C., Patel, B.R., Adams, R.J., Hammond, E.J., 1989. Cholinergic and serotoninergic effects on the P3 potential and recent memory. Journal of Clinical and Experimental Neuropsychology 11, 252–260.

Meador, K.J., Loring, D.W., Hendrix, N., Nichols, M.E., Oberzan, R., Moore, E.E., 1995. Synergistic anticholinergic and antiserotoninergic effects in humans. Journal of Clinical and Experimental Neuropsychology 71 (4), 611–621.

Noldy, N., Stelmack, R., Campbell, K., 1990. Event-related potentials and recognition memory for pictures and words: the effects of intentional and incidental learning. Psychophysiology 27, 417–428.

O'Donnell, B.F., Squires, N.K., Martz, M.J., Chen, J.R., Phay, A., 1987. Evoked potential changes and neuropsychological performance in Parkinson's disease. Biological Psychology 24, 23–37.

Onofrj, M., Thomas, A., Iacono, D., Luciano, A.L., Di Iorio, A., 2003. The effects of a cholinesterase inhibitor are prominent in patients with fluctuating cognition: a part 3 study of the main mechanism of cholinesterase inhibitors in dementia. Clinical Neuropharmacology 26 (5), 239–251.

Perry, E., Walker, M., Grace, J., Perry, R., 1999. Acetylcholine in mind: a neurotransmitter correlate of consciousness? Trends in Neuroscience 22 (6), 273–280.

Phillips, N.A., Connolly, J.F., Mate-Kole, C.C., Gray, J., 1997. Individual differences in auditory middle latency responses in elderly adults and patients with Alzheimer's disease. International Journal of Psychophysiology 27, 125–136.

Polich, J., 2004. Clinical application of the P300 event-related brain potential. Physical Medicine and Rehabilitation Clinics of North America 15 (1), 133–161.

Polich, J., 1987b. Task difficulty, probability and inter-stimulus interval as determinants of P300 from auditory stimuli. Electroencephalography and Clinical Neurophysiology 68, 311–320.

Polich, J., Ehlers, C.L., Otis, S., Mandell, A.J., Bloom, F.E., 1986. P300 latency reflects the degree of cognitive decline in dementing illness. Electroencephalography and Clinical Neurophysiology 63 (2), 138–144.

Polich, J., Herbst, L.K., 2000. P300 as a clinical assay: rationale, evaluation, and findings. International Journal of Psychophysiology 38 (1), 3–19.

Polich, J., Ladish, C., Bloom, F.E., 1990. P300 assessment of early Alzheimer's disease. Electroencephalography and Clinical Neurophysiology 77, 179–189.

Polich, J., Kok, A., 1995. Cognitive and biological determinants of P300: an integrative review. Biological Psychology 41, 103–146.

Portin, R., Kovala, T., Polo-Kantola, P., Revonsuo, A., Muller, K., Matikainen, E., 2000. Does P3 reflect attentional or memory performances, or cognition more generally? Scandinavian Journal of Psychology 41, 31–40.

Sadovnick, A.D., Irwin, M.E., Baird, P.A., Beattie, B.L., 1989. Genetic studies on an Alzheimer clinic population. Genetic Epidemiology 6 (5), 633–643.

Solomon, P.R., Budson, A.E., 2003. Alzheimer's Disease. Clinical Symposia 54, 1–44.

Werber, E.A., Gandelman-Marton, R., Klein, C., Rabey, J.M., 2003. The clinical use of P300 event-related potentials for the evaluation of cholinesterase inhibitors treatment in demented patients. Journal of Neural Transmission 110, 659–669.

Yamaguchi, S., Knight, R.T., 1991. Anterior and posterior association cortex contributions to the somatosensory P300. The Journal of Neuroscience 11, 2039–2054.