Neuropsychological correlates of the P300 in patients with Alzheimer's disease

Moon-Soo Lee, Seung-Hwan Lee, Eun-Ok Moon, Yoon-Jae Moon, Sangrae Kim, Seung-Hyun Kim, In-Kwa Jung

A R T I C L E   I N F O

Article history:
Received 16 May 2012
Received in revised form 4 August 2012
Accepted 17 August 2012
Available online 23 August 2012

Keywords:
Alzheimer's disease
Biological marker
Neuropsychological function
P300

A B S T R A C T

Objectives: The P300 is a useful psychophysiological index that reflects cognitive functions; however, the relationship between P300 indices and neuropsychological tests in Alzheimer’s disease (AD) patients is unclear.

Methods: Thirty-one AD patients and 31 elderly normal control (NC) subjects were recruited. Age and education level were matched between the two groups. The relationship between the P300 and the Korean version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD-K) assessment packet (including 11 neuropsychological tests) was examined in AD patients.

Results: Compared to the NC subjects, the AD patients exhibited significantly decreased P300 amplitudes; however, there was no significant difference between the two groups in terms of P300 latency. After a permutation-based correction for multiple tests, P300 amplitudes at the Cz and Pz electrodes were significantly correlated with performance on the word list recognition, constructional praxis, and word fluency neuropsychological tests in the AD patients. Additionally, P300 latencies at the Pz and C6 electrodes were also significantly correlated with performance on the Mini-Mental State Examination, CERAD-K version (MMSE-K), and Trail Making Test part A (TMT-A) neuropsychological tests in the AD patients.

Conclusions: The results suggest that the P300 is responsive to the deterioration of language, memory, and executive functions observed in AD patients. Although there was no significant difference between the AD patients and NC subjects in the P300 latency, P300 latency has been shown to reflect impaired global cognition and attention deficits associated with AD. Our results suggest that P300 indices could be used as biological markers that indicate impaired neuropsychological functions in AD patients.

© 2012 Elsevier Inc. All rights reserved.

1. Introduction

Alzheimer disease (AD), one of the most common causes of mental deterioration in the elderly, is a progressive neurodegenerative disorder that is characterized by cognitive and behavioral dysfunction. This disease has a slow onset and gradual progression. Early treatment is needed for better treatment outcome; therefore, an early diagnosis of the condition is very important. Although the biological methods used to diagnose and evaluate AD patients are still very rudimentary (Kim et al., 2012), the P300 component of event-related potentials (ERPs) has been used to study dementia and aging (Polich, 2007). There are some distinguishable ERP components in the time range of the P3 wave, specifically a frontally maximal P3a component and a parietally maximal P3b component. The P3a component is characterized by an infrequent, distinct tone presented in a series of frequent tones without a task. The P3b component is a task-relevant potential elicited during target stimulus processing. When ERP researchers refer to the P3 component, they usually mean the P3b component (Luck, 2005; Polich, 2007). The P300 component is easy to observe and reflects both attention and working memory processing (Polich, 2007). Polich et al. reported that the amplitude of P300 was smaller and that the peak latency was longer in AD patients compared to control subjects (Polich et al., 1990). The P300 has been revealed as a sensitive tool to detect the progress of AD in the initial stage (Polich and Corey-Bloom, 2005), and similar findings were found in minimal cognitive impairment (MCI) patients (Frod et al., 2002; Golob et al., 2002, 2007).

Lai et al. (2010) investigated the P300 of probable AD patients, MCI patients, and normal controls in a 1-year prospective study. The cognitive abilities screening instrument (CASI) test was used to screen the
patients (Cullen et al., 2007). In this study, the P300 amplitude reduction and CASI score changes failed to reach statistical significance between the baseline and the follow-up in probable AD and MCI patients; however, the P300 latencies were significantly more delayed in the follow-up (Lai et al., 2010). In general, the P300 amplitude and latency have been revealed as sensitive markers that indicate the progress of cognitive dysfunction in AD patients (Ball et al., 1989; Polich et al., 1986).

The diagnosis of AD is heavily dependent on the neuropsychological test scores of suspected AD subjects. There are relatively few studies, however, that have systematically investigated the relationship between neuropsychological tests and P300 parameters. A larger P300 amplitude has been related to better short- (Verleger, 1988) and long-term memory function (Johnson et al., 1985). Additionally, significant positive correlations were observed between the P300 amplitude and neuropsychological tests, such as verbal IQ, the Wechsler Memory Scale (Lee et al., 1994), digit span (Fjell and Walhovd, 2001), and the Trail Making Test part B (TMT-B), in healthy subjects (Lee et al., 1994) and obsessive–compulsive disorder patients (Kim et al., 2003). In sum, the P300 amplitude has been shown to be highly correlated with neuropsychological tests scores, such as the TMT-B, the Wechsler Memory Scale, and digit span, in patients with several neuropsychiatric illnesses and in healthy controls.

The P300 latency indicates the stimulation classification speed (Katada et al., 2003) and the increased cognitive load (Reza et al., 2006), but it is not generally related to the response selection processes (McCarthy and Donchin, 1981; Pfefferbaum et al., 1986). The P300 latency indicates how long it takes to process information before making a response; therefore, it has often been considered a sensitive temporal index of the neural activity underlying the processes of attention allocation and immediate memory (Polich, 2007). The P300 latency increases as cognitive capability decreases in AD patients (Lai et al., 2010) and is also significantly correlated with neuropsychological tests, such as the TMT-B (Kim et al., 2003), the Stroop task (Kindermann et al., 2000), the Wechsler Adult Intelligence Scale (Liu et al., 2007), and verbal fluency (Souza et al., 1995). Thus, the P300 latency may play an important role in indicating the cognitive dysfunction associated with AD (Katada et al., 2003). To date, no studies have directly evaluated the relationship between the P300 indices and multiple diagnostic neuropsychological tests in AD patients.

Various neuropsychological tests have been used widely for the diagnosis of AD in clinical practices. Recently, the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) also developed standardized clinical and neuropsychological assessment batteries to evaluate patients with AD. Although it is important to make a psychophysiological validation of each neuropsychological test in the CERAD package, it has not been tested in a clinical sample yet. If there is a significant relationship between the neuropsychological tests of CERAD and the P300 parameters, it will provide clinically valuable information for diagnosing dementia. In this study, we hypothesized that changes in the P300 (i.e., reduced amplitude and delayed latencies) would be correlated with the neuropsychological tests of the CERAD in AD patients, thereby providing evidence that the P300 could be used as a biological marker of the cognitive dysfunction associated with AD. In the present study, we have correlated the P300 with the CERAD-K (the Korean version) neuropsychological tests in patients with AD and age- and education-matched normal controls to evaluate the clinical implication of the P300 in AD patients. If significant correlations exist, we may be able to monitor the progress of AD or the effects of therapeutic interventions in AD patients by measuring the P300.

2. Methods

2.1. Participants

Patients with AD and healthy controls were recruited from the Psychiatry Department of Inje University, Ilsan Paik Hospital, Korea. The AD patients were diagnosed as probable AD by the structured diagnostic evaluation using the CERAD-K (Lee et al., 2002) on the basis of the National Institute of Neurological and Communication Disorders and the Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). The Clinical Dementia Rating Scale (CDR) (Morris, 1997) was used to grade dementia severity at the time of the EEG. The subjects underwent neurological, serological, and imaging tests, including computed topography and magnetic resonance imaging. Those with other medical conditions (e.g., severe cardiovascular disease, a history of substance abuse and/or other serious system diseases, such as malignancy, uncontrollable hypertension or seizure disorders) known to cause or affect dementia were excluded from the study. If the AD patients could not voluntarily perform the target detection task well, those subjects were also excluded from our data set. Accordingly, nine AD patients were excluded due to unsatisfactory performances on the oddball task.

The age-, sex- and education level-matched elderly normal control subjects (NC, ages > 70 years old) were recruited from social communities around the hospital through posters and the local newspaper. They were examined by a trained psychiatrist according to the protocol in the CERAD-K (Lee et al., 2002). They had no history of psychiatric or neurological abnormalities. Reliable informants were also interviewed to acquire additional information regarding the cognitive and functional capacities and medical history of the subjects.

The conditions of the NC were confirmed and determined by the results of the CERAD-K neuropsychological tests. The subjects were defined as normal when they did not show any cognitive impairment in the 11 neuropsychological tests. Cognitive impairment was defined as subjects’ test scores that were 1.5 standard deviations below the education- and sex-matched norms (Lee et al., 2002). All subjects provided written informed consent prior to participating in the study. This study was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital.

2.2. Neurocognitive function test

Cognitive function was assessed using the CERAD-K. The CERAD-K assessment packet included the following 11 tests: (1) the Mini-Mental State Examination in the CERAD-K (MMSE-KC); (2) the Korean version of the Short Blessed Test (SBT-K); (3) word list memory (the learning of a visually presented list of 10 words, three trials); (4) word list recall (delayed); (5) word list recognition (the recognition of previously studied words among non-studied words); (6) the Korean version of the Boston Naming Test (K-BNT; the naming of line drawings); (7) word fluency (the animal category; verbal fluency); (8) constructional praxis (copying figures); (9) constructional recall (delayed figure recall); (10) the trail making test A; and (11) the trail making test B (TMT A and B; timed connection of a labeled circle).

These tests allowed us to examine the functional capacity of several cognitive domains: (1) global cognition (MMSE-KC, SBT-K) and attention (TMT-A); (2) memory (word list memory, word list recall, word list recognition, constructional recall); (3) language (K-BNT); (4) visuospatial function (constructional praxis); and (5) executive function (TMT-B, word fluency).

2.2.1. Verbal fluency

Tests of verbal fluency involve the associative exploration and retrieval of words based on phonemic or semantic criteria, usually conducted in the setting of a time constraint. Verbal fluency patterns can be divided into two types: semantic and phonemic fluency (Henry et al., 2004). The verbal fluency test of the CERAD-K measures verbal production, semantic memory, and language. In the test, subjects were asked to name as many examples of the category (e.g., “animal”) as possible for a limited time (Lee et al., 2002). This fluency task evaluates semantic fluency and requires strategic searching and retrieval of information from the semantic memory. Semantic fluency
requires the subject to constrain searching of exemplars from a suporderate category and make semantic associations within the category (Murphy et al., 2006).

2.2.10. SBT-K
The targets were all numbers, but in the TMT-B, the subjects alternat-switching. Two versions were used: TMT-A and -B. In the TMT-A,

2.2.9. TMT-A/B
presented in the constructional praxis task after a delay of a few min.

2.2.8. Constructional recall
This task assesses the ability of the subjects to recall pictures. The subjects were given 90 s to recall 10 words presented in the word list memory test approximately 15 min later.

2.2.7. Word list recognition test
This test was administered after the word list recall test. The subjects were asked to indicate the 10 words that were presented during the word list memory test and 10 distracter words. The number of items that the subjects recognized correctly was counted. This recognition test can be regarded as an explicit memory test (Shimamura et al., 1987).

2.2.6. Word list recall
This test assesses the ability of the subjects to recall words. The subjects were given 90 s to recall the 10 words presented in the word list memory test approximately 15 min later.

2.2.5. Constructional praxis
This task measures visuospatial and constructional abilities and requires subjects to copy four line drawings that are presented in order of increasing complexity.

2.2.4. Word list memory
The subjects were presented with 10 unrelated items. They were instructed to read each word aloud as it was presented and to re-member them. Immediately following the 10 words, subjects were asked to recall as many items as possible. On each of the three learning blocks, the 10 words were presented in a different order.

2.2.3. MMSE-KC
The MMSE-KC is a neurocognitive test designed to screen for cog-nitive impairment. The scores range from 0 to 30, and higher scores indicate better cognition. Scores of 25 are considered to indicate cognitive impairment.

2.2.2. K-BNT
Fifteen items from the 60-item, Korean version of the Boston nam-ing test were used to construct a modified, 15-item test. This test is a widely used assessment tool to measure confrontational word retrieval.

2.2.1. TMT-A/B
The TMT is a neuropsychological test of visual attention and task switching. Two versions were used: TMT-A and -B. In the TMT-A, the targets were all numbers, but in the TMT-B, the subjects alternat-switching. Two versions were used: TMT-A and -B. In the TMT-A,
neuropsychological test scores. To eliminate false-positive relationships between the P300 variables (amplitude and latency) and the neuropsychological test scores, we employed permutation testing to assess whether the correlation value of each of the P300 variables was greater than what occurred by chance (Bae et al., 2011; Coutanche et al., 2011). For each of the P300 variables, we permuted the neuropsychological test scores 10,000 times independently to generate a null distribution of correlation coefficients and then tested whether the original correlation coefficient exceeded the statistical significance of \( p < 0.05 \).

### 3. Results

#### 3.1. Demographic data and neuropsychological test results

Thirty-one AD patients and 31 NC were recruited. Age (AD: 76.45 ± 5.57 years, NC: 75.84 ± 4.74 years) and education level (AD: 5.0 ± 5.36 years, NC: 5.13 ± 3.72) did not differ significantly between the AD patients and the NC subjects. The AD patients were classified as having mild AD (N = 18, CDR score: 0.5 or 1), moderate AD (N = 9, CDR score: 2) or severe AD (N = 4, CDR score: ≥ 3). The mean scores of all subset tests of the CERAD-K (verbal fluency, K-BNT, MMSE-KC, SBT-K, word list memory, constructional praxis, word list recall, word list recognition, constructional recall, TMT-A and TMT-B) in the AD group were significantly lower than those in the NC group. The MMSE-KC scores of the NC subjects were low, but this result could be related to the lower educational levels in the Korean participants rather than the pathological process of Alzheimer’s disease (Kim et al., 2011). Table 1 presents the demographic characteristics (i.e., age and educational years) of the AD and NC groups and the results of each subset test of the CERAD-K.

#### 3.2. Behavioral data

The behavioral results are presented in Table 2. There were no significant differences in the response times (AD: 556.76 ± 129.06, NC: 535.63 ± 105.22, p = 0.52) or the number of accepted epochs (AD: 49.65 ± 8.50, NC: 53.13 ± 6.82, p = 0.08). The percentage of correct hits, however, was significantly different (AD: 59.58 ± 38.31, NC: 88.75 ± 15.87, p = 0.001) between the two groups.

#### 3.3. P300 amplitude and latency

Examples of the P300 waveforms for the target stimuli from the AD patients and the NC subjects are presented in Fig. 1. The P300 amplitude showed significant main effects for group (F = 11.58, df = 1, p = 0.001) and electrode site (F = 3.38, df = 4, p = 0.024). Further analysis revealed that the P300 amplitudes of the AD patients were significantly lower than those of the NC (Table 3), and the P300 amplitude at the Pz electrode was the highest among the 5 electrodes in both the AD patients and the NC subjects (Table 3). Nevertheless, there was no significant interaction between group and electrode sites in the P300 amplitude (F = 2.25, df = 4, p = 0.064).

The P300 latency showed a significant main effect for electrode site (F = 8.06, df = 4, p = 0.00). Further analysis revealed that the P300 latencies were the longest at the Pz electrode (Table 2); however, there was also no significant interaction between group and electrode sites in the P300 latency (F = 0.82, df = 4, p = 0.51).

#### 3.4. Correlation between the P300 and CERAD-K tests

Table 4 summarizes the Spearman correlation between the P300 indices and the scores of the neuropsychological tests in the AD patients. The P300 amplitude showed significant positive correlations with word list recognition (\( \rho = 0.422, p = 0.025 \) at Cz; \( \rho = 0.539, p = 0.002 \) at Pz), constructional praxis (\( \rho = 0.379, p = 0.040 \) at Cz), and word fluency (\( \rho = 0.389, p = 0.032 \) at Cz). The P300 latency showed significant correlations with the MMSE-K (\( \rho = -0.365, p = 0.045 \) at Cz) and the TMT-A (\( \rho = 0.474, p = 0.007 \) at Cz). Fig. 2 is a scatterplot of the scores on the CERAD-K cognitive tests and the amplitude and latency of P300 in patients with AD.

### 4. Discussion

The P300 amplitude was significantly decreased in the AD patients compared to the NC subjects, as observed in almost all of the electrodes. Our results are consistent with previous studies that reported a decreased P300 amplitude in AD patients (Boller et al., 2002; Frodl et al., 2002; Yamaguchi et al., 2000). Ally et al. (2006) reported that the P300 amplitude was significantly decreased in AD patients compared to age- and gender-matched normal controls. Additionally, their biological children showed a significantly decreased P300 amplitude and latency compared to those of age- and gender-matched normal controls. These results support the idea that the P300 amplitude can be used as a biological marker in a preclinical stage as well as in a clinical stage (Ally et al., 2006). The Alzheimer’s Disease Assessment-Cognitive subscale (ADAS-cog) is also commonly used for the assessment of a variety of cognitive functions. The P300 amplitude showed a moderate but significant correlation with the ADAS-cog only at Pz (deurense et al., 2009).

Furthermore, our results revealed that the right hemispheric C6 electrode showed a significant amplitude difference between the AD patients and the NC subjects, while the left hemispheric C5 electrode did not, suggesting that the right hemisphere may be more significantly impaired than the left hemisphere in AD patients. Indeed, previous research has shown that more severe impairment of the right hemisphere may be a characteristic of AD. For example, brain perfusion abnormalities lateralized in the right hemisphere were associated with the minimal cognitive impairment in those who developed AD (Cheliotel et al., 2003; Habert et al., 2011). Additionally, the early involvement of the right hemisphere, not the left hemisphere, in AD.

---

**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AD (N=31)</th>
<th>NC (N=31)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>76.45 ± 5.57</td>
<td>75.84 ± 4.74</td>
<td>0.64</td>
</tr>
<tr>
<td>Males:females</td>
<td>8:23</td>
<td>5:26</td>
<td>0.06</td>
</tr>
<tr>
<td>Educational duration (years)</td>
<td>5.0 ± 5.36</td>
<td>5.13 ± 3.72</td>
<td>0.19</td>
</tr>
<tr>
<td>CERAD-K</td>
<td>MMSE-KC</td>
<td>Short Blessed Test—Korean</td>
<td>Trail Making Test part A</td>
</tr>
<tr>
<td></td>
<td>16.16 ± 5.25</td>
<td>19.13 ± 7.12</td>
<td>262.17 ± 119.86</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Task</th>
<th>AD (N=31)</th>
<th>NC (N=31)</th>
<th>t-Value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response time (ms)</td>
<td>556.76 ± 129.06</td>
<td>535.63 ± 105.22</td>
<td>0.64</td>
<td>0.52</td>
</tr>
<tr>
<td>Percentage of correct hits</td>
<td>59.58 ± 38.31</td>
<td>88.75 ± 15.87</td>
<td>-3.78</td>
<td>0.00</td>
</tr>
<tr>
<td>Number of accepted epochs</td>
<td>49.65 ± 8.50</td>
<td>53.13 ± 6.82</td>
<td>-1.78</td>
<td>0.08</td>
</tr>
</tbody>
</table>

**Table 4**

<table>
<thead>
<tr>
<th>Test</th>
<th>AD (N=31)</th>
<th>NC (N=31)</th>
<th>t-Value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-cog</td>
<td>21.39 ± 3.59</td>
<td>23.12 ± 3.84</td>
<td>-3.01</td>
<td>0.00</td>
</tr>
<tr>
<td>MMSE-KC</td>
<td>16.16 ± 5.25</td>
<td>25.58 ± 3.60</td>
<td>-3.60</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Short Blessed Test—Korean</td>
<td>19.13 ± 7.12</td>
<td>5.87 ± 6.30</td>
<td>-0.37</td>
<td>0.71</td>
</tr>
<tr>
<td>Trail Making Test part A</td>
<td>262.17 ± 119.86</td>
<td>132.77 ± 103.49</td>
<td>-1.31</td>
<td>0.19</td>
</tr>
<tr>
<td>Trail Making Test part B</td>
<td>298.61 ± 17.41</td>
<td>276.32 ± 91.13</td>
<td>-1.09</td>
<td>0.28</td>
</tr>
<tr>
<td>Word list memory</td>
<td>8.59 ± 4.29</td>
<td>13.35 ± 6.21</td>
<td>-1.88</td>
<td>0.06</td>
</tr>
<tr>
<td>Word list recall</td>
<td>2.07 ± 1.79</td>
<td>4.74 ± 2.68</td>
<td>-3.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Word list recognition</td>
<td>4.69 ± 2.83</td>
<td>7.26 ± 3.48</td>
<td>-2.10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Constructional recall</td>
<td>1.37 ± 1.62</td>
<td>5.65 ± 3.51</td>
<td>-1.88</td>
<td>0.06</td>
</tr>
<tr>
<td>Constructional praxis</td>
<td>5.87 ± 2.68</td>
<td>8.55 ± 3.18</td>
<td>-2.10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Boston naming test</td>
<td>6.48 ± 2.85</td>
<td>9.55 ± 3.20</td>
<td>-1.88</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Word fluency</td>
<td>6.29 ± 3.77</td>
<td>12.03 ± 3.89</td>
<td>-3.06</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**CERAD-K**: Consortium to Establish a Registry for Alzheimer’s Disease, Korean version.

**MMSE-KC**: Mini-Mental Status Examination, CERAD-K version.
was previously found in neurophysiological (Jung et al., 2007), neuropsychological (Goldstein and Shelly, 1981) and structural (Good et al., 2001) studies, which is consistent with the right-lateralized P300 amplitude reduction in our AD patients. Our results also suggested that the frontal and parietal regions were relatively more damaged compared to the central region. In fact, AD patients exhibit specific regional deficits, such as the frontal and temporoparietal areas. Duffy et al. (1984) reported that the areas showing maximal group differences in slow waves bilaterally between the senile AD group and their controls were the mid-frontal and anterior frontal lobes (Duffy et al., 1984). Elmstahl et al. (1994) reported that the most marked delta wave activity was observed over the posterior regions of the brain in AD patients (Elmstahl et al., 1994).

The changes in the P300 are not specific for AD. There are similar P300 changes in other neuropsychiatric disorders. For example, the P300 amplitude in non-bipolar, melancholic depression has been assessed. Prior to treatment, the P300 amplitudes in depressives were smaller than those in controls, and they negatively correlated with severity. The P300 amplitudes also significantly increased in patients following recovery and were normalized (Gangadhar et al., 1993). Delayed P300 latency was also reported in major depression (Vandoolaeghe et al., 1998). The P300 has been employed to characterize schizophrenia. Increases in the sample percentage of the paranoid subtype were associated with very strong increases in the effect sizes for both the P300 amplitude and latency. The schizophrenia subtype, especially the paranoid type, was reported to be consistently

### Table 3
Comparison of the P300 amplitude and latency between Alzheimer’s disease (AD) patients and normal control (NC) subjects.

<table>
<thead>
<tr>
<th></th>
<th>AD (N = 31)</th>
<th>NC (N = 31)</th>
<th>t-Value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FZ amplitude (μV)</td>
<td>3.50 ± 3.41</td>
<td>6.59 ± 6.57</td>
<td>−2.330</td>
<td>.023</td>
</tr>
<tr>
<td>CZ amplitude (μV)</td>
<td>4.06 ± 2.82</td>
<td>6.04 ± 4.99</td>
<td>−1.929</td>
<td>.058</td>
</tr>
<tr>
<td>PZ amplitude (μV)</td>
<td>4.12 ± 2.57</td>
<td>7.95 ± 3.87</td>
<td>−4.933</td>
<td>.000</td>
</tr>
<tr>
<td>CS amplitude (μV)</td>
<td>3.72 ± 2.22</td>
<td>4.95 ± 4.18</td>
<td>−1.442</td>
<td>.155</td>
</tr>
<tr>
<td>CG amplitude (μV)</td>
<td>4.00 ± 2.45</td>
<td>6.94 ± 3.37</td>
<td>−3.929</td>
<td>.000</td>
</tr>
<tr>
<td>FZ latency (ms)</td>
<td>362.52 ± 44.23</td>
<td>359.61 ± 38.52</td>
<td>.276</td>
<td>.784</td>
</tr>
<tr>
<td>CZ latency (ms)</td>
<td>362.23 ± 43.52</td>
<td>364.42 ± 39.25</td>
<td>−.208</td>
<td>.836</td>
</tr>
<tr>
<td>PZ latency (ms)</td>
<td>385.16 ± 38.58</td>
<td>371.13 ± 34.67</td>
<td>1.506</td>
<td>.137</td>
</tr>
<tr>
<td>CS latency (ms)</td>
<td>354.29 ± 42.04</td>
<td>358.13 ± 41.58</td>
<td>−.361</td>
<td>.710</td>
</tr>
<tr>
<td>CG latency (ms)</td>
<td>349.23 ± 33.24</td>
<td>347.61 ± 31.01</td>
<td>.198</td>
<td>.844</td>
</tr>
</tbody>
</table>

![Fig. 1. Grand-averaged event-related potentials of Alzheimer’s disease (AD) patients and matched normal control subjects (NC) from a standard oddball ERP paradigm.](image-url)
related to the P300 deficits in schizophrenia patients in a meta-analysis of the P300 and schizophrenia (Jeon and Polich, 2003).

Furthermore, other types of dementia could have characteristic changes in the P300. Bonanni et al. reported that delayed latencies and reduced amplitudes were also found in patients with dementia with Lewy bodies (Bonanni et al., 2010b) and vascular dementia (Xu et al., 2012). The major limitation of the applicability of the P300 as a biological marker of AD is its low specificity.

For these reasons, the combination of the P300 and other more specific neuropsychological tests are needed for the evaluation of AD. The present study compared the P300 amplitude and latency of AD patients and NC subjects in the auditory oddball paradigm, and the relationships between the P300 indices and the neuropsychological tests were explored in the AD patients. We found that the P300 amplitudes in the AD patients were significantly reduced compared to the NC subjects, and there were significant correlations between the P300 indices and the neuropsychological test scores in the AD patients.

In the present study, although the P300 amplitude did not significantly correlate with global cognitive function as measured by the MMSE-K, it was significantly correlated with memory (word list

<table>
<thead>
<tr>
<th>MMSE-KC</th>
<th>SBT-K</th>
<th>TMT</th>
<th>Word List</th>
<th>Constructional</th>
<th>K-BNT</th>
<th>Word Fluency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>Memory</td>
<td>Recall</td>
</tr>
<tr>
<td>FZ amplitude</td>
<td>.107</td>
<td>−.257</td>
<td>−.221</td>
<td>.235</td>
<td>.030</td>
<td>−.077</td>
</tr>
<tr>
<td>CZ amplitude</td>
<td>.157</td>
<td>−.312</td>
<td>−.301</td>
<td>.225</td>
<td>.030</td>
<td>.034</td>
</tr>
<tr>
<td>PZ amplitude</td>
<td>.059</td>
<td>−.259</td>
<td>−.028</td>
<td>.245</td>
<td>.036</td>
<td>.142</td>
</tr>
<tr>
<td>C5 amplitude</td>
<td>.138</td>
<td>−.227</td>
<td>−.070</td>
<td>.276</td>
<td>.001</td>
<td>.054</td>
</tr>
<tr>
<td>C6 amplitude</td>
<td>−.099</td>
<td>.162</td>
<td>−.101</td>
<td>.143</td>
<td>−.188</td>
<td>−.212</td>
</tr>
<tr>
<td>FZ latency</td>
<td>−.115</td>
<td>−.136</td>
<td>.280</td>
<td>.059</td>
<td>.059</td>
<td>−.092</td>
</tr>
<tr>
<td>CZ latency</td>
<td>−.365*</td>
<td>.093</td>
<td>.474**</td>
<td>−.174</td>
<td>−.069</td>
<td>−.147</td>
</tr>
<tr>
<td>PZ latency</td>
<td>−.239</td>
<td>.101</td>
<td>.265</td>
<td>−.195</td>
<td>−.021</td>
<td>.156</td>
</tr>
<tr>
<td>C5 latency</td>
<td>−.191</td>
<td>.186</td>
<td>.066</td>
<td>−.070</td>
<td>−.139</td>
<td>−.027</td>
</tr>
<tr>
<td>C6 latency</td>
<td>.176</td>
<td>−.187</td>
<td>.278</td>
<td>−.103</td>
<td>.337</td>
<td>.287</td>
</tr>
</tbody>
</table>

MMSE-KC: Mini-Mental Status Examination, CERAD-K version; SBT-K: Short Blessed Test-Korean; TMT: Trail Making Test A/B; K-BNT: Korean version of the Boston Naming Test. A permutation-based correction for multiple tests was conducted. *: significant differences at the 0.05 level, **: significant differences at the 0.01 level.

Fig. 2. Bivariate scatterplots of the CERAD-K cognitive test scores and the P300 amplitude and latency in patients with Alzheimer’s disease.
recognition) and visuospatial function (praxis). Previously, the P300 amplitude has been determined to be associated with verbal memory in schizophrenia patients (Kim et al., 2003). The P300 amplitude has been shown to be sensitive and proportional to the amount of attentional resources devoted to a given task (Gonsalvez and Polich, 2002; Johnson, 1995; Wickens et al., 1983). A greater P300 amplitude has been associated with superior memory performance (Fabiani et al., 1990; Johnson, 1995). Additionally, the P300 component has been shown to indicate an update of activity in cortico-limbic circuits that are implicated in attention and working memory (Donchin and Coles, 1988). The P300 amplitude can therefore be considered as a measure of central nervous system activity that reflects the processing of incoming information; however, the neuropsychological origins and meaning of the P300 are not yet clear. The source of the P300 has been identified as the medial temporal lobe (Halgren et al., 1980; McCarthy et al., 1989) and the frontal lobe (Pardo et al., 1991; Posner and Petersen, 1990). The P300 appears to originate when a stimulus commands frontal lobe attention, and its activity is completed when attentional resources are allocated for stimulus evaluation and subsequent memory updating (Polich, 2007).

P300 latency was not significantly different between the AD patients and NC subjects in our study. The ERPs of the AD group were flat during the 300–500 ms, and it therefore appears probable that AD patients have ill-defined peaks for the P300. Although we tried to find a maximal peak within 300–500 ms, this flat response might be related with non-significant differences in the latencies between the two groups; however, the P300 latency was significantly correlated with global cognition as measured by the MMSE-K and TMT-A in the AD patients. The P300 latency is considered to be a measure of stimulus classification speed (Polich, 1986), although unrelated to the response selection processes (Pfefferbaum et al., 1986) and independent of the behavioral response time (Ilan and Polich, 1999). Generally, P300 latency is negatively correlated with mental efficiency, such that shorter latencies are associated with superior cognitive performance on neuropsychological tests (Houillin et al., 1998; Reinvang, 1999). As a result, the P300 latency was considered to be highly sensitive for the early cognitive decline of AD patients (Brown et al., 1982; Ito, 1991; Onofrj et al., 1991). Bonanni et al. (2010a) reported that P300 latencies at Fz and Pz were significantly correlated with the ADAS-cog, the MMSE, and the Frontal Assessment Battery (FAB), as well as behavioral symptoms (Bonanni et al., 2010a). Nioszewska et al. (2009) reported that the P300 abnormality found in Parkinson’s disease patients was significantly correlated with executive function deficits measured by the Wisconsin card sorting test. These results suggest that the neuropsychological tests, such as global cognitive function and frontal executive function, were well correlated with both the P300 latency and amplitude (Nioszewska et al., 2009). Our finding provided additional evidence that the P300 latency reflects global cognition, rather than specific memory, language, visuospatial function, and executive function. In sum, consistent with other studies, our results highlight the usefulness of the P300 latency as a marker of the general cognitive decline in AD patients.

Our study has some limitations. First, we used the relatively higher high-pass filter to analyze the P300 waves. Holinger et al. (2000) reported that the relatively higher high-pass filter cutoff of 1 Hz (compared to the lower filter cutoff of 0.001, 0.1, and 0.3 Hz) may have produced the reduction of the P300 amplitude (Holinger et al., 2000). It is possible that if the relatively higher high-pass filter has caused the reduction of the general P300 amplitudes in both the AD and NC groups, it would increase the possibility of type II errors rather than type I errors statistically. Our study, however, produced significant differences in the P300 amplitude between the two groups in spite of potentially reduced P300 amplitudes. Second, our study is a cross-sectional design, and a longitudinal study would be more helpful in determining the functionality of the P300 as a biomarker in AD.

Recently, new analyses identified the P300 subcomponents, P3a and P3b (Juckel et al., 2008). As reliable separation of the P300 subcomponents is possible by dipole source analysis, it would also be useful to investigate the correlation of the neuropsychological studies and the P300 subcomponents in further studies. Our study revealed that the P300 amplitude and latency are associated with the neuropsychological decline in AD patients. There was a significant difference in the P300 amplitude between the AD patients and the NC subjects. The P300 was significantly correlated with executive function, memory, and visuospatial function in the AD patients. Although we did not find any significant differences in the P300 latency between the AD patients and the NC subjects, the P300 latency was significantly correlated with impaired global cognitive function and attention in AD patients. As the P300 amplitude and latency showed significant correlations with neuropsychological ability in AD patients, we may use the P300 as a follow-up screening test to assess the cognitive decline in AD patients. Additionally, it could be a useful tool for evaluating symptom improvement after treatment intervention. Our results suggest that the P300 indices are useful in reflecting the psychopathology of AD patients, and the P300 can be used as another assessment tool of AD patients in combination with other neuropsychological tests.

Acknowledgements

This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (no. A08-4117-A22023-08N1-00010A).

References


Houlihan M, Stelmack R, Campbell K. Intelligence and the effects of perceptual processing demands, task difficulty and processing speed on P300, reaction time and movement time. Intelligence 1998;26:9–25.


