Auditory Event-related Potentials in Children With Attention Deficit Hyperactivity Disorder

Min-Lan Tsai a,*, Kun-Long Hung b, d, Hui-Hua Lu c

a Department of Pediatrics, Cheng-Hsin General Hospital, Taipei, Taiwan
b Department of Pediatrics, Cathay General Hospital, Taipei, Taiwan
c Department of Psychiatry, Cathay General Hospital, Taipei, Taiwan
d School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan

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Key Words
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Background: Recording of event-related potentials (ERPs) from the scalp is a noninvasive technique reflecting the sensory and cognitive processes associated with attention tasks. Attention deficit hyperactivity disorder (ADHD) is a disorder involving deficits in attention and behavioral control. The aim of this study was to investigate the difference in ERPs between normal children and those with ADHD.

Methods: We examined 50 children with ADHD and 51 age-matched controls. All children with ADHD met the full criteria for ADHD according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). The auditory oddball paradigm was applied, and event-related long-latency components (N1, P2, N2 and P3) from Fz, Cz and Pz were measured in each test subject.

Results: Children with ADHD showed a significantly longer latency and a lower amplitude of P3 compared to normal control children ($p < 0.01$). Delayed N2 latency at the Pz electrode was shown in children with ADHD compared to normal controls ($p < 0.01$). No differences in other ERP indices were found between children with ADHD and controls. When divided into four age groups, the latency of P3 was significantly increased in all age groups and a significantly smaller amplitude in P3 over the central region was found in children with ADHD > 10 years of age ($p < 0.05$).

Conclusion: We found that the endogenous ERPs (P3 and N2) were significantly affected in children with ADHD, compared to exogenous ERPs (N1 and P2). Increased latency of P3 suggests a slower processing speed, and decreased P3 amplitude is interpreted as disruption of inhibitory control in children with ADHD. These results indicate a neurocognitive abnormality in ADHD, as presented by a reduction in ERP response.

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1. Introduction

The recording of event-related potentials (ERPs) from the scalp is a noninvasive technique providing information regarding neural activity associated with sensory, cognitive, attention and decision-making processes. ERPs have been used as an electrophysiological tool for studying neural bases of cognitive activities and in clinical applications for patients with psychopathological and neurological diseases, disorders of learning and attention, dementia, and other cognitive deficits.

Attention deficit hyperactivity disorder (ADHD) is characterized by developmentally inappropriate attention, behavioral and cognitive impulsivity, and restlessness. Evidence has shown that ADHD is associated with a deficit in response selection, motor adjustment, and inhibition of prepotent responses. A variety of studies of children with ADHD have reported abnormalities in visual, auditory, and alternating visual and auditory ERPs.

Abnormalities in auditory ERP waves are a reflection of tasks associated with selective attention and the categorization of stimuli involved in cognitive functions. Studies on ERP have identified N1 and P2 components in response to frequent tones and P3 components in response to rare tones. P3, namely the P300 wave, is a late positive waveform occurring with a latency of approximately 300 milliseconds or more after an infrequently presented target stimulus (so-called “oddball paradigm”). P3 is thought to be an endogenous potential generated in the medial cortical or subcortical region, sensitive to the delivery of task-relevant information requiring a decision or response from the participant. Research has shown that P3 is also a presentation of an updating of working memory. Understanding alterations of the ERPs in ADHD children helps to take into account their cognitive control processes and pathophysiology.

Many investigations into attention and cognition have conducted analysis of ERPs, and P3 responses are the most widely investigated waveform. As mentioned by Barry et al., the most common ERP-related discovery associated with ADHD is a significant reduction in the amplitude of P3 during the performance of oddball tasks. The results concerning latency in P3 with regard to ADHD have been mixed. Changes in other ERP waveforms such as N2, P2 and N1 have not been thoroughly studied in children with ADHD. The results of behavioral performance have been inconsistent when reported by measurements of reaction time, total hits, and false alarms.

Behavioral studies of children of various ages have shown the importance of age with respect to the regulation and direction of attention. Age-dependent changes in the ERPs of normal children have been reported in several studies. Some reports have found that the age specificity of lower P3 amplitude in ADHD patients exists mostly in children, but not in adolescent subjects. Age effect should be considered in studies of the ERP in children with ADHD.

In Taiwan, changes in ERP waveforms in children with ADHD have rarely been reported. The aim of this study was to investigate the differences in ERP responses, focusing on the differences in the latencies and amplitudes of P3, N2, P2 and N1 among children with ADHD and normal children between 6 and 13 years of age. Furthermore, the subjects in this study were divided into different age groups to evaluate the developmental effects of age on ERPs in children with ADHD.

2. Materials and Methods

2.1. Subjects

The ADHD group consisted of 50 children, aged 6–13 years old (42 boys and 8 girls) and recruited from our outpatient clinic. Children were divided into four age groups for testing: (1) 6–7 years; (2) 8–9 years; (3) 10–11 years; and (4) 12–13 years. All children with ADHD completed both the parents and teacher versions of the Child Activity Checklist in Chinese with their scores over P85 (85 percentile). The teacher version of the Child Activity Checklist included children’s behavioral control in general, during classroom, in groups, and responses to teachers such as “staying in seat according to classroom rules”, “complying with usual request or direction of teachers”, and school performance. The parents’ version of Child Activity Checklist included behavior control and attention at home or other daily activity such as “interrupting another person’s conversation or activity”, or “unable to stick with one game or toy”. All children with ADHD met the full criteria of ADHD according to Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association, 1994). Of 50 children who were diagnosed with ADHD, 48 (96%) had combined-type ADHD and two had predominantly inattentive type of ADHD. Full-scale Wechsler Intelligence Scale for Children (WISC) IV in children with ADHD was 80 or higher. A detailed history and physical and psychiatric examination were conducted, and the diagnosis was confirmed by a child psychiatrist, and none of the children were taking any medication. The patients with Tourette’s syndrome, seizure disorders, learning disabilities, autism, Asperger diseases, mental retardation, and other psychiatric disorders were excluded.

A comparable age- and sex-matched control group of 51 children aged 6–13 years old (40 boys, 11 girls) was assembled from patients who had previously visited our outpatient clinic suffering from various acute illnesses or for health examinations unconnected with neurological or psychiatric illness. Subjects with hearing problems were also excluded. Informed consent was obtained from participants’ parents or guardians in accordance with the requirement of the ethics boards of the Cathay General Hospital (CGH-CT9762) and Cheng-Hsin General Hospital (CHGH-IRB-165-98-49).

2.2. Methods

The subjects were tested in a relaxed sitting position with their eyes closed in a silent room after cleaning the skin and scalp. Bioelectrical signals were measured by placing a surface electrode (plate-shape electrode, 11 mm in diameter; Dantec Electronics A/S, Skovlunde, Denmark) along the midline frontal (Fz), central (Cz) and parietal (Pz) region, according to the 10–20 international system of EEG.
electrode placement and grounding, using a surface electrode located midway between the Fz and the midline frontopolar (FPz) points. An electrode was placed infraorbitally to monitor eye movement. A reference electrode was placed on the mastoid, and the impedance was measured at less than 5 kΩ. The filter band pass was set at 0.1–50 Hz and the analysis time was 1 second. Waveforms were averaged, and any electroencephalograms or electro-oculograms over 100 μV were automatically rejected.

We applied the "oddball paradigm" of auditory stimulation (Medtronic Keypoint V3.22; Medtronic Functional Diagnostic A/S, Skovlunde, Denmark). ERPs were elicited binaurally through headphones with a typical intensity of 60 db above the hearing level, depending upon the subject. In total, 200 tones were delivered. According to the paradigm, 20% of the tones were "target" (rare), while the remaining were "nontarget" (frequent), and the delivery sequences of frequent and rare tones were randomized. The target tones were 3000 Hz, while the nontarget tones were 2000 Hz, delivered at a rate of 0.7 Hz. Instructions were given by the technician before the test, with the subject tasked to press the button when they heard a rare tone or count the number of rare tones presented. The test was repeated twice for each subject.

All artifact-free ERP responses related to the rare tones were analyzed visually. Latency windows for potentials were designated in the following ranges: 75–150 milliseconds for N1, 120–250 milliseconds for P2, 150–350 milliseconds for N2 and 250–700 milliseconds for P3. In the analysis of potentials, the amplitude of P3 was measured from the peak of N2 to peak of P3 (N2–P3); that of N2 was measured from the peak of P2 to the peak of N2 (P2–N2); that of P2 was measured from the peak of N1 to the peak of P2 (N1–P2); and that of N1 was measured from the first deflection to the peak of N1.1

2.3. Statistical analysis

Mean reference values of the ERP indices (amplitude and latency) from the two groups were derived in this cross-sectional study. Student’s t test was used to compare ERP indices between children with ADHD and control subjects. Nonparametric Mann–Whitney U test was used when appropriate. Linear regression analysis and Pearson’s correlation testing were performed to study the relationship between P3 latency and age in the normal control and ADHD groups separately. Comparisons were considered significant at p < 0.05, unless otherwise indicated. All statistical analysis was performed using SPSS version 17.0.

3. Results

The age range of the ADHD group (42 male, 8 female) and control group (40 male, 11 female) was between 6 and 13 years. The mean age of the ADHD group was 8.9 ± 1.9 years, and the mean age of the control group was 9.0 ± 2.0 years. No significant difference in the ages or sexes of the children was noted between the ADHD and control groups.

Table 1 shows the mean latency and amplitude of each ERP component with standard deviation in the ADHD and control groups at each of the electrode sites. The P3 latency at Pz in patients with ADHD was 384.6 ± 51.1 milliseconds, which was significantly longer than that of 329.0 ± 32.3 milliseconds in normal, age-matched controls (p < 0.01, Table 1 and Figure 1). P3 latencies at Fz and Cz electrode sites were also significantly longer in children with ADHD compared to the controls (p < 0.01, Table 1). The N2 at the Pz electrode was found to be longer in children with ADHD compared to control subjects (4.3 ± 12.8 milliseconds) compared to normal controls (3.8 ± 10.8 milliseconds, p < 0.01).

| Table 1 Latency and amplitude of auditory ERP components in the children with ADHD (n = 50) and in healthy control children (n = 51). |
|-------------------------|-------------------------------|-------------------------|-------------------------|
|                         | Latency (msec)                | Amplitude (μV)          |
|                         | ADHD Mean ± SD                | Controls Mean ± SD      | p value                |
|                         | ADHD Mean ± SD                | Controls Mean ± SD      | p value                |
| **P3**                  |                               |                         |                         |
| Fz                      | 387.5 ± 41.6                  | 332.8 ± 31.1            | <0.01                   |
| Cz                      | 387.0 ± 45.1                  | 332.1 ± 31.2            | <0.01                   |
| Pz                      | 384.6 ± 51.1                  | 329.0 ± 32.3            | <0.01                   |
| **N2**                  |                               |                         |                         |
| Fz                      | 247.7 ± 22.1                  | 239.2 ± 24.3            | N.S.                    |
| Cz                      | 249.2 ± 21.1                  | 240.7 ± 27.3            | N.S.                    |
| Pz                      | 254.7 ± 22.6                  | 238.4 ± 28.9            | <0.01                   |
| **P2**                  |                               |                         |                         |
| Fz                      | 192.5 ± 24.8                  | 182.8 ± 25.5            | N.S.                    |
| Cz                      | 189.7 ± 19.6                  | 181.1 ± 25.4            | N.S.                    |
| Pz                      | 190.6 ± 27.1                  | 181.2 ± 28.0            | N.S.                    |
| **N1**                  |                               |                         |                         |
| Fz                      | 128.6 ± 20.3                  | 126.2 ± 21.7            | N.S.                    |
| Cz                      | 122.3 ± 21.0                  | 119.5 ± 21.1            | N.S.                    |
| Pz                      | 117.8 ± 19.9                  | 114.8 ± 21.4            | N.S.                    |

ADHD = attention deficit hyperactivity disorder; Cz = midline central; ERP = event-related potential; Fz = midline frontal; N.S. = not significant; Pz = midline parietal.
Table 1). However, no statistically significant difference was found in the latencies of N2 at Fz or Cz. The latencies of P2 and N1 did not differ at any of the electrode sites between the children with ADHD and the controls.

The amplitude of P3 was $12.5 \pm 4.5 \mu V$ at Pz in children with ADHD and $14.7 \pm 4.6 \mu V$ at Pz in the control children. Children with ADHD showed significantly lower amplitude in P3 for all electrodes compared to normal controls ($p < 0.05$, Table 1). However, the amplitudes of other ERPs, including N2, P2 and N1, did not show a statistically significant difference in any of the electrodes for children with ADHD compared to the matched control groups.

Figure 1 illustrates longer P3 latencies and smaller amplitude of P3 in children with ADHD compared to normal children.

Linear regression analysis demonstrated a significant negative linear correlation of P3 latency at Pz with age in the normal control group (correlation coefficient $r = -0.33$, $p = 0.02$; Figure 2); however, children with ADHD did not show significant difference in linear correlation between P3 latency and age (coefficient $r = -0.17$, $p = 0.24$; Figure 2). Similar findings were observed at other electrode locations (Fz and Cz).

When divided into four age groups, the P3 latency appeared to be significantly increased in each age group of the ADHD children compared to the controls (Table 2). The N2 latencies of Pz in the age groups 8—9 years, 10—11 years and 12—13 years appeared significantly longer in the ADHD group compared with the normal controls, but not in the 6—7 years group (Table 2). The P3 amplitude at Cz was significantly lower in the age groups 10—11 years and 12—13 years ($p < 0.05$), and with a trend of significantly lower amplitude at Pz in the age groups 10—11 years and 12—13 years for children with ADHD compared to the corresponding age groups of normal controls ($p = 0.07$ and 0.09, respectively, Table 3). The P3 amplitude in the age groups 6—7 years and 8—9 years did not differ between children with ADHD and controls. A lower P2 amplitude was also found in 10—11-year-old and 12—13-year-old children with ADHD compared to controls ($p < 0.05$, Table 3). Other ERP indices in each age group did not differ significantly compared to those of the normal controls.

4. Discussion

In recent decades, auditory ERP and P300 (P3) studies have been widely used as a noninvasive method to evaluate the function of cognition and attention in children. For clinical purposes, the most convenient protocol to elicit ERPs is the
amplitude in 6
testified a significantly increased P3 latency and lower P3
response has a large amplitude in its response to rare tones,
each clinical evoked-potential diagnostic machine. The P3
of the children with ADHD, and a significantly smaller
latency of P3 was significantly increased in each age group
to normal controls. When divided into four age groups, the
so-called oddball paradigm,1,8 which is now available with
Figure 2
The solid and dotted lines represent the regression
lines from our data obtained from 51 normal controls (solid
line) and 50 children with ADHD (dotted line) from 6 to 13 years
of age, respectively. A significantly negative linear correlation
of P3 latency at Pz with age was found in the normal control
group (r = −0.33, p = 0.02), while children with ADHD did not
show a statistically significant linear correlation between P3
latency and age (r = −0.17, p = 0.24). ADHD = attention deficit hyperactivity disorder; Pz = midline parietal.

Table 2  Mean value of ERP latency at Pz (midline parietal) electrode (mean ± standard deviation in milliseconds) between children with ADHD and normal controls in different age groups.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N1</th>
<th>P2</th>
<th>N2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–7 y</td>
<td>ADHD</td>
<td>128.1 ± 16.4</td>
<td>192.1 ± 24.0</td>
<td>259.0 ± 26.6</td>
</tr>
<tr>
<td>n = 15</td>
<td></td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–9 y</td>
<td>ADHD</td>
<td>109.2 ± 15.9</td>
<td>183.4 ± 17.9</td>
<td>251.3 ± 20.7</td>
</tr>
<tr>
<td>n = 18</td>
<td></td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–11 y</td>
<td>ADHD</td>
<td>116.0 ± 20.4</td>
<td>191.7 ± 24.5</td>
<td>246.2 ± 14.3</td>
</tr>
<tr>
<td>n = 11</td>
<td></td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–13 y</td>
<td>ADHD</td>
<td>120.8 ± 30.8</td>
<td>187.0 ± 34.1</td>
<td>269.5 ± 25.8</td>
</tr>
<tr>
<td>n = 6</td>
<td></td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADHD = attention deficit hyperactivity disorder; ERP = event-related potential; N.S. = not significant.

P3 latency is thought to reflect the timing involved in the
categorization of stimuli.6,7 Increased P3 latency in a set of
ERP responses reflects a defect in the cerebral processing
of attention and a reduction in the speed of processing in
children with ADHD.21 Several ERP studies have suggested
the existence of abnormal sensory or cognitive information
processing in patients with ADHD.21,22 Our results have
shown an increase in the latency of P3, which is consistent
with the results of previous studies.22–24 However,
a number of studies have not reported a difference in
latency between ADHD and normal controls.25,26 Such
a discrepancy might have been due to different case
inclusion criteria and methodologies. Our case selection
included mostly combined-typed ADHD (96%), whereas
other studies have recruited patients with only inattentive-
type or other ADHD-comorbid groups.25,27 Further studies
are needed to investigate the effect of comorbid disorders
associated with ADHD on ERPs.

P3 amplitude is believed to provide a psychophysiological
signature of deficits related to inhibitory control. Reduction in P3 amplitude elicited from an auditory oddball
task is specific for children with ADHD,5,21 in contrast to
healthy children and children with autism or dyslexia.23,28
A number of children with ADHD have never produced
P3 waveforms.29 A small P3 amplitude is explained as a reflection of behavioral disinhibition,10 a failure of
behavioral control,31 and CNS hyperexcitability.32 We found
a decrease of P3 amplitude in children with ADHD, which
corresponded to previous results.10,21,24,25; however, some
studies have found no difference in P3 amplitude between
control and ADHD subjects.6

A negative correlation has been identified between
ERP latencies and age in normal children in previous
studies.1,8,15 Our study showed an age effect of P3 latency
in normal controls, but not in children with ADHD, which paralleled the results of other studies in children with other cognitive defects.\(^{22,37}\) ERPs have shown an age difference in selective attention disorders.\(^{5,6}\) We also identified the effect of age on P3 amplitude, with significantly lower amplitude in the central area in children older than 10 years of age, but not in those younger than 9 years old. Other studies have also found a significant difference in P3 waveform in older children (8–12 years) with ADHD, but not in younger children (<7 years).\(^{5,23}\)

A significantly increased N2 latency in the parietal region of ADHD children was identified in the present study. N2 waveforms are believed to be related to signal detection and discrimination.\(^{5,34}\) Inconsistent findings in N2 latency between ADHD and normal controls have been reported, and the results may be related to the age of the test subjects.\(^5\) A number of reports have suggested a decrease in N2 amplitude in the frontal and parietal areas in ADHD patients compared to controls,\(^{13,35}\) whereas others have not found such a difference.\(^{27,36}\) Our study showed a decreased amplitude of N2 in children with ADHD compared to normal controls, but did not reach statistical significance.

P3 in ERPs has been used as a predictor of the response to treatment with CNS stimulants such as methylphenidate and atomoxetine. Administration of methylphenidate normalizes ERP indices, P3 amplitude, and latencies in children with ADHD.\(^{22,37}\) Recently, ERP studies combined with functional magnetic resonance imaging have shown alterations in the frontal striatal and parietal lobe function and its modulation during response inhibition following administration of methylphenidate in children with ADHD.\(^{17,38}\) Hemodynamic deficits in the right middle frontal gyrus and right anterior superior temporal gyrus in functional magnetic resonance imaging have been associated with lower P3 in patients with ADHD.\(^{10,39}\)

In conclusion, children with ADHD show a significant increase in P3 latency, with a reduction in the amplitude compared to normal age-matched controls. A longer latency in P3 suggests slower processing of attention tasks, and lower P3 amplitude is interpreted as disruption in the inhibitory control of children with ADHD. These results suggest that children diagnosed with functional psychiatric disorder such as ADHD may have physiologically related neurocognitive abnormality. However, an important limitation of this study was that ADHD with comorbid disorders was not investigated. The change in P3 and N2 waveforms are also linked to other diseases with attention and inhibition disturbances such as mental retardation, autism, speech—language disorders, learning disability, and other behavioral and cognitive abnormalities. Future studies should involve analysis of detailed comorbid behavior or learning disorder. It should be noted that ERP study may be used as an adjunctive neurophysiological reference for the cognitive abnormality in ADHD children but not as a replacement for clinical diagnosis of ADHD.

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