Event-related potentials study in attention deficit hyperactivity disorder

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Summary

Attention deficit hyperactivity disorder (ADHD) is a childhood disorder characterized by lack of sustained attention, hyperactivity and impulsivity. Children with ADHD have functional impairment occurring at multiple levels. In the present study, cognitive status was assessed using auditory event-related potentials (ERPs). Twenty ADHD children and 20 controls were recruited for the study and ERPs were recorded on a computerized evoked potential recorder, using the international 10-20 system of electrode placement. The ADHD children showed a statistically significant N200 latency prolongation and amplitude decrease compared with the controls; the latencies of the other waves, i.e. N100, P200, P300, were prolonged in the ADHD children but the difference versus the controls was statistically insignificant. Reaction time was significantly longer in the ADHD subjects as compared with the controls. The above findings are suggestive of dysfunctions in the discrimination of task-relevant stimuli and a slower motor response in ADHD children.

KEY WORDS: attention deficit hyperactivity disorder, cognitive function, event-related potentials, information processing

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most disruptive psychiatric disorders of childhood whose principal features are lack of sustained attention, hyperactivity and impulsivity (1). It has been seen that children diagnosed as having attention deficit disorders with hyperactivity show abnormalities in one or more of the cognitive processes. The prevalence of ADHD in different countries varies. Among US children, the prevalence rate ranged from 4% to 12% (2). In the Indian literature, the prevalence of ADHD has been found to range from 1% to 15.5% (3, 4). Children with ADHD usually have functional impairments across multiple settings including home, school and play, and these impairments are especially evident at school. These children are at risk for learning difficulties and often demonstrate academic failure and underachievement, especially during elementary schooling. Various studies have explored attention deficits in children and their findings indicate that ADHD patients perform worse than normal controls across a broad range of cognitive and attentional tasks. The diagnosis of ADHD is essentially a clinical one, based primarily on the subjective impression of teachers, physicians and parents.

Several electrophysiological studies have reported different findings in the central nervous system (CNS) of children with ADHD. Emission topography has shown decreased blood flow in striatal areas (5). Quantitative EEG studies have found increased slow wave activity, mostly theta, in ADHD children compared with normal controls during resting and activation conditions (6). Nowadays, various non-invasive methods (7) are being used to study and understand the neuronal functions and connectivity in the brain and to help in evaluating quantitatively the neurophysiological functions in different disease states (8). Event-related potentials (ERPs) are those potentials of the EEG which are evoked by the perception of or the preparation for events and they include an early sensory evoked potential and a late cognitive response (P300 component) (9). ERPs, which can be recorded through the scalp, are generated by neural activity associated with specific sensory, cognitive and motor processes. In specific neurophysiological tasks, behavioral responses (accurate detection or reaction time) are analysed to detect possible attentional disorders, whereas ERPs provide a continuous index of processing between the stimulus and the response, allowing mental chronometry. As a result, ERP data can be used to isolate different processing stages. The different waves of the auditory ERP have been found to reflect cognitive processes associated with different aspects of selective attention.

The N100 and P200 components are believed to reflect the activity occurring in neural areas that are activated by sensory stimuli and they are independent of the subject’s attention (10). The N200 component is related to the degree of unexpectedness of the stimulus (11). The P300 component of the ERP is associated with psychological processing. It is generated from various sites of the brain including the cortical and subcortical areas, particularly the auditory cortex, hippocampus, amygdala, brainstem and thalamic structures (12). The P300 wave is believed to reflect cognitive processes underlying attention allocation and memory updating (13) and its amplitude indicates the amount of difficulty encountered in differentiating target from non-target stimuli in the "oddball" paradigm of the ERP (14). The ERP might
provide a valuable tool in assessing various childhood behavioral disorders such as ADHD, where it is desirable to differentiate deficits in motor response systems from cognitive dysfunction.

The aim of the present study was to explore the use of electrophysiological measures as a means of objectively investigating the cognitive functioning of children diagnosed with ADHD, as these measures may allow early detection of ADHD and thus timely intervention to improve these subjects' higher function and life performance.

**Materials and methods**

The study was conducted at the Electrophysiology Laboratory of the Department of Physiology, University College of Medical Sciences, Delhi. The study sample was made up of 20 male ADHD children with a mean age of 10.29±2.29 years, while the control group comprised 20 normal male children with a mean age of 10.44±2.3 years. The ADHD subjects were selected from a school for special children (i.e. children with ADHD, dyslexia, or mental retardation, slow learners, etc.) in Delhi. The subjects recruited for the study were among those identified by their respective class teachers as having behavioral or academic problems and subsequently referred to the school's clinical psychologist. Only those subjects diagnosed with ADHD of the combined type, according to the DSM IV criteria, were recruited for the study. Conners' Teacher Rating Scales (CTRS) and Conners' Parent Rating Scales (CPRS) were used to assess the subjects (15). Children born preterm and with a history of perinatal asphyxia, CNS infection, convulsive disorders, mental retardation or psychiatric or neurological abnormalities were excluded from the study.

The 20 controls (age- and IQ-matched) were recruited from an elementary school in the vicinity of our institution. No member of the control group showed any indication of symptoms of ADHD, as evaluated using the CTRS and CPRS, nor had a history of neurological disorder or substance abuse.

All the children underwent a standard IQ test (Malin's Intelligence Scale for Indian Children, MISC), which is an Indian adaptation of the Wechsler Intelligence Scale for Children (WISC), administered by a clinical psychologist. Only those with an IQ of over 85 were included in the study. All the children had been medication-free for at least 24 hours before the electrophysiological recording.

Ethics committee clearance was obtained and informed written consent was given by all the children's parents after the recording procedure had been explained to them. All subjects and controls were tested under similar laboratory conditions. They were familiarized with the experimental and environmental (laboratory) conditions. The recording was done in the presence of either a parent or a teacher.

**Recording procedure**

The recordings were done in a soundproofed room and the subjects underwent a trial session a day before the recording to familiarize them with the stimuli and the recording procedure. The ERPs were recorded on a computerized evoked potential recorder (Nihon Kohden Neuropack μMEB 9100, Japan) using silver-silver chloride disk electrodes at Fz, Cz and Pz (active electrodes) with FPz as the ground electrode and A1 and A2 as the ear reference electrodes, placed according to the international 10-20 system. The skin-electrode contact impedance was kept below 5KΩ. The subjects were instructed to close their eyes to avoid blink artifacts.

The auditory ERPs were recorded using an "oddball paradigm" wherein two stimuli (target and non-target) were presented in a random order by headphones. The target stimulus was a 2 KHz click sound with 20% occurrence and the non-target a 1 KHz beep with 80% occurrence. The auditory stimuli had a 10 msec rise/fall time, a 100 msec duration and an intensity of 60 dB above the hearing threshold. The evoked potentials were filtered with a bandpass of 0.1-50 Hz and averaged for 30 responses. The response time ranged from 0 to 500 msec. The subjects pressed a button in response to the target stimulus. Data for two trials were obtained, stored and averaged by computer. The peak latencies of the ERPs were evaluated from stimulus onset (stimulus artifact) to the peak point of the particular wave, i.e. the point of greatest amplitude. Amplitude was measured as the distance of the corresponding peak from the baseline.

**Statistical analysis**

The data obtained were analyzed using SPSS software (Version 13.0). The statistical analysis for the comparison between the ADHD children and the controls for the three electrode montages, i.e. Fz, Cz, Pz, was performed using repeated measures ANOVA followed by Tukey's test. The repeated measures ANOVA used one between factor and one within factor. The three electrodes (montages-Fz,Cz,Pz), combined, served as the within factor, while the between factor was group (control and ADHD).

All tests were two-tailed. The results are expressed as mean values ± SD.

**Results**

Table I shows the absolute peak latencies of the N100, P200, N200 and P300 waves of the ERPs in the controls and ADHD children. A significant prolongation of the N200 latency was seen in the ADHD children as compared with the controls; the other waves, i.e. N100, P200, P300, were also prolonged in the ADHD children, although the difference versus the controls was statistically insignificant.

The amplitude of the N200 was significantly decreased in the ADHD children as compared with the controls (Table II). Reaction time was significantly longer in the ADHD subjects as compared with the controls (Table III).

A multivariate analysis was done to study the influence of Conners scores on N200 latency and it was found that the N200 latency was not significantly different in the two groups when adjusted for Conners scores. A representative waveform of ERPs recorded in control and ADHD children is given in figure 1 (see p. 90).
Discussion

The present study shows a significantly prolonged latency and decreased amplitude of the N200 wave in subjects with ADHD. Our findings are comparable to those of other studies. Lazzaro et al. (16) found a significantly smaller N200 amplitude and larger P200 amplitude across the midline sites in ADHD patients compared with controls, although they found no significant group differences in N100 amplitude. They also found a significant delay in N200 latency across midline sites along with a delay in P300 latency in the ADHD group compared with controls. They concluded that ADHD patients showed deficits in information processing as reflected by their ERP findings. Satterfield et al. (17) reported significant reductions of auditory N100, N200, and P3b and visual N200 amplitudes in ADHD subjects as compared with normal subjects. They concluded that ADHD boys suffer from deficient preferential processing of attended stimuli and that the P3b and N200 abnormalities found point to deficiencies in two independent cognitive processes thought to be crucial to what we perceive, learn, and remember. Johnstone et al. (18), in their study, found the P3b component to target stimuli to be smaller in the posterior region and larger in the frontal region in the ADHD group compared with the control group. They also found that the mean reaction time to

Table I - Mean latencies (msec) of event-related potential components

<table>
<thead>
<tr>
<th>Waveform</th>
<th>Electrodes</th>
<th>Controls</th>
<th>ADHD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fz</td>
<td>133.22±20.87</td>
<td>136±17.6</td>
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<tr>
<td>N100</td>
<td>Cz</td>
<td>114.22±24.93</td>
<td>132.33±24.67</td>
<td>0.171</td>
</tr>
<tr>
<td></td>
<td>Pz</td>
<td>111.89±20.12</td>
<td>138.83±37.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fz</td>
<td>194.78±19.32</td>
<td>205.6±23.76</td>
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</tr>
<tr>
<td>P200</td>
<td>Cz</td>
<td>187.44±14.78</td>
<td>205.2±30.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pz</td>
<td>193.44±37.85</td>
<td>220±44.98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fz</td>
<td>234.5±24.37</td>
<td>332±55.7</td>
<td></td>
</tr>
<tr>
<td>N200</td>
<td>Cz</td>
<td>235±23.62</td>
<td>321.4±46.48</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>Pz</td>
<td>241.5±46.69</td>
<td>287.6±67.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fz</td>
<td>352.3±29.88</td>
<td>400±81.42</td>
<td></td>
</tr>
<tr>
<td>P300</td>
<td>Cz</td>
<td>337.4±30.11</td>
<td>403.67±85.42</td>
<td>0.095</td>
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<tr>
<td></td>
<td>Pz</td>
<td>368.1±50.89</td>
<td>415±105.05</td>
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</table>

\*p<0.001

Table II - Mean peak amplitudes (µV) of event-related potential components

<table>
<thead>
<tr>
<th>Waveform</th>
<th>Electrodes</th>
<th>Controls</th>
<th>ADHD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fz</td>
<td>11.78±2.43</td>
<td>13.52±7.78</td>
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<tr>
<td>N100</td>
<td>Cz</td>
<td>9.45±4.97</td>
<td>8.2±3.04</td>
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<tr>
<td></td>
<td>Pz</td>
<td>6.89±3.87</td>
<td>5.65±2.87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fz</td>
<td>3.9±2.79</td>
<td>10.13±6.44</td>
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<tr>
<td>P200</td>
<td>Cz</td>
<td>7.8±4</td>
<td>5.96±4.66</td>
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<tr>
<td></td>
<td>Pz</td>
<td>5.04±3.81</td>
<td>5.54±4.48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fz</td>
<td>23.45±14.29</td>
<td>8.15±3.11</td>
<td></td>
</tr>
<tr>
<td>N200</td>
<td>Cz</td>
<td>10.76±4.23</td>
<td>5.54±5.76</td>
<td>0.014*</td>
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<tr>
<td></td>
<td>Pz</td>
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<td>3.46±4.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fz</td>
<td>7.25±5.95</td>
<td>14.39±10.1</td>
<td></td>
</tr>
<tr>
<td>P300</td>
<td>Cz</td>
<td>15.82±9.07</td>
<td>6.78±2.91</td>
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</tr>
<tr>
<td></td>
<td>Pz</td>
<td>17.71±9.59</td>
<td>10.58±11.79</td>
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</tbody>
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\*p<0.05

Table III - Mean reaction time (msec)

<table>
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<tr>
<th>Control</th>
<th>ADHD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>468.7±112.82</td>
<td>762.17±200.86</td>
<td>0.002*</td>
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</table>

\*p<0.05

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targets was longer in the ADHD group than in the control group, although the difference was not significant. They concluded that the ADHD subjects compared with the controls use an additional cognitive process when processing task-relevant stimuli. This process is more frontally distributed and may reflect an additional compensation mechanism in ADHD subjects. Contrary to our observations, Loiselle et al. (19) found decreased P300 amplitudes to attended signals at site Cz in their clinical group. Holcomb et al. (20) recorded ERPs to an oddball task in two groups, i.e., attention-deficit disorder with hyperactivity (ADHD) and attention-deficit disorder without hyperactivity (ADDWH) respectively. They found that parietal P3b amplitude to target stimuli differentiated the control from the clinical groups but not the clinical groups from each other. The P200 component was found to be larger at Cz in the ADHD group than in the ADDWH and control groups. Sunohara et al. (21) found that their ADHD group, at baseline, was more impulsive and inattentive than controls and had shorter P200 and N200 latencies and longer P300 latencies. Satterfield et al. (22) suggested that the abnormally low P3b response to attended target stimuli found in ADHD boys may be due in part to insufficiency of the noradrenergic activity of the locus coeruleus (LC), activity that is normally triggered by attended task-relevant or novel stimuli. Johnstone et al. (23) recorded ERPs using an oddball paradigm in two subtypes of ADHD (attention deficit hyperactivity disorder combined type: ADHD-C and attention deficit hyperactivity disorder predominantly inattentive type: ADHD-IA). They found significantly longer reaction time in the ADHD-C subjects versus the controls, but not in ADHD-IA subjects. Their study revealed differing patterns of abnormal component development for each subtype, indicating qualitative differences in information processing stage deficits in each of these ADHD subtypes. Puente et al., in a sample of children with attention deficit disorder (24), found significant prolongation of the P300 latency and a significant decrease in P300 amplitude. Idiazábal-Alecha et al. (25) performed P300 wave recording using auditory and visual oddball paradigms and found significantly longer latencies and smaller amplitudes of P300 in ADHD patients compared with controls. They concluded that there is an abnormal processing of cognitive information in children with predominantly inattentive type of ADHD and thus a dysfunction in attentional mechanisms. Although the ADHD literature shows a considerable level of consistency, there are also many contradictory findings. Studies of ERPs have used continuous performance, oddball paradigms and selective attention tasks across the sensorimotor processing chain and produced highly variable results. Studies have recorded both visual and auditory ERPs in ADHD children and, again, produced extremely variable results. Various differences in ERP methodology and experimental procedures can account for many of the discordant results. Auditory ERPs have different waves and each has been found to reflect cognitive processes associated with different aspects of selective attention. The N100 component is thought to represent the initial extraction of information from the sensory analysis of the stimulus or the excitation associated with allocation of a channel for information processing from the primary cortex (26). The P200 component may represent inhibition of sensory input from further processing (27) possibly via automatic stimulus identification and discrimination/classification or inhibition of other channels of information competing for attention and further processing (28). The N200 component is thought to represent an endogenous mismatch detection process related to stimulus discrimination. This component has been associated with response identification (29) and response selection. Reduced N200 amplitudes in our study group (ADHD children) may reflect dysfunctions in the discrimination of task-relevant stimuli (17), thus suggesting delayed discrimination processing in ADHD subjects. P300 latency has been associated with the timing of stimulus evaluation processes and its amplitude indicates the amount of processing required by a given stimulus (30). P300 generation has been associated with a number of subcortical regions including the LC and the hippocampus. The P300 component has also been found to be generated in a number of cortical regions including the temporal-parietal lobes. The P300 wave is one of the cognitive components of the ERP frequently used to investigate attention and cognitive processes. The lack of significant P300 amplitude differences between the control and the ADHD patients in our study suggests that there were no deficits in the allocation of processing resources to task-relevant stimuli during the auditory oddball paradigm. It has been proposed that the core disturbance in ADHD is a dysfunctional non-adrenergic system and its interaction with posterior attentional and executive networks (31). Mesocortical dopaminergic pre-frontal networks are known to be involved in the control of motor activity and cognitive processes and are thought to be disturbed in ADHD children (32). Our finding of prolonged reaction times in ADHD children is suggestive of a dysfunction in attentional mechanisms along with a slowing of motor responses in these children. Studies have shown that the posterior parietal cortex, the frontal lobes, the limbic system and the reticular ac-

Figure 1 - Representative waveforms of event-related potentials recorded in controls and ADHD subjects.
Activating system play a role in attention. The primary noradrenergic pathway has a reticular origin in the LC and it projects extensively throughout the CNS (33). Both spontaneous and sensory LC discharges fluctuate with behavioral state, LC excitability increases with increasing degrees of attention to the external environment and LC discharge (like P3b discharge) is triggered by unexpected sensory stimuli. Noradrenaline release in LC terminal areas enhances signals (parietal P3b) in the brain systems engaged by endogenous attended sensory stimuli. Decreased N200 amplitudes, as seen in our study, also support the hypothesis of low noradrenergic system activity, thus reflecting a dysfunction in the discrimination of task-relevant stimuli.

The above findings/results indicate that ADHD pathophysiology impairs brain systems that are important for allocating attention and using cognitive representation to guide cognition and behavior. Attention-related neural dysfunction is thus an important factor to consider in neurobiological theories of ADHD. Due to the small number of subjects recruited, these results may not reflect the true variability of neurophysiological variables in the general population. The authors plan to further extend the study by recruiting more cases and conducting follow-up evaluations of all the recruited subjects.

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