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P300 WAVE OF AUDITORY EVENT RELATED POTENTIALS IN CHILDREN DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

Physiology

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ABSTRACT

Objective: P300 wave of Event related brain potentials (ERPs) is a non-invasive technique to study neural activity associated with sensory and cognitive information processing. The aims of the present study were to investigate amplitude and latency of P300 wave in children with attention deficit hyperactivity disorder (ADHD) and to determine the cognitive deficits as measured by the P300 component of ERPs in children with ADHD. **Methodology:** This study included 28 children in the age group of 6 to 12 years. 18 children with ADHD were compared with 10 healthy age matched siblings. P300 Latency and amplitude were measured in both the groups and comparison was done. **Results:** In ADHD cases value of P300 Latency is significantly delayed at Fz, Cz and Pz as compared to the control group (Fz: 375.4 ± 27.20 vs 317.4 ±19.62 ms, p=0.0001; Cz: 383.2 ± 21.45 vs 312.8 ± 16.69 ms, p=0.0001; and Pz 374.4 ± 29.40 vs 308.9 ± 18.39 ms , p=0.0001). Moreover, In ADHD cases value of P300 amplitude is significantly reduced at Fz, Cz and Pz as compared to the control group (Fz: 4.2 ± 1.84 vs 11.2 ± 3.29 µV, p=0.0001; Cz: 5.2 ± 2.35 vs 13.2 ± 2.49 µV, p=0.0001 and Pz: 4.7 ± 2.16 vs 12.8 ± 1.48 µV, p=0.0001). **Conclusion:** The study shows that in children diagnosed with ADHD, there is a significant delay in P300 latency and reduction in P300 amplitude as compared to healthy age matched siblings. The neurophysiologic deficits are substantial and objectively identifiable by the P300 wave of ERP.

KEYWORDS

ADHD, P300, ERP

INTRODUCTION

ADHD is characterized by a pattern of diminished sustained attention and higher levels of impulsivity in a child or adolescent than expected for someone of that age and developmental level [1]. There is high prevalence of ADHD among primary school children in India showing the prevalence ranging from 7.2% [2] in adolescents to 11.32% [3].

In ADHD a global maturational delay based on reduced gray and white matter volumes and cortical thickness is present along with altered maturational courses of selected regions such as the caudate nucleus and frontal cortical mantle. There are functional activation differences between ADHD and control subjects which include frontal-striatal-cerebellar networks, affecting executive function, Limbic-frontal networks affecting motivational function and parietal-temporal networks affecting attentional function.[4].The P300 (also known as P3 or P3b) is a large, broad, positive component in the ERP that typically peaks 300 ms or more after onset of a rare, task-relevant stimulus. The P300 has a centro-parietal scalp distribution that is maximal over midline scalp sites. The generator sites for ERPs P300 in the brain are the inferior patrietal lobe/temporo-parietal junction (TPJ), the supplementary motor cortex (SMA) and the anterior cingulate cortex (ACC), the superior temporal gyrus (STG), the insula and the dorsolateral prefrontal cortex. These structures are also involved in attention [5].

In a study by Jonkman et al [6], ADHD children and normal controls (7-13 yrs old) performed an auditory and visual selective attention task. In the auditory task, controls had more correct detections (hits), less false alarms, larger P3b amplitudes to non target stimuli , a larger central PN and larger early frontal positivity (100-250 ms) to target stimuli than ADHD subjects. In the visual modality, controls had more correct detections, less false alarms, larger P3b amplitudes to non target stimuli (but not to hits), and larger frontal P3(1) amplitudes to infrequent than to frequent stimuli. So, in ADHD children in both the auditory and the visual task, there was a deficit in the activation of the P3b process[6]. P3a subcomponent of P300 wave originates from stimulus-driven frontal attention mechanisms during task processing, whereas P3b originates from temporal-parietal activity associated with attention and appears related to subsequent memory processing [7].

In a review of various studies of children with ADHD have reported abnormalities in visual and auditory ERP, and children with this diagnosis have small P300 amplitudes to both auditory and visual stimuli. A decrement in P300 at posterior electrode sites was seen in conjunction with an augmentation at frontal sites suggesting a shift in source activity or different activity of P300 in AD/HD [8]. Children with ADHD show deficits in auditory information processing [9]. In another study in ADHD children, P300 amplitude and latency were attenuated and prolonged compared to controls at the frontocentral, centroparietal, and parietal positions. Furthermore, levels of P300 latency at these positions were positively correlated with the inattention subscale scores[10].

ERPs from four groups of children: reading disabled, attentional deficit disorder with and without hyperactivity, and normal controls showed that P3 amplitude between targets and non targets was smaller in the two attentional deficit groups and also P3 latency was significantly longer in only the attentional deficit groups across blocks of the task[11]. A recent meta analysis by Kaiser et al [12] on earlier versus later cognitive ERPs in ADHD showed in these individuals the smaller Cue-P300-amplitudes, longer Go-P300-latencies, smaller NoGo-P300-amplitudes and longer NoGo-P300-latencies. They also observed significant heterogeneity in the results obtained from various studies with respect to ERP [12].

Therefore, the review of the literature shows that limited studies are available in which the ERPS have been used to study neurophysiological changes in children with ADHD and parameters used in these studies are different. Moreover, these studies showed variable results. Not many studies on the ADHD children are available in Indian context. So, the present study was planned to study the cognitive deficits as measured by the P300 component of ERPs in children with ADHD.

MATERIAL AND METHODS

A permission from the institutional ethics committee was obtained regarding the scientific validity, research plan and ethical issues before beginning the study which was conducted between November 2016 to January 2021. A total of 37 children were recruited for the study in which there were 20 cases and 17 controls. Out of the total 37 children, 9 subjects (2 tests and 7 controls) whose MMN and P300 components were difficult to analyze due to excessive movements were excluded from the study.

All newly diagnosed patients attending Psychiatry OPD fulfilling the inclusion criteria of either gender in the age range of 6 to 12 years for the study were included subject to written informed consent from the parents as approved by the institutional ethics committee. The diagnosis of ADHD was based on the DSM-V criteria. The diagnosis

of ADHD was based on the DSM-V criteria A. For inclusion in the study , ADHD children included were theNewly diagnosed cases of ADHD confirmed by the Psychiatrist as mentioned in diagnostic criteria according to the DSM – V of either gender in the age range of 6 to 12 years. Control children were the apparently healthy siblings of the ADHD children in the age group of 6 to 12 years .For exclusion from the study, The Patients with hepatic, renal, cardiovascular diseases, diabetes mellitus, cancer and systemic inflammatory disorders were excluded from the study. Similarly, the patients with Tourette's syndrome, seizure disorders, learning disabilities, autism, mental retardation, and other psychotic disorders were also excluded. Any patient having received any medication for at least two months prior to the initiation of the study and presence of any significant visual or hearing impairment were not included.

ADHD rating scales

Connors' parent rating scale[13]:- The short version of Connors' rating scale was used as it is the most useful diagnostic tool for ADHD because of its brevity and high accuracy. This scale has ten questions regarding the child's behavior in the last one month with four possible answers: Not at all (0), Just a little (1), Pretty much (2) and Very much (3). The questions were read one by one to the parents, and the responses were marked on the rating scale accordingly. Connors' abbreviated parent rating scale has a maximum score of 30. A score of more than 15 is suggestive of ADHD. Reduction in the score after treatment signifies clinical improvement .

Vanderbilt ADHD Parent rating scale[14]:- The Vanderbilt ADHD Parent rating scale is based on DSM-V criteria. The scale has two components: symptom assessment and impairment in performance. On this scale the symptom assessment screens for symptoms that meet criteria for both inattentive (items 1–9) and hyperactive ADHD (items 10–18). To meet DSM-V criteria for the diagnosis, one must have at least six positive responses to either the inattentive 9 or hyperactive nine symptoms or both. A positive response is marked as a 2 or 3 (often, very often). There is a place to record the number of positives in each sub-segment, and a place for the total score for the first 18 symptoms. The scale also has symptom screens for three other co-morbidities oppositional-defiant, conduct, and anxiety/ depression. To meet criteria for ADHD, there must be at least one item of the Performance set in which the child scores a 4 or 5; i.e., there must be an impairment, and not just symptoms to meet the diagnostic criteria. The scale has a place to record the number of positives (4s, 5s) and an Average Performance Score is calculated by adding the number of positives and dividing it by the number of Performance criteria answered.

P300 wave of Auditory ERP[15]: Recordings were done as per the guidelines of International Federation of Clinical Neurophysiologists (IFCN). Electrophysiological study for assessment of P300 variables were done over SCHWARZER TOPAS EMG neurophysiological measuring system. A 4 channel EMG/NCV/EP system. ERPs were recorded in context of a standard auditory oddball paradigm stimulus. The signal is picked by electrodes, then filtered, amplified, averaged and displayed on screen. The "oddball paradigm" of auditory stimulation was applied. ERP's were elicited binaurally through headphones with a typical intensity of 60dB above the hearing level, depending upon the subject. The 132 sweeps were randomly presented to the subject, of which 20% given at frequency of 4000 Hz were the rare stimuli (target stimuli) and rest 80% of the tones were frequent stimuli given at frequency of 1000 Hz. Instructions were given to press the button when they heard a rare tone or count the number of rare tones presented. All artifact free ERP responses to the rare tones were analysed visually. Latency for P300 was in the 250-700 msecrange . In the analysis of potential, amplitude of P300 was measured from the peak of p2 to the peak of p3. (N2-P3)

Statistical Analysis: Data was coded, entered and analyzed in Graph pad prism 8.4 and SPSS version 26. The data obtained was tested for normal Gaussian distribution by using Shapiro Wilk & Kolmogrov Smirnov test and accordingly parametric and nonparametric tests were applied. For all continuous variables the data was expressed in term of mean ± S.D./S.E.M

RESULTS:

Both the ADHD and control group were comparable in terms of age and socioeconomic status. The mean age of the ADHD group was 8.6 ± 1.81 Years and the control group was 9.8 ± 1.54 years (p = 0.1083, not significant). There were 16 boys and 2 girls in the ADHD group and 7 boys and 3 girls in the control group. No significant difference by Chi Square test was found in the group distribution(p=0.315).

The ADHD and control groups differed highly significantly in Connors test scores by Mann Whitney test (ADHD group median 23.0, control group median 9.0, P value <0.0001). The ADHD group showed inattentive symptoms in 14 subjects (77.8%), hyperactivity in 16 subjects (89 %), anxiety-depressive symptoms in 4 subjects (22.2%) and conduct disorder in 11 subjects (61%). Impulsive and inattentive combined symptoms were shown in 12 subjects (67%).

Table 1: Statistical analysis of the P300 latency values between ADHD group and Control group of children

S. No	PARAMETER	ADHD Group (Mean ± SD) N=18	Control Group (Mean ± SD) N=10	P value
1	P300 latency (ms) Fz	375.44 ± 27.20	317.40 ± 19.62	<0.0001
2.	P300 latency (ms) Cz	383.28 ± 21.45	312.80 ± 16.69	<0.0001
3	P300 latency (ms) Pz	374.44 ± 29.40	308.90 ± 18.39	<0.0001

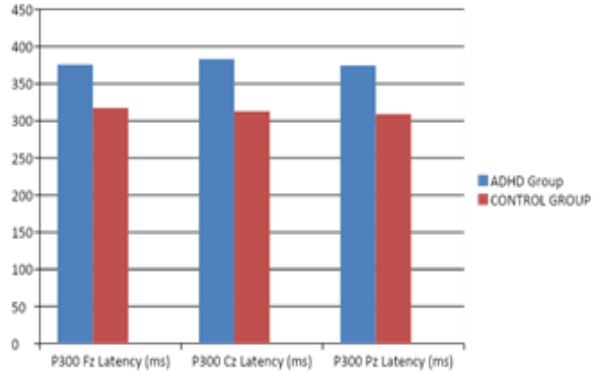

Figure 1: Bar diagram showing the P300 latency values comparison between ADHD group and Control group of children

Table 1 and Figure 1 shows significant difference in the P300 Latencies recorded at Fz, Cz & Pz among ADHD & normal controls. In ADHD cases, value of P300 Latency is significantly delayed at Fz, Cz and Pz as compared to the control group (Fz: 375.4 ± 27.20vs 317.4 ± 19.62 ms, p=0.0001; Cz: 383.2 ± 21.45 vs 312.8 ±16.69ms, p=0.0001; and Pz 374.4 ± 29.40 vs 308.9 ±18.39ms , p=0.0001)

Table 2: Statistical analysis of the P300 amplitude values between ADHD group and Control group of children

S. No	Parameter	ADHD GROUP (Mean ± SD) N=18	Control GROUP (Mean ± SD) N=10	P value
1	P300 amplitude (μV) Fz	4.28 ± 1.84	11.20 ± 3.29	<0.0001
2.	P300 amplitude (μV) Cz	5.28 ± 2.35	13.20 ±2.49	<0.0001
3	P300 amplitude (μV) Pz	4.78 ± 2.16	12.80 ±1.48	<0.0001

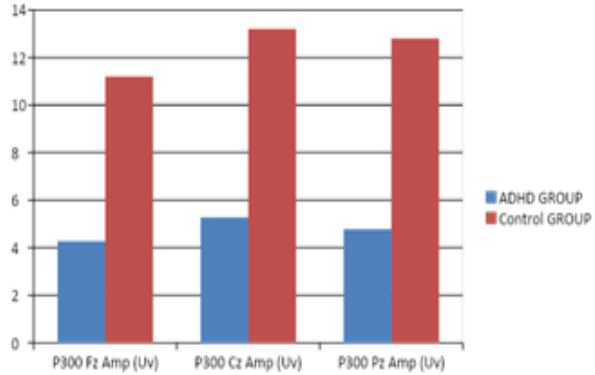

Figure 2: Bar diagram showing the P300 amplitude values comparison between ADHD group and Control group of children

Table 2 and Figure 2 show significant differences in the P300 amplitudes recorded at Fz, Cz & Pz among ADHD & normal controls. In ADHD cases value of P300 amplitude is significantly reduced at Fz, Cz and Pz as compared to the control group (Fz: 4.2 ± 1.84 vs 11.2 ± 3.29 μV, p=0.0001; Cz: 5.2 ± 2.35vs 13.2 ± 2.49 μV, p=0.0001 and Pz: 4.7 ± 2.16 vs 12.8 ±1.48μV, p=0.0001).

DISCUSSION

In present study, there was increased latency of P300 and decreased amplitude in children with ADHD children as compared to controls. These findings are similar to the various studies already mentioned [8, 10, 11]. Additionally, similar findings with respect to P300 amplitude were obtained in a study by Kemner et al[16] who studied ERPs of ADHD and normal children in response to visual and auditory stimuli in a condition without task relevance as well as in a task-relevant condition. ADHD children showed smaller P300 amplitudes and smaller MMN to auditory deviant stimuli, irrespective of task relevance. The P300 deficits were attributed to defects in the cognitive process related to attention[16]. In a longitudinal study, ERP waves of young ADHD boys the degree of abnormality in the P3b responses to target stimuli in ADHD boys (lower than normal boys) was found to increase with age[17]. Yoon et al [18] similarly showed that ADHD-comorbid but not ADHD-pure subjects displayed significant P300 amplitude reduction and poorer task performance compared to controls.

A recent met analysis by Kaiser et al [12] involved database search of 52 relevant articles which included n = 1576 ADHD and n = 1794 non-ADHD subjects. In this meta-analysis, it was observed that for earlier components of ERPs , individuals with ADHD showed shorter Go-P100-latencies than non-ADHD. For later ERPs, individuals with ADHD showed smaller Cue-P300-amplitudes, longer Go-P300-latencies, smaller NoGo-P300-amplitudes, longer NoGo-P300-latencies, smaller CNV-amplitudes, and smaller Pe-amplitudes. The moderate to large effects obtained for these later components indicate core deficits in later, higher-order cognitive processing stages and might represent possible biomarkers of ADHD while shorter P100-latencies might be interpreted as a failure to further engage in such attentional processing necessary for successful cognitive modulation of sensory processing. Moreover, stronger effects were observed in children compared to adolescents or adults, for the P100, the N200, the P300, and the Pe components in different task conditions, thus explaining the heterogeneity in the results of various studies with respect to different parameters used and also due to different age groups included in the respective studies[12]. A decreased amplitude or small P300 amplitude in ADHD directs towards behavioral dis-inhibition and a failure of behavioral control, the oppositional defiant disorder, conduct disorder, antisocial personality disorder, alcoholism, nicotine dependence, and illicit drug abuse and dependence [19].

Hence, the findings in our study on Indian children diagnosed with ADHD show that the deficits in neuro-physiological correlates of cognition as shown by a significant delay in latency of P300; and a significant reduction in amplitude of P300 corroborate with the findings of various national and international studies. It also shows these deficits are substantial and objectively identifiable by the Neurophysiologic parameters such as P300 wave of event related potentials.

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