**ABSTRACT:**

P50 sensory gating in children and adolescents with ADHD and effects of methylphenidate administration on P50 sensory gating

**Objective:** The P50 is thought to reflect a sensory gating mechanism and prevent information overload in humans. Failure to inhibit the P50 auditory event evoked response can occur in attention deficit hyperactivity disorder (ADHD) patients. The aims of the present study were to examine the inhibition of the P50 auditory event evoked potential and the effects of methylphenidate administration on P50 parameters in children and adolescents diagnosed with ADHD.

**Methods:** Twenty-two drug-free subjects, aged 9-14, who were diagnosed with ADHD (the combined type) according to the DSM-IV criteria, and 18 mentally and physically healthy subjects, aged 9-12, were included in the study. First, P50 parameters were measured in drug-free ADHD subjects and healthy controls. Following this measurement, 10 mg of methylphenidate was administered to the ADHD group. The P50 measurement was repeated 1 hour following methylphenidate administration in the ADHD subjects. The healthy control group was not re-examined.

**Results:** A significant difference was found in P50 test latency, test amplitude, and P50 ratio values between the ADHD group and healthy controls. Significant differences were also found in conditioning latency, test latency, test amplitude, and P50 ratio values between before and after methylphenidate administration in the ADHD group.

**Conclusions:** The results of the present study point out an association between P50 and ADHD and they also show that methylphenidate administration increases the P50 suppression level. Since, this is the first study evaluating sensory gating in children and adolescents with ADHD, it should be considered as a preliminary study. Further studies with large study samples are warranted.

**Key words:** Attention deficit hyperactivity disorder, children, P50, sensory gating

**Bulgular:**

HEV ve sağlıklı kontrol grubu arasında P50 test latansı, test amplitütü ve P50 oranları açısından belirgin düzeyde anlamlı fark ölçümlerde koşullanma latansı, test latansı, test amplitütü ve P50 oranları açısından belirgin fark bulunmuştur.

**Sonuç:** Bu araştırmaın sonuçları HEV ile P50 arasında bir ilişki olduğuna ve metilfenidat uygulamasının P50 baskılanma içerisinde olduğu artırıldığına işaret etmektedir. Bu araştırma HEV olan çocuk ve ergenlerde duyusal kapılama mekanizmasına olan etkisini ortaya konulmuştur. Dikkat eksikliği hiperaktivite bozukluğu (DEHB) hastalarında P50 işitsel olayla ilişkili yanıtın baskılanması saptanmıştır. Dikkat eksikliği hiperaktivite bozukluğu (DEHB) hastalarında P50 işitsel olayla ilişkili yanıtın baskılanması ve DEHB tanılı çocuk ve ergenlerde metilfenidat tedavisinin P50 parametreleri üzerine olan etkilerinin ortaya konmasıdır.

**Yöntem:** Araştırma DSM-IV tanı ölçütlerine göre DEHB hastaları ve sağlıklı kontrol grubu ile P50 işitsel olaya ilişkili yanıtın baskılanmasını ve DEHB tanılı çocuk ve ergenlerde metilfenidat tedavisinin P50 parametreleri üzerine olun etkilerinin ortaya konmasını amaçlamaktadır. Bu araştırmaın amaçları P50 işitsel olaya ilişkili yanıtın baskılanması ve DEHB tanılı çocuk ve ergenlerde metilfenidat tedavisinin P50 parametreleri üzerine olan etkilerinin ortaya konmasını amaçlamaktadır. Bu araştırmaın amaçları P50 işitsel olaya ilişkili yanıtın baskılanması ve DEHB tanılı çocuk ve ergenlerde metilfenidat tedavisinin P50 parametreleri üzerine olan etkilerinin ortaya konmasını amaçlamaktadır.
INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is an early onset disorder of developmentally inappropriate levels of attention, hyperactivity, and impulsivity. A core feature of ADHD is the inability to regulate attention and to inhibit distraction of attention by irrelevant stimuli (1). Individuals with ADHD have structural abnormalities in brain areas that are considered to regulate attention and executive functions (2). Dopamine and norepinephrine functions have been implicated in the pathophysiology underlying ADHD (3,4). Stimulants are the most widely used drugs in children with ADHD and are highly effective in alleviating ADHD symptoms (5). Methylphenidate (MPH) is the most commonly prescribed psychostimulant. MPH can speed the discrimination of target and non-target stimuli (6).

Sensory gating is a normal physiological process that is mediated by the central nervous system which allows an organism to filter or gate irrelevant or intrusive cognitive or sensory processes. Disruption of sensory gating is considered to lead to abnormalities in attention related information processing, which are observed in different neuropsychiatric illnesses (7). The most widely used methods to measure sensorimotor gating is prepulse inhibition (PPI) of the startle reflex and the inhibition of P50. Whereas PPI is a measure of sensorimotor gating, P50 is a measure of sensory gating without a significant motor contribution (7). The change in P50 amplitude is typically measured as the response to click pairs separated by 500 msec (9,10). Sensory gating is usually defined as the ratio of P50 amplitude after the second click (S2) to the P50 amplitude after the first click (S1) (11). P50 is thought to reflect a sensory gating mechanism and prevent information overload in humans (12). The deficit in the P50 suppression has been suggested to reflect an impairment of central inhibitory circuits that modulate cortical responses to sensory inputs (13).

Event related potentials are considered as measures of attention (14). N100, P300, and mismatch negativity amplitude reductions have been reported in children with ADHD (15-18). The P200 latency range is also greater in children with ADHD (17,18) and stimulant administration enlarges these late positive waves in children with ADHD and shortens the latencies of the P200 (19). To our knowledge, no published study has measured P50 auditory event-evoked potential gating in children with ADHD. Moreover, there is so far only one report in the literature about P50 suppression in adults with ADHD (20). P50 inhibition in adults with ADHD was found to be comparable to healthy controls and significantly higher compared to schizophrenic subjects (20).

There is increasing evidence suggesting that the frontal cortex plays an important role in mediating P50 suppression (21,22). It is an interesting speculation that maturation of P50 suppression may depend on maturation of regions of the frontal lobes responsible for the suppression of irrelevant or superfluous stimulus information (23). There is considerable evidence suggesting ADHD is characterized by a delay rather than a deviance in cortical maturation (24). Shaw and colleagues showed that the median age by which 50% of the cortical points had attained peak thickness for the ADHD group was 10.5 years, which was significantly later than the median age of 7.5 years for the typically developing controls. Interestingly, the differences were most prominent in the middle prefrontal cortex and to a lesser extent in the superior prefrontal and medial prefrontal cortices. As the prefrontal cortex modulates cortical responses to repetitive sensory stimuli (21), the association between the P50 gating deficit and frontal dysfunction in ADHD is a plausible suggestion.

The current study had two main aims. The first aim was to compare P50 suppression in children and adolescents with ADHD and healthy controls, in order to test whether the underlying pathophysiological deficit of inhibition is or is not present in ADHD. The second aim of the study was to examine the effects of MPH administration on P50 suppression in children and adolescents diagnosed with ADHD.

METHODS

Subjects

Twenty-two drug-free subjects (thirteen boys, nine girls), aged 9-14, who were admitted to the Department of Child and Adolescent Psychiatry of Gulhane Military Medical Academy, and diagnosed with ADHD-combined type according to the DSM-IV criteria, requiring at least six hyperactive-impulsive or inattentive symptoms of ADHD by 7 years of age and at the time of assessment,
were included in the study. Exclusion criteria for the study group were: (i) having any current or past psychiatric or neurological disorder other than ADHD and (ii) taking any psychotropics within last month. One child with borderline intellectual functioning, one child with pervasive developmental disorder (not otherwise specified), one child with developmental stuttering and two children with learning disorder were excluded from the study group. Eighteen comparable mentally and physically healthy subjects (eight boys, ten girls), aged 9-12, who had similar socio-demographic characteristics were included in the study as a healthy control group. Exclusion criteria for the control group were: (i) seizure disorders, (ii) mental retardation, (iii) severe head injury, (iv) organic brain damage and any other acute or chronic physical or mental illnesses, and (v) use of medication in the last month that can affect the central nervous system. This study was carried out in accordance with the Helsinki Declaration of the World Medical Association and was approved by the National Ethics Committee of the Ministry of Health in Turkey. Informed parental consent was obtained for all children before their inclusion in the study.

Psychiatric evaluation

A psychiatric evaluation was performed by a pediatric psychiatrist for all the children and adolescents participating in the study, and the structured interview technique of the Schedule for Affective Disorders and Schizophrenia for School Aged Children- Present and Lifetime Version (Kiddie-SADS-PL) (25,26) was administered.

Procedures

P50 Procedure

Following the initial baseline clinical evaluation, P50 measurements were made in the drug free ADHD group and the healthy controls. All subjects with ADHD had taken a stable dose of MPH for at least 1 month and none of them reported MPH use within 24 h (approximately eight half-lives) prior to the P50 measurement. After the first P50 measurement, short-term MPH (Ritalin®, 10 mg) was administered to the ADHD group. The P50 measurement was repeated approximately 1 h following MPH administration. The healthy control group was not re-examined.

P50 Measurement

The electrophysiological examination was performed only during the afternoon hours (at the same time of the day for all subjects) at the Laboratory of Clinical Neuropsychology of Department of Neurology at Gulhane Medical Military Academy. The electroencephalogram (EEG) was recorded with an Electromyography/evoked potential (EMG/EP) device Medelec™ Synergy T-EP - EMG/EP Made in Ireland.

The subjects were seated in a comfortable recliner in a quiet, lighted room while wearing headphones for presentation of the auditory stimuli. They were instructed to relax, to keep their eyes open, and to focus on a fixed point. Eye movements were recorded by using electro-oculography (EOG) with Ag/AgCl electrodes placed at the outer canthus of the left eye and below the right eye. Electrodes were used at seven recording sites (Fz, Cz, Pz, C3, and C4, according to the 10/20 system) with a forehead ground and reference linked to the left earlobe. All electrode resistances were less than 10 kohm. The stimuli were generated by means of computer-driven pulses with 1 msec duration by using a signal generator and data acquisition system for the recording of EEG waveforms. Auditory stimuli were presented in pairs in a conditioning-testing (C-T) design with a 0.5-second intrapair interval and a 10-second interstimulus interval by the Brain Data Acquisition System, and were delivered through a headphone. Peak intensity was 70-dB sound pressure level above normal thresholds. Each average consisted of the responses to 120 pairs of stimuli. The EEG responses were amplified and band-pass filtered with an analog filter of 0.1 to 200 Hz and no 60-Hz notch filter, at a sampling rate of 1000 Hz, for a total of 1000 msec (100 msec before to 400 msec after the stimuli with a 500-msec gap between stimulus 1 and stimulus 2).

The wave peaks were determined visually and the latencies and amplitudes were marked manually. The most positive peak between 40 and 90 ms after the conditioning stimulus was selected as the P50 final latency and the wave amplitude (S1=conditioning) was measured from baseline to peak. The second wave (S2= test) was determined using the corresponding peak between S1 ±10 ms. away from the latency of the first wave form (conditioning) and its amplitude was also measured from baseline to peak. The percentage of P50 suppression was
calculated by using the formula \[1 - \left(\frac{\text{stimulus 2 amplitude}}{\text{stimulus 1 amplitude}}\right)\] x100. A minimum of -100% suppression (or 100% facilitation) was used to prevent outliers from disproportionately affecting the group means, consistent with the methods of Nagamoto et al. (27). Sample graphs of P50 measurement of some subjects are shown on Figure 1.

**Statistics**

P50 latencies, amplitudes, and P50 ratios were compared by using the Mann-Whitney U test between the two groups. The changes of amplitude and latency of P50 indices under MPH administration in the ADHD group were investigated by the Wilcoxon signed rank test. All statistical tests of significance were made using two-tailed tests with \(p = 0.05\).

### Results

There was no statistical difference between the age \((p=0.12)\) and the gender \((p=0.36)\) distribution of the ADHD group and healthy controls. P50 test latency, test amplitude, and P50 ratio values were found to be higher in the ADHD group than in the healthy controls \((Z=2.43, \ p=0.01; \ Z=3.22, \ p=0.001, \ \text{and} \ Z=3.12, \ p=0.002, \ \text{respectively})\). There was no statistically significant difference in P50 conditioning latency and conditioning amplitude between the ADHD and control groups \((Z=1.59, \ p=0.11 \ \text{and} \ Z=1.61, \ p=0.10, \ \text{respectively})\) (Table 1).

In the ADHD group, there were significant differences between before and after MPH, in condition latency, test latency, test amplitude, and P50 ratio values \((Z=2.71, \ p=0.007; \ Z=3.27, \ p=0.001; \ Z=3.06, \ p=0.002 \ \text{and} \ Z=3.97, \ p=<0.001, \ \text{respectively})\). No difference was found in

#### Table 1: Comparison of P50 parameters in ADHD patients and healthy controls. §

<table>
<thead>
<tr>
<th>P50 Parameters</th>
<th>ADHD ((n=22))</th>
<th>Healthy Controls ((n=18))</th>
<th>Z</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning latency (ms)</td>
<td>59 (42-73)</td>
<td>55 (41-65)</td>
<td>1.59</td>
<td>0.11</td>
</tr>
<tr>
<td>Conditioning amplitude (µV)</td>
<td>5.60 (1.50-15)</td>
<td>4.30 (1.80-8.10)</td>
<td>1.61</td>
<td>0.10</td>
</tr>
<tr>
<td>Test latency (ms)</td>
<td>66.50 (45-77)</td>
<td>62 (43-69)</td>
<td>2.43</td>
<td>0.01**</td>
</tr>
<tr>
<td>Test amplitude (µV)</td>
<td>4.95 (0.20-13)</td>
<td>3.10 (1-6.70)</td>
<td>3.22</td>
<td>0.001**</td>
</tr>
<tr>
<td>P50 ratio</td>
<td>84.62 (13.33-114.20)</td>
<td>61.25 (34.50-91.40)</td>
<td>3.12</td>
<td>0.002**</td>
</tr>
</tbody>
</table>

§ Data are showed as median (min-max)

** \(p <0.01\)

#### Table 2: P50 values of ADHD patients \((n=22)\) before and after MPH administration. §

<table>
<thead>
<tr>
<th>P50 Parameters</th>
<th>Before MPH</th>
<th>After MPH</th>
<th>Z</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition latency (ms)</td>
<td>59 (42-73)</td>
<td>55.50 (40-68)</td>
<td>2.71</td>
<td>0.007**</td>
</tr>
<tr>
<td>Condition amplitude(µV)</td>
<td>5.60 (1.50-15)</td>
<td>5.80 (1.70-28)</td>
<td>0.11</td>
<td>0.91</td>
</tr>
<tr>
<td>Test latency (ms)</td>
<td>66.50 (45-77)</td>
<td>62.50 (44-71)</td>
<td>3.27</td>
<td>0.001**</td>
</tr>
<tr>
<td>Test amplitude (µV)</td>
<td>4.95 (0.20-13)</td>
<td>3.35 (0.90-13)</td>
<td>3.06</td>
<td>0.002**</td>
</tr>
<tr>
<td>P50 ratio</td>
<td>84.62 (13.33-114.20)</td>
<td>56.05 (25.56-81.10)</td>
<td>3.97</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

§ Data are showed as median (min-max)

** \(p <0.01\)
condition amplitude ($Z=0.11$, $p=0.91$) values between before and after MPH administration (Table 2).

**DISCUSSION**

The present study, which aimed to evaluate sensory gating in children and adolescents with ADHD, found an association between ADHD and sensory gating. The ADHD group exhibited higher P50 ratios than those of healthy controls and MPH administration decreased the P50 ratios in the ADHD group. To our knowledge, this is the first study to evaluate sensory gating and the effect of MPH on P50 suppression for ADHD patients in this age group. These findings may supply new perspectives to understand the specific role of P50 suppression in cognition and the nature of attention abnormalities in ADHD and to learn the effects of MPH on them.

A core feature of ADHD is the inability to volitionally regulate attention and to inhibit distraction of attention by irrelevant stimuli (1). Therefore, people with ADHD cannot efficiently ignore or filter unimportant and irrelevant repetitive stimuli. In the P50 procedure, healthy people typically display suppressed P50 amplitude to the second click relative to a first click. This suppression of P50 amplitude has been related to the inhibitory ‘gating’ effects of the first click (28). Impaired suppression to the second click is thought to reflect poor sensory gating, which may be associated with an influx of irrelevant auditory information causing perceptual and attentional deficits (21,29,30). In our study, having higher P50 ratios in children and adolescents with ADHD as compared to healthy controls might indicate weaker sensory gating in ADHD. In other words, these results suggest that children and adolescents with ADHD are deficient in their ability to filter out repeated auditory input and fail to selectively regulate their sensitivity to sensory stimuli.

Our findings are different from those of some studies evaluating sensory gating by P50 and PPI in adult ADHD populations (7,20), and that of one study evaluating sensorimotor gating in boys with ADHD by PPI (31). Our results are in agreement with some of the studies carried out to investigate sensorimotor gating by PPI in boys with ADHD; however, in those studies ADHD was accompanied by enuresis (32,33) and Tourette’s syndrome (34). The divergence between the finding that the P50 suppression deficit present in our current study and the absence of a P50 deficit in an adult ADHD population (20) may suggest an effect of age on the P50 event related potential because of the fact that the P50 suppression scores significantly improve with age (23,35). The age-related increase of P50 suppression mainly depends on a decrease of P50 amplitude to the second click. This age trend may reflect maturation of inhibitory mechanisms and age related improvement of the capacity for suppression of irrelevant repetitive auditory input (11).

The prefrontal cortex, Heschl’s gyrus and surrounding areas, and the hippocampus have been associated with the sensory gating processing (36,37). The frontal cortex has been implicated as one of the key brain areas contributing to P50 suppression (21,22,35), and it has been speculated that the maturation pattern of the of P50 suppression effect is related to the documented maturation processes of the frontal cortex during childhood and preadolescence. The US NIMH researchers (24) have reported that cortical development in children with ADHD generally lags behind by several years compared to typically developing children. They also found that the greatest maturational delay occurs in prefrontal regions important for control of cognitive processes such as attention and working memory. A relatively large percentage of healthy children exhibit a lack of P50 suppression due to variability in the maturation of prefrontal systems that mediate sensory gating (38).

Freedman et al. (39) have suggested that adult levels of P50 suppression cannot be seen until late adolescence. In our study, due to the similar age distribution in both groups, having more prominent P50 ratios in the ADHD group may reflect a maturational delay in frontal areas.

Our finding that MPH improved sensory gating is consistent with the results of Douglas (40) and Hawk et al. (31). In his study, Douglas concluded that MPH affected the allocation of controlled resources (i.e. selective attention) (40). In the study of Hawk et al. (31) it was suggested that MPH influenced prepulse inhibition during attended prestimuli. The cholinergic subtype of the nicotinic system plays an important role in regulating the diminished response to repeated stimuli, through stimulation of $\alpha$7 nicotinic receptors (41). Suppression of auditory sensory gating may be associated with a MPH-induced dopamine increase and result from the indirect effect of dopamine on the nicotinic system.

This study has some limitations. First, it has a small sample size. The number of boys and girls were not enough to evaluate the findings of the present study in the context
of gender. Second, the participants in this study are not newly diagnosed ADHD patients. The duration of MPH treatment before P50 measurement was not also controlled in the present study. Third, P50 gating is highly variable during childhood, with adult levels of P50 suppression not being seen until late adolescence (39). Myles-Worsley and colleagues (42) found that P50 suppression showed greater stability and a different developmental time course in the 10–14-year-old age group and was at the same level as that of adults. Taking into account the age effect on P50 suppression, we tried to minimize the effect by maintaining a similar age range (9–14 years) in our study.

CONCLUSION

The present study points out that P50 non-suppression indicates cognitive disturbances (i.e. inattention) in the ADHD group and that MPH administration diminishes the non-suppression. To our knowledge, this is the first study to investigate P50 inhibition and the effects of MPH administration on P50 suppression in children and adolescents with ADHD. For this reason, this study should be considered as a preliminary study. Further studies with larger samples are warranted in this area.

References:


