

## Effects of Methylphenidate on Reaction Time in Children with Attention Deficit / Hyperactivity Disorder

### Dikkat Eksikliği / Hiperaktivite Bozukluğu Olan Çocuklarda Metifenidatın Reaksiyon Süresine Etkileri

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#### ABSTRACT

**Introduction:** Attention-deficit/hyperactivity disorder (ADHD) is associated with a broad range of neuropsychological impairments that are attenuated with methylphenidate (MPH) treatment. The aim of this study was to determine how MPH effects attentional functioning in terms of reaction time (RT) in ADHD.

**Methods:** Eighteen pre-medicated ADHD children (7 to 12 years old) and eighteen gender matched normal controls (7 to 12 years old) were included in the study. Participants performed an auditory attention task and the RT of participants to each target response was calculated automatically. The same test was repeated 3 months after OROS-MPH administration for ADHD group. RT, RT standard deviation (RTSD), and response errors (omission and commission errors) were compared between control and pre-MPH ADHD groups, and between Pre-MPH and post-MPH ADHD groups.

**Results:** Relative to control subjects, significantly longer RTs, higher RTSD and more errors of omission were observed in unmedicated ADHD

children during auditory attention task. Analyses revealed significant effects of medication across all measures except commission errors. After treatment RTs were faster, RTSD values were lower, and errors of omission were attenuated compared to pre-medication condition in ADHD group. There were no significant differences in terms of commission errors between groups.

**Conclusion:** In this study it was observed that MPH reduced RTs to stimuli, attenuated omission errors during the task in ADHD group and after 3 months of treatment ADHD children showed similar patterns in RT as compared to controls. Results suggest that when treating ADHD, it might help clinicians to evaluate objective and non-invasive cognitive outcomes such as RT, RTSD and response errors to evaluate the effects of treatment.

**Keywords:** Attention deficit hyperactivity disorder, reaction time, auditory attention task, methylphenidate

#### ÖZ

**Amaç:** Dikkat eksikliği/hiperaktivite bozukluğu (DEHB), metilfenidat (MPH) tedavisi ile düzeltme gözlenen bir çok nöropsikolojik bozuklukla ilişkilendirilmiştir. Bu çalışmanın amacı, MPH'in DEHB'de dikkat işlevini nasıl etkilediğini reaksiyon süresi (RS) ile belirlemektir.

**Yöntem:** Çalışmaya daha önce tedavi görmemiş onsekiz DEHB'li çocuk (7-12 yaş) ve on sekiz cinsiyet eşleştirilmiş sağlıklı çocuk (7-12 yaş) dahil edildi. Katılımcılara işitsel dikkat testi uygulandı ve hedef uyarınlara verdikleri reaksiyon süresi otomatik olarak hesaplandı. DEHB grubundan uzun süreli MPH ilaç tedavisinden üç ay sonra kayıtlar yeniden alındı. RS, RS standart sapması (RSSS) ve yanıt hataları (ihmal ve görev hataları) kontrol grubu ve MPH öncesi grubu arasında ve MPH öncesi ve sonrası DEHB'li grup arasında karşılaştırıldı.

**Bulgular:** İşitsel dikkat görevi sırasında, tedavi öncesi DEHB'li grupta kontrol grubuna göre anlamlı bir şekilde daha uzun RS, daha yüksek RSSS

ve daha fazla ihmal hatası gözlenmiştir. Yapılan analizler, tedavinin görev hataları dışındaki tüm ölçümlerde anlamlı etkisi olduğunu göstermiştir. Tedavi sonrası DEHB'li grupta tedavi öncesi duruma göre, anlamlı olarak RS daha hızlıydı, RSSS değerleri daha düşüktü ve ihmal hataları daha azdı. Görev hataları açısından gruplar arasında istatistiksel olarak anlamlı farklılık yoktu.

**Sonuç:** Yapılan çalışmada, MPH'in çocukların uyarana verdikleri reaksiyon süresini azalttığı, görev esnasında ihmal hatalarını azalttığı ve üç aylık tedavi sonrası kontrol grubıyla benzer örnekler gösterdiği gözlenmiştir. Sonuçlar, DEBH tedavisinde klinisyenlerin RS, RSSS ve yanıt hataları gibi objektif ve non-invazif kognitif çıktıları kullanmalarının, tedavinin etkilerini değerlendirmelerine yardımcı olabileceğini göstermektedir.

**Anahtar kelimeler:** Dikkat eksikliği ve hiperaktivite bozukluğu, reaksiyon süresi, işitsel dikkat testi, metilfenidat

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## INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is a highly prevalent neuropsychiatric disorder of childhood that is characterized by the symptoms of inattentiveness, impulsivity, and hyperactivity (1). Moreover, ADHD is associated with various neurocognitive impairments in executive and non-executive functioning including response inhibition (2), working memory (3), planning and set-shifting (4), timing (5), reaction time and reaction time variability (6). Reaction time (RT) that is the length of time between the presentation of the target stimulus and the initiation of the subject's motor response is an important and informative tool in the study of cognitive ability in psychology and other disciplines. One of the more consistent findings in the ADHD neuropsychology literature is that these children demonstrate, slower and more variable RTs compared to typically-developing children on a number of different tasks. (7). Intra-individual RT variability (RTV) has been identified as a potential endophenotype for psychopathological disorders. Increased RTV has been observed in individuals with bipolar dementia (8) autism (9), schizophrenia (10), and ADHD (11). Studies have demonstrated that increased RT variability in ADHD is mostly related to extremely slow responses (12) that are caused by periodic lapses of attention in goal-directed processing (13-14).

The stimulant medication was found to reduce RT and RTV among children with ADHD. In a meta-analytic review of 319 studies Kofler et al. demonstrated RTV was attenuated by stimulants, but unaffected by non-stimulant medical and psychosocial treatments (6). Methylphenidate (MPH) is currently the most effective treatment for the symptoms of ADHD. MPH improves neurocognitive functioning on inhibitory control (15), visual-spatial working memory (16), sustained attention (17) and selective attention (18) in children with ADHD. Many studies have reported that the ADHD children showed better performance in attentional tasks after treatment with MPH, manifested in faster RTs to a target stimuli, reduced omission and commission errors and reduced RTV (7, 19, 20).

Tasks range from simple choice discrimination tasks (20) to more complex response inhibition tasks such as Go/No-Go task (21) and Stop Signal task (SST) (22) which are introduced to evaluate effects of MPH medication on RT in patients with ADHD. However, surprisingly very few studies have investigated auditory RT in this context. The existing, limited literature is inconsistent with respect to effects of MPH on treatment in terms of auditory RT and RTV, where some of these studies did not detect significant effects of MPH on RT during auditory attention task and some showed enhancement in task accuracy and RT after treatment by MPH during both the visual and auditory modality in children with ADHD. Thus more work is needed to evaluate MPH effects on auditory RT, RTV and task accuracy. Since MPH has commonly been reported to reduce RTs to targets in ADHD, in this study we hypothesized that there will be significantly reduced RT and RTV after administration of stimulant medication. In addition to the medication effects we compared pre-MPH ADHD group with normal controls and hypothesized that controls would show faster RTs, lower RTV and higher task accuracy compared to ADHD group according to the afore-mentioned literature.

The aim of this study was to obtain more insight into the effects of MPH on auditory attention task which is less investigated compared to other tasks in ADHD children and to assess the differences in RT, RTV and task accuracy between ADHD children and normal children.

## METHODS

The study was conducted on 18 pre-medicated, ADHD children with a mean age of 9.50 (SD 1.94, range 7-12 years) and 18 healthy children with a mean age of 9.78 (SD 1.86, range 7-12 years). Controls underwent

a standard clinical assessment comprising neurological, endocrine and psychiatric evaluations. The ADHD patients were referred from Children Psychiatry Department of Erciyes University, Medical Faculty Hospital. All patients met criteria for ADHD according to DSM-IV. ADHD participants did not have any comorbidity with other psychiatric disorders such as obsessive-compulsive disorder, major depressive disorder, epilepsy, schizophrenia, and autism spectrum disorder. After the first assessment of children with ADHD, OROS-MPH at a dose of 0.5 mg/kg/day was prescribed to patients (min 27 mg/d, max 54 mg/d). Doses of OROS-MPH was titrated up to 1.2 mg/kg/day with increments at 2-week intervals. The time to reach optimal dose was generally 4-6 weeks; thus, effects of therapy was assessed 3 months after starting therapy. The Wechsler Intelligence Scale for Children-Revised (WISC-R) (23) full IQ scores of subjects were all over 80. All subjects were right handed, native Turkish speakers and had normal hearing functions. The hearing functions were tested with Rinne and Weber test. The research protocol was approved by the ethics committees of Erciyes University and was in accordance with the latest version of the Declaration of Helsinki. Written consent was obtained from the parents of all participants.

## Task

In this study 160 auditory stimuli that consist 128 standard (2000 Hz) and 32 target (1500 Hz) stimuli were presented in a random order. The interstimulus intervals (ISI) were randomized between 1250 and 2500 msec. Prior to the first run of the experiment, the participants were instructed to press the button when they hear target stimulus presented through headphones. The data acquisition was conducted in the Electrophysiology Laboratory of the Department of Physiology at Erciyes University, Medical Faculty. Patients and controls were tested under similar laboratory conditions after becoming familiarized with them. RT of 32 target stimulus were obtained using Matlab R2015a automatically by calculating length of time between the presentation of the target stimulus and the initiation of the subject's motor response. In Fig. 1, the first ten stimuli of 128 stimuli sequence and a child's response is presented.

## Statistical Analyses

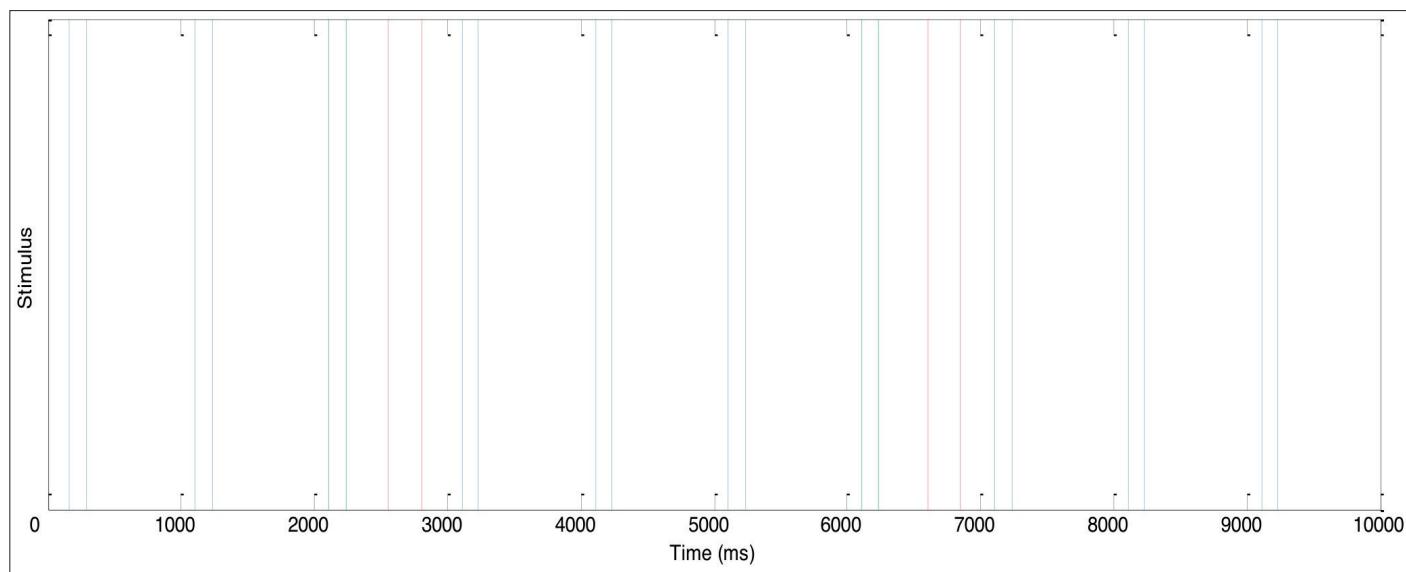
We compared the variables between the ADHD (pre-treatment) and the control group using a student's t-test and the variables before and after treatment using a two-tailed paired t-test with a statistical threshold of 0.05. Shapiro-Wilk normality test was used to confirm the normal distribution of variables. Mean RT for each participant was computed by averaging RTs. RT standard deviation (RTSD) was derived by computing the SD of each individual's RTs which provides a measure of RT variability. Error of omission occurs when the participant fails to respond to a target stimulus (1500Hz) while error of commission occurs when the participant responds to a standard stimulus (2000Hz). All the statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS Inc.; Chicago IL, ABD) Version 16.0.

## RESULTS

We analyzed clinical characteristic of the participants and compared selected features between control and pre-MPH ADHD group as well as between pre-MPH and post-MPH ADHD group. ADHD children and controls did not differ statistically in terms of age, years of education, IQ and gender (Table 1). Measures including errors of commission, error of omission, mean RT and RT standard deviation (RTSD) are presented with statistical analyses between groups in Table 2.

### Pre-MPH comparison of variables between controls and ADHD patients

Children with ADHD showed longer RT ( $p<0.01$ ) than controls. RT variability, as measured by RTSD was higher than controls ( $p<0.01$ ).



**Figure 1.** The first 10 stimuli sequence and responses of a child to the stimuli in control group. Blue and green blocks represent standard and target stimulus, respectively. Red blocks represent pressed button as the response of the child.

**Table 1.** Clinical characteristics of the participants

	ADHD	Control	t; df; p
Participants	18	18	
Gender (Male: Female)	14:4	14:4	
Age in years	9.5±1.94	9.78±1.86	0.437; 33.9; 0.66ns
Education in years	3.5±1.94	3.78±1.86	0.437; 33.9; 0.66ns
WISC-R	108.6±10.04	109.11±9.27	0.328; 33.78; 0.74ns

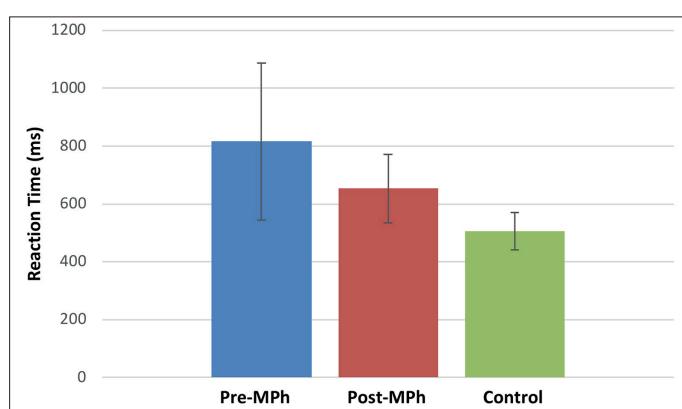
Note: Mean ± standard deviation. Groups were compared with two-tailed unpaired Student's t-tests. Abbreviations are as follows; t, t-value; df, degree of freedom; p, p value; ns, non-significance.

**Table 2.** Statistical tests of medication effects with several potential confounding variables

	Control n=18		Pre-MPH n=18		Post-MPH n=18		Control vs. Pre-MPH		Pre-MPH vs. Post MPH**	
	mean	SD	mean	SD	Mean	SD	t	p	t	p
RT (ms)	506.5	66.9	816.1	279.1	653.4	121.8	4.57	<0.01	2.41	0.027
RTSD (ms)	53.46	43.6	232.9	143.1	84.46	85.43	5.086	<0.01	4.25	0.001
OE	2.56	2.99	7.33	5.841	4	4.55	3.088	<0.01	2.78	0.013
CE	1.39	2.16	0.89	2.56	0.28	0.826	0.634	0.53	1.66	0.213

Abbreviations: RT, Reaction Time; RTSD, Reaction Time Standard Deviation; OE: Omission Errors; CE, Commission Errors

\*\*Paired t-tests for their variables.



**Figure 2.** A comparison of groups between the values of mean RT. Errors bars are the standard deviation of the calculated values from different subjects of each group.

Compared to healthy children, children with ADHD made significantly more errors of omission ( $p<0.05$ ) and there were no significant differences in terms of commission errors between groups ( $p>0.05$ ).

#### Pre-MPH vs. post-MPH comparison of variables

RT was shorter and RTSD was lower in post-MPH compared to pre-MPH in children with ADHD. Compared to post-MPH, children with ADHD made significantly more errors of omission before treatment ( $p=0.013$ ), there was no significant group differences in commission errors. Fig. 2 demonstrates mean RTMRT of groups. Errors bars are the standard deviation (SD) of the calculated values from different subjects of each group.

## DISCUSSION

The present study investigated deficits in RT, RTV and task accuracy in children with ADHD. Consistent with our hypothesis, children with

ADHD demonstrated significantly slower RT, higher RT variability and more response errors than controls. These results are in accordance with many previous studies in which individuals with ADHD across a wide range of tasks, including tasks measuring RT on choice decision, working memory, sustained attention has long been observed as slower and more variable compared to controls (13, 16, 22). Our results also supported the vigilance studies that assume slow RT, high RTV and increased errors of omission are associated with inattentive response (19).

The effects of stimulant medication on neuropsychological outcomes were also examined in this study by comparing ADHD participants before and after MPH treatment. We observed, MPH treatment reduced RTV, RT and task errors. The results were in agreement with the literature. In general, the effect of MPH medication on reducing these variables are consistent across studies despite different task characteristics. (24). A range of cognitive tasks evaluated in ADHD to examine effects of MPH medication on RT in patients with ADHD. Monden et al. claims selective tasks are more appropriate than one using a task and a rest period for ADHD children, because it is difficult for ADHD patients to stay still without performing any task, it may lead to unexpected movements or hyperactive behaviors that can cause loss of attention (25). Similarly, we used standard auditory stimuli as baseline and did not adopt rest period. We selected an easy, short task containing standard and target paradigm with random sequence that can be appropriate for ADHD children who have difficulty performing effortful cognitive tasks.

This current study was one of few studies using the selective auditory attention task to investigate the effects of stimulant medication on RT in ADHD children. The limited literature is inconsistent with respect to effects of MPH on treatment in terms of auditory RT and RTV. Although MPH commonly been reported to reduce RTs to target stimuli in ADHD subjects during attention tasks, Jonkman did not detect significant effects of MPH on RT during auditory attention task (26). They implemented 4 tasks composed of 2 auditory and 2 visual tasks. Their auditory task consisted of series of 300 stimuli which contains 60 target stimuli. The duration of each task took 10 minutes that is relatively long for ADHD children. Instead we choose shorter auditory task that contains only 160 stimuli that would be more appropriate for ADHD children. In this study we observed that omission errors increased especially in ADHD group towards the end of the record, suggesting a graduated loss of attention although the task took only five minutes. Our observation indicate that long attentional tasks may not be appropriate for ADHD children which may cause more error of omissions that is associated with long RT (14). In accordance with our study, Korman et al. reported reduced RTs to the targets and enhancement in task accuracy by MPH in children with ADHD during both the visual and auditory modality (18). Epstein et al suggest that treatment with MPH created an optimal energetic state so that children with ADHD had normalized RT patterns (27). In this study we observed improvement on RT patterns but not normalized as controls. This is maybe because of the duration of the treatment before assessing post-MPH results that took 24 months in their study which was three months in our study.

The important role of attention in auditory processing and listening has been reported in several studies. Auditory attention that is defined as the ability to focus on a specific source of sound (28) has been also declined in people with ADHD via impairment of P3 activation (29). Recently, Kemner et al. indicated that auditory cortical activity is modulated less in children with ADHD than in control children during performance of selective auditory task (30) and Baghdadi et al showed that the sensitivity of ADHD subjects to the sound intensity was lower than the normal group by means of RT (31). Furthermore, RT during an auditory attention task was utilized to investigate various other psychiatric disorders such as stress recognition (32), anxiety (33), autism (34), bipolar disorders (35).

Inconsistent and limited auditory RT ADHD literature, positive effects of MPH in Auditory evoked potentials parameters in ADHD (36, 37) and positive findings in other psychiatric disorders have motivated us for evaluating MPH effects on auditory RT. The present study provided more insight into the effects of MPH on auditory attention task.

There are several limitations of this present study. Small sample size of our study is one of those limitations. Although we tested hearing functions with Rinne and Weber test, there would be difference in hearing threshold between subjects. Another limitation is we introduced only one task and RTV could change in multiple tasks.

In conclusion, RTV, which is one of the robust indicators of cognitive deficit, in patients with ADHD RTV was significantly attenuated by MPH treatment. It was found that MPH treatment enhanced task accuracy and reduced RTs of ADHD children in the auditory modality that is poorly introduced in literature, suggesting that the auditory attention task can be another possible test to be used in the evaluation of these patients. Results suggest that when treating ADHD, it might help clinicians to evaluate objective and non-invasive cognitive outcomes such as RT, RTSD and response errors to evaluate the effects of treatment. In future work, intra-individual RTV can be investigated via-exgauss parameters with other cognitive tasks in addition to auditory stimuli such as visual tasks and go/no-go paradigms.

**Ethics Committee Approval:** The research protocol was approved by the ethics committees of the Erciyes University (2014/195).

**Informed Consent:** Written consent was obtained from the parents of all participants.

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