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# Processing speed may improve earlier than response inhibition/ interferens in children with ADHD-combined type receiving methylphenidate: a single-center study

Fatih Hilmi Çetin, Hasan Ali Güler, Sevde Afife Ersoy and Serhat Türkoğlu

Department of Child and Adolescent Psychiatry, Faculty of Medicine, Selcuk University, Konya, Turkey

#### **ABSTRACT**

**OBJECTIVES:** The aim of this study was to determine the order of improvement in response inhibition, interference capacity, and processing speed in the Stroop test after starting methylphenidate treatment in children with ADHD.

METHODS: This study included a total of 52 children aged 7–16 years who were diagnosed with combined-type ADHD for the first time and who began to use methylphenidate treatment. The Stroop test was applied to each subject at least 3 times (before treatment and at the first and second months of treatment) in the follow-up visits.

**RESULTS:** The participants completed the fifth section of the Stroop test at a median duration of42.09 sec (quartiles: 35.58-54.0 sec) before treatment, while the median duration was 34.49 sec (quartiles: 27.43–34.48 sec) at the first month of treatment and 32.18 sec (quartiles: 26.97-32.18 sec) at the second month of treatment. The task completion duration showed a statistically significant improvement from the first month of treatment (p < 0.001). When the participants were compared in terms of the number of errors and corrections they made in the fifth section of the Stroop test, there was no significant difference between pretreatment measurements and post-treatment first month measurements (p > 0.05). The number of errors and corrections were statistically significantly lower in the second month of treatment compared to pretreatment and 1st mont of the treatment (p < 0.05).

CONCLUSIONS: This study demonstrated that processing speed, response inhibition, and interference capacity assessed by the Stroop test improved with methylphenidate treatment in children with ADHD. This study is the first study to show that these improvements occur in a certain order over time.

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#### **KEYWORDS**

Attention deficit hyperactivity disorder; Stroop test: response inhibition: processing speed; methylphenidate

### Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder in childhood with a prevalence of 5-12% and characterized by developmentally inappropriate inattentiveness, impulsivity, and hyperactivity [1]. Under the core symptoms of ADHD, there is insufficient prefrontal cortical activation caused by the problems in dopaminergic and noradrenergic systems [2,3]. In this manner, in different neuroimaging studies, poor functioning, hypometabolism, and hypoactivation during performing various tasks, especially in the prefrontal cortex, were determined. Because of prefrontal cortex is associated with executive functions, this hypoactivation is defined as "executive dysfunction" by behavioural neuropsychological theorists [4,5]. Barkley explains executive function problems with a hierarchical model in ADHD, mainly with executive function deterioration resulting from inadequate response inhibition [6]. "Response inhibition" is defined as the ability to suppress the usual behaviour patterns in the direction of changing demands and under a disruptive effect and to perform an unusual behaviour [7]. Another researcher, Thomas Brown, presented a descriptive model instead of a hierarchical structure, and stated that the main problem is the inability to shift attention in ADHD [8]. For these reasons, determining the presence and severity of executive dysfunction is important in the diagnosis and treatment process of ADHD. In this context, the Stroop test is frequently used in experimental and clinical neuropsychological practice to assess executive dysfunction including attention skills, especially selective attention and response inhibition capacity, and is accepted as the gold standard [9]. This test assesses three basic executive functions: (a) response inhibition; in other words, the suppression of word-reading processes, which is a stimulus that our brain becomes more accustomed to doing something [7], (b) interference capacity of a functioning brain that fulfils an unusual task for naming the colour of the ink, and (c) "processing speed" which is the measure of how fast you perform this task. The task completion score obtained from the Stroop test shows the measure of "processing speed"; error and correction scores provide an assessment of response inhibition and interference capacity [10,11]. Studies combining neuropsychological and neuroimaging techniques have shown that executive function skills assessed by the Stroop test are primarily carried out by the anterior cingulate cortex (ACC), and that error/correction scores are more related to the left dorsolateral prefrontal cortex, and that duration scores are more related to the left mediofrontal cortex [5,12].

In studies which used the Stroop test in children with ADHD, it has been shown that these children have poor response inhibition skills, slower "processing speed" and lower interference capacity [13-15]. And also, it has been shown that methylphenidate treatment has a positive effect on processing speed in both children and adults [9,16,17]. An important result - methylphenidate treatment has no therapeutic effect on response interference, but has a significant improvement in colour naming and word naming abilities - was detected in a study by Bedard et al. [9]. In another study; It has been determined that methylphenidate treatment has a positive effect on response inhibition but has no effect on "reflection" impulsivity [16]. In studies conducted with adults; it has been reported that methylphenidate treatment has a positive effect on response inhibition and this positive effect can be used to monitor treatment effect [17]. The results of studies evaluate how the improvements seen in the Stroop test with methylphenidate treatment are incompatible with each other [18,19]. Besides studies showing that response inhibition deficits improve, interference capacity increases and processing speed accelerates; there are also studies reporting that only processing speed improves [9,20]. The inconsistent results in previous studies may arise from the fact that the Stroop test was applied at different times after treatment, and the drug was administered at different doses and durations. According to our opinion about the inconsistent findings, only "processing speed" improves when the Stroop test is applied in the early post-treatment period, but there are positive changes in all parameters evaluated by the Stroop test when it is applied in the late post-treatment period. To the best of our knowledge, there is no study evaluating changes in Stroop test performance, which are documented by repeated measures after initiation of the drug, with methylphenidate treatment.

In the light of all these data, the aim of this study was to determine the order of improvement in response inhibition, interference capacity, and processing speed in the Stroop test after starting methylphenidate treatment in children with ADHD. In this context, we aimed to test the hypothesis that processing speed would increase with methylphenidate treatment at the early stage of treatment, and then response inhibition and interference capacity would improve.

#### Material and method

#### **Subjects**

This study was carried out in children who had been diagnosed with combined-type ADHD for the first time and who began to use methylphenidate treatment at the Department of Child and Adolescent Psychiatry, Faculty of Medicine, Selcuk University between January 2018 and July 2018. The study was performed by retrospectively screening medical records of patients who met the inclusion/exclusion criteria, 1428 children diagnosed with ADHD-combined type from medical record were screened. Thus, the study had a retrospective descriptive design. The Stroop test evaluation is a routine procedure of the department before and after the treatment at the first and second months. Because of this, when including cases, the cases were selected who had the Stroop test evaluation in their files at least three times. 863 patients due to missing data and 197 patients due to exclusion criteria were excluded. A total of 52 children aged 7-16 years were included in the study. Figure 1 is a study flow chart demonstrating the design.

The diagnostic process had been carried out by child psychiatrists at our department. The patients were diagnosed with combined-type ADHD as a result of clinical examination and psychometric scales. The Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S) for ADHD were filled by their teachers. The patients were re-examined by the executive researcher. Thus, the diagnosis of ADHD was confirmed. After the second clinical examination, if the patient was diagnosed with combined-type ADHD according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR), both the child and his/her parents underwent the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-T), a semi-structured diagnostic tool, by a child psychiatrist. The diagnostic evaluation process is also a routine procedure for all cases referring to the outpatient clinic of our department. In our department, methylphenidate application is started as short-medium duration effective and low dose (0.5 mg/kg/day and below) as standard and then the optimal dose and form (immediate release or extended-release) are determined within two weeks according to the treatment response and side effects. The subjects were selected from patients who did not change the dose during the follow-up period and continued to take the same dose. Thus, it is aimed to exclude the effects due to dose increase. In this study, only those patients, who were using the extendedrelease form and who were not dose-changed after the optimal doses were determined, had been included.

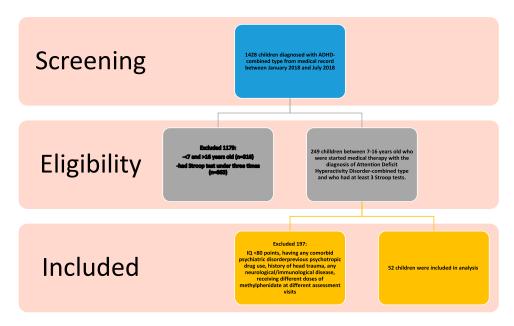


Figure 1. Flow-chart of the study.

The exclusion criteria for the study were as follows: IQ <80 points, having any comorbid psychiatric disorder other than "oppositional defiant disorder (ODD)" together with ADHD, previous psychotropic drug use, history of head trauma, and any neurological/immunological disease, and receiving different doses of methylphenidate at different assessment visits. The study protocol was approved by the Clinical Research Ethics Committee of Selcuk University School of Medicine (approval date: 04.07.2018, no:264).

#### **Data tools**

Stroop Test TBAG Form. It was developed by Stroop [10] and standardized for Turkish children by Kılıc et al. [21]. The Stroop Test TBAG Form consists of four white cards in dimensions of 14.0 cm  $\times$  21.5 cm. Each card has 6 rows with 4 items each, randomly allocated. It consists of five sections presented in a fixed order where these four cards are used. The fifth section is the critical section where the disruptive effect emerges. Thus, response inhibition and interference capacity are assessed. The other sections are the control conditions in which the basic levels of reading and colour discrimination abilities are identified. The Stroop test is closely related to the frontal lobe and many other cerebral regions. It provides information about several cognitive processes such as selective attention, response inhibition, interference control, and input processing speed [22].

## Schedule for affective disorders and Schizophrenia for school age childrenpresent and lifetime version-Turkish version (K-SADS-PL-T)

It was used to diagnose the patients in the study group. They were diagnosed after the patients and one of their parents were interviewed by the responsible resident researcher, and then the clinical assessment was performed by the executive researcher. It is a semi-structured interview tool developed by Kaufman et al. to determine past and current psychiatric disorders in children and adolescents (6-18 years of age) [23]. The Turkish validity and reliability study was performed by Gokler et al. [24]. The child psychiatrist who performed these clinical interviews has been trained and has received a relevant certification to conduct this semi-structured interview.

## Turgay DSM-IV-based child and adolescent behavior disorders screening and rating scale (T-DSM-IV-S)

It was developed by Turgay based on the DSM-IV criteria. The validity and reliability of the Turkish version was done by Ercan. This 4-point Likert-type scale has four sub-headings: inattention, hyperactivity/impulsivity, behavioural disorientation, and opposition/ defiance [25,26].

#### Statistical analysis

Data were analyzed using SPSS version 22.0 software (SPSS Inc., Chicago, IL). The variables were invesitgated using visual (histogram, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Since interference capacity, response inhibition and processing speed are assessed by the fifth section of the Stroop test, only this section was included in the statistical analysis. From among the Stroop test scores, processing speed displayed a normal distribution at the first measurement but not at the second and third measurements. Errors and correction

scores indicating interference capacity and response inhibition displayed a normal distribution neither at the first measurement nor at the second and third measurements. The practice order of the Stroop test was shown with 1st number, and the section of Stroop test were with 2nd number. So, for example, "s05" means that the fifth section of the test and the baseline administration. Freidman tests were conducted to test whether there is a significant change. The post-hoc Wilcoxon tests were performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. An overall %5 type-1 error level was used to infer statistical significance.

#### Results

All patients included in the study had a diagnosis of combined-type ADHD. There were 38 (73.1%) boys and 14 (26.9%) girls in the study. The mean age was  $10.13 \pm 2.44$  years (min-max: 7-16 years). All patients were treated with methylphenidate extended release form  $0.81 \pm 0.18$  mg/kg/day (mean  $\pm$  SD; min-max: 0.55-1.33 mg/kg/day). The sociodemographic characteristics of the participants (including parental age, parental education level, family integrity, and socioeconomic status) are presented in Table 1.

The participants completed the fifth section of the Stroop test at a median duration of 42.09 sec (quartiles: 32.58-54.0 sec) before treatment, while the median duration was 34.49 sec (quartiles: 27.43-41.91 sec) at the first month of treatment and 32.18 sec (quartiles: 26.97-35.92 sec) at the second month of treatment. When Friedman's non-parametric analysis of the repeated time measures was conducted, there was a significant decrease in processing speed over time (p < 0.001). Then, post-hoc Wilcoxon tests while controlling p values with Bonferroni correction were conducted and it has been seen that the processing

Table 1. Sociodemographic – clinic characteristics of the study

	Study group $(n = 52)$		
Age	10.13 ± 2.44 (7–16)		
(years) (mean±stand.deviasyon, min- max)			
Gender	14/38 (%73.1 / %26.9)		
(Female/male, %)			
Mean drug dose	$0.81 \pm 0.18$		
(mean±stand.deviasyon) (mg/kg/day)	(min-max: 0.55–1.33 mg/kg/ day)		
Parent marriage status (n,%)			
Married	42 (%80.8)		
Divorced	10 (%19.2)		
Socioeconomic level (n,%)			
Low	29 (%55.8)		
Moderate	21 (%40.4)		
High	2 (%3.8)		
Parent education (father-mother; n, %)			
Elementary school	26 (50%)-28 (53.8%)		
Middle school	19 (36.5%)-19 (36.5%)		
High school	7 (13.5%)–5 (9.7%)		

speed showed a statistically significant improvement from the first month of treatment (s05 duration vs. s15 duration p <0.001; s05 duration vs. s25 duration p < 0.001).

When the participants were compared in terms of the number of errors and corrections they made in the fifth section of the Stroop test, there were a significant differences with Friedman's non-parametric analysis at both measurements (p < 0.05). After the post-hoc Wilcoxon tests while controlling p values with Bonferroni correction were conducted, there was no significant difference between pretreatment measurements and post-treatment first month measurements (s05 error vs. s15 error p = 0.207; s05 correction and s15 correction p = 0.222). The number of errors and corrections were statistically significantly lower in the second month of treatment compared to pretreatment (s05 error vs. s25 error p < 0.05; s15 correction vs. s25 correction p < 0.05). Table 2 summarizes numbers of errors and corrections together with the task completion durations at pretreatment and at the first and second months of treatment.

#### **Discussion**

In this study, we investigated how response inhibition, interference capacity and processing speed in the Stroop test changed with methylphenidate treatment in children with ADHD. According to our results, methylphenidate treatment improved processing speed first, and then response inhibition and interference capacity, which is the first study in the literature. Thus, the hypothesis that methylphenidate treatment in children with ADHD provides improvement in response inhibition, interference capacity and processing speed, and that this improvement occurs in this order over time, has been supported by the analysis of our data.

The Stroop effect refers to the fact that people find this task difficult when the ink colour differs from what the word spells. This effect arises from people's effort to overcome their automatic tendencies to read the word [27]. The Stroop interference effect refers to the increased amount of time it takes to name the colour of a word when the ink colour and the word are incongruent, compared to when the ink colour and the word are congruent [28]. The Stroop test has been shown to be the "gold standard" for the measurement of disruptive effect and attention [29]. Seidman et al. found that children diagnosed with ADHD between the ages of 6-17 were more likely to fail in all scores from the Stroop test compared to healthy controls [30]. Homack and Riccio examined 33 studies in their meta-analysis to determine the sensitivity and specificity of the Stroop test in ADHD and found that children and adolescents with ADHD had lower performance than healthy peers [31]. In another

Table 2. Variables of the Section 5 (interference control) of Stroop Test Scale Scores at baseline, 1st and 2nd month of the treatment.

	Baseline (t0)	1st month (t1)	p value* (t0-t1)	2nd month (t2)	p value* (t1-t2)	p value* (t0-t2)
Time+	42.09 (32.58-54.00)	34.49 (27.43-41.91)	<0.001	32.18 (26.97-35.92)	0.33	<0.001
Error <sup>+</sup>	0 (0-2)	0 (0-1)	0.207	0 (0-0)	0.117	0.024
Correction <sup>+</sup>	4 (2–6)	4 (2–6)	0.222	3 (1–5)	0.009	0.111

<sup>\*</sup>Friedman's non-parametric analysis of variance for repeated measures followed by post-hoc Wilcoxon tests while controlling p values with Bonferroni correction.; all values are median (quartiles). Significant between score difference p < 0.05; statistically significant results are boldface.

meta-analysis by Sergeant et al. 12 studies using the Stroop test in ADHD were examined and no disruptive effect was observed in only two of them [32]. All these results support that the Stroop test is a sensitive neuropsychological test for clinical use in ADHD. In our study, we used the Stroop test to observe the ability to sustain interference effect, response inhibition and processing speed in children with ADHD and in what order and how they changed during the treatment process.

There are numerous studies showing how and to what extent the parameters measured by the Stroop test improve after methylphenidate treatment. Kiris et al. conducted a clinical follow-up study in 20 male patients with ADHD in order to assess the effects of 6 months of long-acting methylphenidate treatment on intelligence, selective attention, focused attentiveness, ability to change attentional setting, interference resistance, processing speed and short-term memory functions and showed that methylphenidate treatment significantly improved executive functions [33]. In another study that aimed to evaluate the efficacy of methylphenidate treatment on executive functions by the WISC-R, Visual Immediate-Memory Span (VIMS), Bender Visual-Motor Gestalt Test (BGT) and Stroop Color and Word Test (SCWT), the authors repeated all assessments in children with ADHD aged 9-13 years who received methylphenidate treatment for 6 months. According to the results of this study, the authors reported that there was no significant change in the WISC-R and VIMS after treatment compared to pretreatment, but significant improvements were observed in the BGT and SCWT. These results suggested that motor coordination, interference resistance, and ability to hold on response improved with methylphenidate treatment [34]. According to a meta-analysis by Coghill et al. in 2014, which included 36 studies that investigated the efficacy of methylphenidate treatment on executive functions in adolescents, almost all studies have shown that methylphenidate treatment has an improving effect on executive functions compared to placebo. However, while commenting on this conclusion, the authors noted that neuropsychological test results, which revealed no significant effect, were ignored in publications; on the other hand, positive results have been mostly reported in this regard [35]. When examining the results of

comparative studies on this subject, in a 12-week follow-up study which included 26 patients with ADHD between the ages of 8 and 14, the effects of orosmethylphenidate and atomoxetine treatments were evaluated by using neuropsychological test battery (Wisconsin Card Mapping Test, Visual Memory Test, and Stroop Test). Both drugs showed a marked improvement in executive functions compared to pretreatment. It has been also shown that oros-methylphenidate treatment is more effective on some of the variables such as perseveration and interference resistance [36]. In another study involving 33 ADHD patients aged 7-12 years with a similar pattern, the Wisconsin Card Sorting Test (WCST), Visual-Aural Digit Span Test-Form B (VADS-B) and Stroop Test were administered before treatment and at the twentieth week of follow-up. Similarly, improvements in executive functions were observed in both groups; however, atomoxetine treatment was found to be more effective in auditory, verbal and written task performance measured by the VADS-B [19]. In a placebocontrolled study using the Stroop Test in 2002, which included 31 ADHD children; methylphenidate treatment has been shown to significantly improve colour naming and word naming abilities. As the limitation of the study, it has been reported that the acute effect of treatment is shown and longer-term studies are needed [9]. In another placebo-controlled study involving 21 boys with ADHD, methylphenidate treatment showed a therapeutic effect on response inhibiton [16]. There are also studies with adults in the literature. In a study in which 28 ADHD patients with substance use disorder comorbidity were included; methylphenidate treatment has been shown to have a positive effect on processing speed [37]. In another study including 40 ADHD-diagnosed adults; showed that the efficacy of methylphenidate treatment could be monitored with processing speed [17]. When studies examining the effect of methylphenidate treatment on Stroop performance are evaluated, some studies have determined that methylphenidate treatment has an accelerating effect on duration scores, in parallel with the findings of our study [19,33,34,36]. Despite studies in the literature reporting that methylphenidate treatment has no effect on interference resistance [36,38], there are several studies showing that methylphenidate treatment shortens the task completion duration and reduces

The "time" of the Stroop test is about processig speed. The "error" and "correction" measurements of the Stroop test are about response inhibition and interference capacity.

the number of errors and corrections in the fifth section of the Stroop test measuring interference resistance, in consistent with our study [39]. When the results of all previous studies are evaluated, it can be concluded that there is a significant impairment in Stroop test performances assessing variables such as the ability to sustain setup against disturbance, selective attention, and psychomotor speed in ADHD and that medications improve test performances. In our opinion, researchers have agreed that there was an increase in processing speed performance with treatment, but the difference in the improvement of response inhibition and interference capacity after treatment might result from the fact that post-treatment re-tests were performed only once and that tests were performed at different times in different studies. For the first time in the literature, our study has assessed the patients at two different time points after treatment, and response inhibition, processing speed, and interference capacity have been shown to improve in a certain order compared to pretreatment. We observed that processing speed improved first, and then the number of errors and corrections was significantly reduced. Thus, response inhibition and interference capacity improved after treatment. This may be due to the fact that response inhibition and interference capacity together with processing speed are tasks related to different regions of the prefrontal cortex. Therefore, methylphenidate may optimize dopamine transmission at different times in different regions of the prefrontal cortex. In other words, while dopaminergic transmission may reach an optimal level in the left mediofrontal cortex related to processing speed in the early period of treatment, dopaminergic transmission may reach an optimal level in the left dorsolateral prefrontal cortex and the anterior cingulate cortex related to response inhibition and interference capacity in the late period of the treatment.

Although this study has some strengths, there are some limitations. Patients with combined-type ADHD without comorbidity other than ODD might not reflect the general population properly since ADHD is known to have a high rate of comorbidity and this restricts the generalization of our results. Other limitations include small sample size and inability to estimate effects on learning duration due to the absence of control or placebo groups. The lack of blinding procedures for clinicians also limited the generalization of our results.

In conclusion, this study demonstrated that processing speed, response inhibition, and interference capacity assessed by the Stroop test improved with methylphenidate treatment in children with ADHD. This study is the first study to show that these improvements occur in a certain order over time. The next step for researchers would be that the answer is investigated for the question of why it occurs so. In this context,

further studies are needed to determine to what extent dopamine transmission and related brain regions are active in re-test applications where similarly designed studies will be combined with neuroimaging and genetic testing. Future results will shed light on the understanding of the etiopathogenesis of ADHD and the establishment of new treatment strategies.

#### **Disclosure statement**

No potential conflict of interest was reported by the authors.

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