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Methylphenidate significantly improves neurocognitive impairments in children with ADHD

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ABSTRACT

This study aimed to investigate the effects of methylphenidate (MPH) on scores on a neurocognitive test battery for individuals with various presentations of attention deficit/hyperactivity disorder (ADHD) and the effect of comorbidities on executive function. This study included 861 children and adolescents aged 7–17 years who were diagnosed with ADHD according to DSM-V criteria. The CNS Vital Signs Battery was utilized to compare the neuropsychological characteristics and MPH treatment responses of patients with predominantly inattentive (ADHD-I) and combined (ADHD-C) presentations of ADHD. Before MPH administration, a statistically significant difference was observed between groups only for complex attention. In addition, the overall prevalence rate of psychiatric comorbidities was 45.5%, and no statistically significant differences were found in the ADHD-I group pre- versus post-MPH administration. Prior to the administration of MPH, statistically significant differences were observed within the ADHD-C group between those with or without comorbidities. However, after MPH administration, these differences between the groups disappeared. The effects of MPH on improving scores on neuropsychological subtests were similar between the groups with different presentations of ADHD. Additionally, MPH treatment was effective despite the presence of comorbidities.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a heritable neurodevelopmental disorder with an estimated global prevalence of approximately 5.29% in children and adolescents (Polanczyk, 2007). In addition, ADHD is one of the most common disorders in school-age children, with a 5% prevalence across cultures (American Psychiatric Association, 2013). ADHD is a complex syndrome of developmental impairments in executive function (EF), which is the self-management system of the brain that mostly consists of unconscious operations. These impairments are variable and chronic, and they significantly interrupt the individual's functioning in many aspects of daily life (Brown, 2013).

One of the most accepted explanations for the characteristics of children with ADHD is EF deficiency Barkley (1997). and Brown (2005) proposed multiple versions of an alternative model conceptualizing the relationship between ADHD and EF. Both models attempt to synthesize an understanding of EF as the brain's mechanism for self-regulation. Furthermore, both describe ADHD as a disorder that involves delays or inadequacies in the development of an individual's capacity for EF. In the EF model proposed by Russell Barkley, deficiencies in behavioral inhibition are proposed in individuals with ADHD, and four EFs are associated with these deficits. EF consists of working memory, self-regulation of affection, motivation-arousal, internalization of speech, and reconstitution. Behavioral impairment and the four associated executive dysfunctions are also thought to affect motor control, fluency and syntax (Barkley, 1997).

The EF model proposed by Thomas Brown suggests that impairments in individuals with ADHD are classified into six categories: activation, focus, effort, emotion, memory and action. Activation includes organizing, prioritizing, and activating work. Focus is described as focusing, sustaining and shifting attention to tasks. Effort, which is the third cluster of EF, includes regulating, alertness, sustaining effort and processing speed. Emotion involves utilizing working memory and accessing recall. The last cluster of EF is action, which includes monitoring and self-regulating action (Brown, 2013). Nevertheless, a widely accepted view is that EF is an 'umbrella term' referring to complex multifaceted, goal-directed responses to novel or difficult situations (Anderson et al.,

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2002; Antshel et al., 2014).

Children with ADHD have difficulties with executive dysfunctions during both real-life activities and neuropsychological tests (Lawrence et al., 2004). The performances of patients diagnosed with ADHD are worse than those of the control group when response inhibition is assessed using Stroop, do/stop and stop signal tasks (Goldberg et al., 2005) Biedermen et al. (2004). indicated that children with both ADHD and executive dysfunction are at greater risk of poor academic outcomes (e.g., learning disabilities or repeating a grade level) than children diagnosed with ADHD without concurrent executive dysfunction. Overall, patients with ADHD alone exhibit the most impaired neurocognitive profile, consistent with previous observations (Barkley, 1990; Cardo et al., 2008; Mostofsky and Simmonds, 2008; Nigg, 2001; Tseng et al., 2004). As defined in DSM-V, ADHD has three presentations: predominantly hyperactive/impulsive (ADHD-H), predominantly inattentive (ADHD-I) and combined (ADHD-C). According to previous studies, these three presentations are differentiated based on inattention symptoms and related features, motor function, demographic variables, and reactions to stimulant medications (Beery et al., 2013; Durak et al., 2014; Sobanski et al., 2008). Previous studies indicated that patients with the predominantly inattention and combined subtypes showed worse performances than control groups on tests assessing the complex attention domain, which included the continuous performance test (CPT), Stroop test, and shifting attention test Pineda et al. (2007). reported that individuals with ADHD presentations significantly differed from the control subjects in the remaining domains of the neuropsychological test battery.

Stimulants have shown efficacy in the management of ADHD symptoms in children (Brown, 2005). Methylphenidate (MPH) is the most frequently used pharmacological agent for the treatment of ADHD. Most previous studies have indicated that MPH improves EF, such as inhibition and working memory (Aron et al., 2003; Sheres et al., 2001). As shown in the study by Chelonis et al. (2011), MPH enhances motivation to perform and execute more adequately on a wide range of tasks associated with EF Solanto et al. (2009). reported a double-blind crossover study of children diagnosed with ADHD-I and ADHD-C. The results of this study showed that MPH affects CPT performance but does not affect Stroop test performance.

EF deficits are not specific to ADHD but are also associated with other psychiatric conditions, such as symptoms of anxiety/depression (Emerson et al., 2005), obsessive compulsive disorder (Chamberlain et al., 2007) and conduct disorder (Pajer et al., 2008; Toupin et al., 2000). Comorbidity is a rule and not an exception in ADHD, as more than 70% of children with ADHD have comorbid psychiatric disorders (Jensen et al., 2001). Subsequently, several studies have examined EF deficits among children with a diagnosis of ADHD and comorbid disorders. However, these studies are limited in number and have yielded inconsistent results (Doyle, 2006; Ter-Stepanian et al., 2017).

The aims of the present study were to investigate the effects of MPH on scores on a neurocognitive test battery for children with various presentations of ADHD and the effect of comorbidities on EF.

2. Methods

2.1. Participants

This study included 861 children and adolescents (608 boys, 253 girls) aged between 7 and 17 years (11.07±2.84) who were diagnosed with ADHD at a child and adolescent psychiatry clinic. The children's diagnoses were based on DSM-V criteria. The assessment was conducted at the first psychiatric admission using the Turkish version of the Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version (K-SADS-PL). The subjects were grouped according to ADHD presentations as ADHD-I (n = 309) and ADHD-C (n = 352). In addition, the ADHD-H presentation group was removed from the study due to the lack of an adequate number of participants. Two hundred healthy children were recruited into the study to serve as the control group. The exclusion criteria for this study were a diagnosis of schizophrenia, bipolar disorder, personality disorder, or mental retardation; a history of head injury with a loss of consciousness; a neurological disease or any other serious medical diseases; and a total IQ score < 80 on the Weschler Intelligence Scale for Children-Revised (WISC-R). In addition, only treatment-naive children were included in the study.

2.2. Assessment procedure

First, the subjects were evaluated with the K-SADS-PL by an expert child and adolescent psychiatrist (E.S. E) to assess ADHD comorbidities and presentations. CNS Vital Signs (CNSVS), a computerized neurocognitive test battery, was used to assess the EF of the participants. Once a child was diagnosed, they were asked to complete the CNSVS. After this baseline measurement, immediate-release MPH was administered to the patients at a dosage of 0.5 mg/kg. The drug was administered following a meal. A wait time of 1 hour was used to allow the effects of MPH to become observable before a second CNSVS measurement was applied. The level of clinical improvement was evaluated using the Turgay DSM-IV-based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV Scale). This study was approved by the Ethics Committee of Hasan Kalyoncu University.

2.3. Measures

2.3.1. Kiddie-SADS-Lifetime version (KSADS-PL)

a) The KSADS-PL is a highly reliable semistructured interview for the assessment of a wide range of psychiatric disorders in children and adolescents according to the DSM-III-R and DSM-IV criteria. The Turkish study of the reliability and validity of the K-SADS-PL was conducted by Gökler et al. (2004).

2.3.2. CNS vital signs battery (CNSVS)

The CNSVS is a computerized test that evaluates the neurocognitive features of the participant. Seven subtests are included in the battery: visual and verbal memory, finger tapping, symbol digit coding, the Stroop test, the shifting attention test and the continuous performance test. The psychometric features of the CNSVS have been reported to be valid and reliable. The sum of the correct responses on the verbal memory (VBM) and visual memory (VIM) tests generates a "composite memory" score. The VBM test is an adaptation of the Rey Auditory Verbal Learning Test, and the VIM test is based on the Rey Visual Design Learning Test. In the former, the participant is required to recognize the words that were previously shown in a word list that also included nontarget words. The VIM test is parallel to the VBM test, in which geometric figures are presented to the participant. The subject are asked to identify geometric figures presented in a memory set from the subsequently displayed response set.

The finger tapping test (FTT) enables the evaluation of motor speed and fine motor control. Once the total taps of the right and left from the FTT are combined with the total correct responses in the symbol digit coding (SDC) test, the "psychomotor speed" of the subjects is obtained. The SDC test is a variant of the Weschler Digit Symbol Substitution Test (DSST), and in the SDC test, the subject is required to press the number that corresponds to the related symbol. Before the trial, the participants were provided a training session.

The Stroop test (ST) is an index for simple/complex reaction times and processing speed. The shifting attention test (SAT) measures the ability of subjects to shift their attention from one task to another. In the SAT, the participant is trained to match geometric figures by either shape or color. The mean cognitive flexibility score is computed by taking the number of correct responses in the SAT and subtracting the number of errors on the SAT and the Stroop test. Although an identical

version of the SAT is not available among the conventional neuropsychology tests, the Wisconsin Cart Sort test is considered similar to the SAT.

The continuous performance test (CPT) is used to estimate sustained attention or vigilance. The CPT has been widely employed in ADHD research. In the CNSVS CPT test, the subject is presented with 200 letters over 5 min and asked to press a button when "B" is shown. Of all the stimuli presented, 40 are the letter "B," and the remaining stimuli are nontargets. At the end of the test, the number of correct responses, commission errors (impulsive responding), and omission errors (inattention) is computed. The commission error reflects a state in which the subject is required not to respond, and the omission error indicates a situation in which the subject lacks a response that should have been given. The CPT also reports the choice reaction time of the subjects for each variable. The complex attention score is generated by summing the errors from the CPT, SAT, and ST (see Gualtieri and Johnson (2006) for a detailed explanation of CNSVS).

2.3.3. Turgay DSM-IV-based child and adolescent behavior disorder screening and rating scale

This instrument was developed by Turgay in 1994 and adapted into Turkish by Ercan et al. (2001). It is based on DSM-IV diagnostic criteria and assesses inattention (9 items), hyperactivity-impulsivity (9 items), opposition-defiance (8 items), and conduct disorder (15 items). The items are rated on a 4-point Likert-type scale that ranges from 0 to 3 points.

2.3.4. Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences 18 (SPSS 18). Descriptive statistics were calculated to assess the demographic features of the children. All continuous variables were tested for normality and homogeneity of variance. The continuous variables were normally distributed; therefore, independent samples t tests and Pearson's chi-square analyses were performed. To compare the means of CNSVS scores, one-way ANOVA and paired samples t tests were performed. In addition, Tukey's post hoc test was performed for normally distributed diagnostic groups. *P* values less than 0.05 were accepted as statistically significant.

3. Results

This study included 861 participants. The subjects were separated according to diagnostic ADHD subgroups. The age and sex distributions of the participants are presented in Table 1. Statistically significant differences in mean ages were observed between the groups (F (10,860) = 9.531; $p<0.001$). Additionally, the sex distribution was significantly in favor of males in all groups ($\chi^2 = 45.84$; $p = 0.001$). Moreover, statistically significant differences in the mean WISC-R total scores were observed between the groups (F (74,860) = 11,469; $p<0.001$).

In comparisons of CNSVS domain scores measured before MPH administration, no statistically significant differences were observed between the ADHD-I and ADHD-C groups in terms of standard scores on tests of the neurocognition index, memory, psychomotor speed, reaction time and cognitive flexibility ($p>0.05$). However, a statistically significant difference was identified between the ADHD-I and ADHD-C groups in standard scores for complex attention (t (658) = 2.42; $p<0.05$). Additionally, FTT scores; correct responses in the SDC; complex reaction time in the ST; correct responses in the SAT; and correct responses, omission errors, commission errors and correct choice reaction time in the CPT significantly differed between subjects with ADHD-C and ADHD-I ($p<0.05$). The baseline values for the domain scores of CNSVS are presented in Table 2. According to these results, the control group had significantly higher scores than both the ADHD-I and ADHD-C groups for all CNSVS domains except reaction time. Moreover, the results of the Pearson correlation analysis showed a significant correlation between symptom severity and standard scores for the neurocognition index and cognitive flexibility ($r = -0.09, p < 0.05$; $r = -0.08, p < 0.05$). In other words, the standard scores for the neurocognition index and cognitive flexibility decreased as the number of ADHD symptoms increased.

After MPH administration, statistically significant differences in standard memory scores on the CNSVS were observed between the groups (t (658) = 2.51; $p<0.05$). In addition, immediate correct passes in the VIM; FTT scores; correct responses in the SDC; complex reaction time in the ST; correct reaction time in the ST; correct responses and errors in the SAT; and correct responses, omission errors and correct choice reaction time in the CPT significantly differed between the subjects with ADHD-C and those with ADHD-I ($p<0.05$). The comparisons of CNSVS domain scores between the groups after MPH administration are presented in Table 3.

The CNSVS domain scores of the ADHD-I group before versus after MPH administration were compared using repeated measures t tests. Statistically significant differences in the CNSVS domain scores were observed before and after MPH usage ($p<0.05$), indicating increases in the neurocognition index (t (307) = −15.67, $p<0.001$), psychomotor speed (t (307) = −3.24, $p<0.001$), reaction time (t (307) = −8.44, $p<0.001$), complex attention (t (307) = −13.67, $p<0.001$) and cognitive flexibility (t (307) = −17.13, $p<0.001$) scores when MPH was used. In addition, the memory score decreased with the use of MPH (t (307) = 3.08, $p<0.001$). When the CNSVS domain scores of the ADHD-H group were compared before and after MPH administration, statistically significant differences were detected ($p<0.05$). This finding indicated increases in the neurocognition index (t (350) = −17.17, $p<0.001$), psychomotor speed (t (351) = −12.17, $p<0.001$), reaction time (t (351) = −7.43, $p<0.001$), complex attention (t (351) = −16.76, $p<0.001$) and cognitive flexibility (t (350) = −20.51, $p<0.001$) scores when MPH was used. In addition, the memory score decreased with the use of MPH (t (351) = 4.41, $p<0.001$). The evaluation of the mean differences in the CNSVS scores revealed that the largest difference between the ADHD-I and ADHD-C groups was in the cognitive flexibility domain, with 49% and 54% increases, respectively, after MPH administration, and the smallest change was in the memory score, with decreases of 0.03% and 0.05%, respectively. All domain scores decreased following MPH administration in both groups. Moreover, each of these decreases was statistically significant, except for immediate and delayed correct hits in VBM, immediate and delayed correct hits in VIM, delayed correct passes in VIM and errors in SDC (Table 4). Furthermore, the CNSVS domain scores of the control group pre- and post-MPH administration were compared to exclude learning effects. Based on the results of the analysis, no significant differences were observed in performance on the two tests performed one hour apart ($p > 0.05$) for the control group. In addition, the results of the Pearson correlation analysis showed no significant relationship between age and mean differences in the CNSVS scores ($p>0.05$).

When the prevalence of psychiatric comorbidities was assessed, the overall prevalence rate was 45.5% ($n = 301$). Oppositional defiant disorder, conduct disorder, depressive disorder and anxiety disorder accompanied ADHD in 29.2%, 6.3%, 5.1% and 4.9% of the patients, respectively. Among these children, 56.5% ($n = 199$) were diagnosed with ADHD-C, and 33% ($n = 102$) were diagnosed with ADHD-I.

Table 1
Age and Gender Distributions of Participants.

	Age	p[a]	Boys	Girls	Total	p[b]
Groups	Mean (SD)	0.000	n%	n%	n%	0.000
ADHD-I	12.02±3.07		210 67.7	99 32.3	309 35.9	
ADHD-C	10.43±2.86		288 80.4	64 19.6	352 40.9	
Control	10.73±1.92		110 55	90 45	200 23.2	

$p<0.001$.
[a] One-way ANOVA.
[b] Chi-square test.

Table 2
Comparisons of CNSVS Domain Scores Between Groups pre-MPH Administration.

Baseline Measurements	ADHD-I Mean (SD)	ADHD-C Mean (SD)	Control Mean (SD)	p	Pairwise Comparisons
Neurocognition Index	85.78 (16.42)	84.79 (15.50)	98.93 (12.57)	0.00***	ADHD-*I*=ADHD-C < Control
Memory	87.42 (20.81)	84.29 (22.84)	97.13 (17.75)	0.00***	ADHD-*I*=ADHD-C < Control
Psychomotor Speed	91.94 (14.31)	93.04 (13.20)	103.07 (17.90)	0.00***	ADHD-*I*=ADHD-C < Control
Reaction Time	80.27 (23.18)	80.69 (21.25)	84.50 (32.70)	0.14	
Complex Attention	84.02 (28.70)	78.79 (30.99)	104.40 (13.21)	0.00***	ADHD-*I*=ADHD-C < Control
Cognitive Flexibility	86.90 (19.81)	87.00 (18.21)	105.57 (17.19)	0.00***	ADHD-*I*=ADHD-C < Control
Verbal Memory Test					
Correct Hits-immediate	12.07 (6.21)	11.67 (2.68)	12.82 (2.57)	0.01*	ADHD-C <ADHD-I =Control
Correct Passes-immediate	13.96 (1.86)	13.67 (2.29)	13.89 (1.18)	0.12	
Correct Hits-delay	10.12 (3.27)	10.49 (3.27)	11.89 (2.50)	0.00***	ADHD-*I*=ADHD-C < Control
Correct Passes-delay	13.75 (2.30)	13.46 (2.53)	13.48 (1.65)	0.23	
Visual Memory Test					
Correct Hits-immediate	11.60 (2.31)	11.49 (2.36)	12.17 (2.06)	0.00**	ADHD-*I*=ADHD-C < Control
Correct Passes-immediate	11.23 (2.68)	10.90 (2.67)	11.83 (2.16)	0.00***	ADHD-*I*=ADHD-C < Control
Correct Hits-delay	10.35 (2.52)	10.35 (2.77)	10.91 (2.64)	0.03*	ADHD-*I*=ADHD-C < Control
Correct Passes-delay	14.04 (51.44)	10.66 (3.59)	11.12 (2.67)	0.34	
Finger Tapping Test					
Right Taps Average	50.48 (10.23)	48.53 (9.01)	49.26 (7.74)	0.02*	ADHD-C=Control < ADHD-I
Left Taps Average	46.27 (9.54)	44.96 (8.57)	46.01 (7.53)	0.12	
Symbol Digit Coding					
Correct Response	43.10 (16.11)	39 (14.64)	48.40 (12.10)	0.00***	ADHD-C < ADHD-I< Control
Errors	1.22 (1.64)	3.22 (38.71)	3.59 (5.12)	0.47	
Stroop Test					
Simple Reaction Time	373.65 (123.28)	394.76 (153.45)	464.33 (295.59)	0.00***	ADHD-*I*=ADHD-C < Control
Complex Reaction Time Correct	761.55 (171.34)	795.69 (172.34)	794.46 (240.77)	0.04*	ADHD-*I*<ADHD-C =Control
Stroop Reaction Time Correct	913.91 (188.98)	945.64 (182.84)	919.79 (232.63)	0.10	
Stroop Comission Errors	3.10 (3.13)	3.82 (3.36)	2.65 (2.85)	0.00***	ADHD-I= Control < ADHD-C
SAT					
Correct Responses	36.52 (11.72)	33.84 (10.77)	42.27 (10.85)	0.00***	ADHD-C <ADHD-I< Control
Errors	16.78 (16.31)	21.04 (47.64)	11.64 (6.02)	0.00**	ADHD-C > Control
Correct Reaction Time	1201.61 (181.32)	1201.29 (228.51)	1193.15 (247.57)	0.89	
CPT					
Correct Responses	37.87 (3.90)	37.21 (3.99)	39.24 (1.07)	0.00***	ADHD-*I*=ADHD-C < Control
Omission Errors	2.01 (3.38)	2.95 (4.56)	0.76 (1.07)	0.00***	Control < ADHD-*I* < ADHD-C
Commission Errors	4.03 (6.92)	8.85 (41.59)	1.57 (1.58)	0.00**	Control < ADHD-*I* < ADHD-C
Choice Reaction Time Correct	501.05 (88.52)	543.65 (217.74)	472.71 (155.53)	0.00***	ADHD-I = Control < ADHD-C

* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.

According to the comparisons of CNSVS domain scores measured before MPH administration, no statistically significant differences in standard scores for the neurocognition index, memory, psychomotor speed, reaction time and cognitive flexibility were observed between the participants stratified based on the presence of psychiatric comorbidity ($p>0.05$). However, statistically significant differences in terms of standard memory scores on CNSVS were observed between the groups after the administration of MPH ($t(658) = 2.05$; $p<0.05$). When CNSVS scores were assessed according to the presence of comorbidities in the groups with various presentations of ADHD, no statistically significant differences were found in the ADHD-I group ($p>0.05$) before or after MPH administration. In the preadministration period of MPH, statistically significant differences in standard scores for the neurocognition index ($t(349) = 1.97$; $p<0.05$) and psychomotor speed ($t(349) = 2.26$; $p<0.05$) were observed between the ADHD-C groups with or without comorbidities. However, after MPH administration, no statistically significant differences remained between those groups (Table 5).

When a detailed assessment based on accompanying comorbid disorders was performed, the only statistically significant differences were detected in standard memory scores between the ADHD groups with or without comorbidities after MPH administration ($F(2659) = 5.32$; $p<0.01$). The children with ADHD and disruptive behavior disorder had lower memory scores than the children with ADHD and anxiety disorder, ADHD and depressive disorder and ADHD with no comorbidities. The mean scores for standard memory in the children with ADHD and disruptive behavior disorder were 77.30 ± 22.77, whereas the same metric was 84.15 ± 22.87 and 84.09 ± 22.84 in the children with ADHD and anxiety disorder and ADHD and depressive disorder, respectively. In addition, the mean score for standard memory in the children with ADHD without comorbidities was 83.24 ± 21.91, and it was 97.13 ± 11.75 in the children in the control group.

4. Discussion

This study compared the neuropsychological characteristics and MPH treatment responses of children and adolescents stratified according to ADHD presentation. In addition, the effects of existing

Table 3
Comparisons of CNSVS Domain Scores Between Groups post-MPH Administration.

Baseline Measurements	ADHD-I Mean (SD)	ADHD-C Mean (SD)	P
Neurocognition Index	95.39 (13.75)	93.99 (14.31)	0.22
Memory	83.93 (21.25)	79.45 (23.23)	0.01*
Psychomotor Speed	103.47 (62.86)	98.61 (12.38)	0.19
Reaction Time	89.60 (19.43)	87.53 (19.26)	0.18
Complex Attention	101.66 (25.45)	100.85 (22.45)	0.68
Cognitive Flexibility	102.82 (17.90)	103.21 (18.31)	0.75
Verbal Memory Test			
Correct Hits-immediate	11.99 (2.34)	11.86 (2.49)	0.53
Correct Passes-immediate	13.49 (2.25)	13.22 (2.55)	0.16
Correct Hits-delay	9.92 (3.04)	10.15 (3.03)	0.33
Correct Passes-delay	12.57 (2.47)	12.40 (2.67)	0.41
Visual Memory Test			
Correct Hits-immediate	11.56 (2.12)	11.87 (2.49)	0.11
Correct Passes-immediate	11.55 (2.76)	10.90 (2.67)	0.01*
Correct Hits-delay	10.43 (2.53)	10.26 (2.55)	0.41
Correct Passes-delay	10.61 (3.08)	9.99 (3.55)	0.01*
Finger Tapping Test			
Right Taps Average	52.37 (10.05)	50.56 (8.59)	0.02*
Left Taps Average	47.67 (10.09)	46.26 (8.29)	0.05
Symbol Digit Coding			
Correct Response	50.65 (16.57)	46.15 (15.72)	0.00***
Errors	1.34 (3.58)	1.29 (1.56)	0.80
Stroop Test			
Simple Reaction Time	369.40 (204.37)	378.43 (125.49)	0.51
Complex Reaction Time Correct	712.44 (146.74)	759.90 (150.86)	0.00***
Stroop Reaction Time Correct	843.14 (165.78)	881.73 (171.42)	0.00**
Stroop Comission Errors	2.07 (1.96)	2.42 (2.20)	0.14
SAT			
Correct Responses	44.55 (11.89)	42.39 (11.41)	0.02*
Errors	10.03 (8.47)	11.42 (8.78)	0.04*
Correct Reaction Time	1162.56 (194.47)	1177.03 (183.34)	0.32
CPT			
Correct Responses	39.15 (1.91)	38.81 (2.22)	0.03*
Omission Errors	0.84 (1.91)	1.16 (2.19)	0.04*
Commission Errors	2.39 (7.58)	3.08 (5.36)	0.17
Choice Reaction Time Correct	476.14 (87.99)	499.16 (89.80)	0.00**

* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.

comorbidities on EF were assessed. Before MPH administration, the ADHD-I and ADHD-C groups exhibited similar performances on all neuropsychological tests, except the standard complex attention test. Moreover, the children with ADHD-I and ADHD-C presented poorer performances on CNSVS domain tests than the children in the control group. The current study did not observe significant differences between the groups with various presentations of ADHD and the control group. This result is consistent with the literature (Durak et al., 2014; Nigg, 2001). Furthermore, the response of the participants with ADHD-I to MPH differed from that of the participants with ADHD-C in terms of performance on standard memory tests and some other neuropsychological test scores.

The children with ADHD-I performed worse than those with ADHD-C in the complex attention domain. Moreover, previous studies have indicated that omission errors (associated with inattention) are assumed to reflect the symptoms of inattention, while commission errors (associated with impulsive responding) are assumed to reflect symptoms of impulsivity (Conners et al., 2003; Epstein et al., 2003). In this sense, omission errors are expected to be more prevalent in individuals with ADHD-I, and commission errors are expected to be more prevalent in individuals with ADHD-C. However, this study found that the children with ADHD-C presented both more commission and omission errors. Consistent with the current findings, previous studies show that individuals with ADHD tend to make more errors in both omission- and commission-associated attention tasks. (Christensen and Lundwall, 2018; Johnstone and Galletta, 2013; O'Connell et al., 2009; Van der Oord et al., 2008).

According to previous studies, individuals with different ADHD presentations are similar in regard to MPH response and the effect of MPH on neuropsychological test scores. The current results are consistent with previous findings. MPH was substantially effective in improving the performance of children with various presentations of ADHD on neuropsychological subtests, and this improvement was similar between children with various presentations of ADHD (Durak et al., 2014; O'Driscoll et al., 2005). In addition, the absence of changes in the CNSVS domain scores of the control group clearly indicated that the changes in the ADHD-I and ADHD-C groups were due to MPH. Therefore, the changes cannot be attributed simply to taking the test twice, also known as the learning effect. In addition, a meta-analysis revealed moderate and consistent effects of MPH on neuropsychological performance in individuals with ADHD (Tamminga et al., 2016). Cognitive processes are more closely related to brain maturation. Therefore, the current study considered the effect of age on neurocognitive performance. Consistent with previous studies, our results revealed no correlation between age and the mean differences in the CNSVS scores (Tamminga et al., 2016; Van der Oord et al., 2008). Moreover, neurocognitive functioning may serve as a predictor of symptom severity and overall functioning of individuals with ADHD, as neurocognitive dysfunction is a key aspect of the disorder (Willcutt et al., 2008) and is at the heart of several models of ADHD (Barkley, 1997; Brown, 2005). Consistent with the findings of previous studies, the results of the current study show a relationship between symptom severity and neurocognitive functioning (Sjöwall et al., 2015; Van Lieshout et al., 2017).

Of the 661 children with ADHD included in the present study, 45.5% had one psychiatric comorbidity. Consistent with the present study, Barkley (2006) stated that up to 44% of children with ADHD have at least one other psychiatric disorder, while Inci et al. (2019) revealed this rate as 41.3%. Our findings indicate that the presence of comorbid disruptive behavior disorder, depressive disorder or anxiety disorders affects the EF performance of children. Similar to previous studies (Brown, 2013; Ter-Stepanian, 2017), the children and adolescents in this study who were diagnosed with comorbid disruptive behavior disorder had more difficulties in the neurocognition index and a lower psychomotor speed than their peers diagnosed with ADHD without comorbid disruptive behavior disorder. After MPH treatment, the differences in those areas disappeared. In addition, the current study shows that the children and adolescents who were diagnosed with ADHD-C and additional comorbidities had difficulties remembering and recalling visual and verbal stimuli before MPH treatment. Disruptive behavior disorder is associated with poor neurocognitive performance regardless of the ADHD diagnosis, and some studies indicate that more severe hyperactive, impulsive or inattentive symptoms are present in children with ADHD accompanied by comorbid disruptive behavior disorder (Baving et al., 2006; Sergeant et al., 2002). However, researchers have not clearly determined whether the presence of comorbid disruptive behavior disorder also increases the intensity of EF impairment in individuals with ADHD (Clark et al., 2000; Scheres et al., 2003). Other studies report that impairments in EF are greater in children with ADHD and disruptive behavior disorder than in children with ADHD without any comorbidity (Hummer et al., 2011; Jensen et al., 2001).

In conclusion, MPH improved performance on neuropsychological subtests, and this effect was similar between the groups with various presentations of ADHD. Additionally, MPH treatment was effective at improving neuropsychological functioning, despite the presence of existing comorbidities. The present results should be viewed based on the strengths and limitations of this study. This study is one of the largest to date to investigate the effects of MPH on neurocognitive test battery scores in participants with various presentations of ADHD and the effects of comorbidities on EF. In addition, symptom severity and age-related development were considered during the evaluation and statistical

Table 4
Differences in CNSVS Domain Scores Between the Groups pre- and post-MPH Administration.

	ADHD-I			ADHD-C		
	%Difference, Mean (SD)	t	p	%Difference, Mean (SD)	T	p
Neurocognition Index	−9.64 (0.61)	−15.67	0.00***	−9.17 (0.53)	−17.17	0.00***
Memory	3.44 (1.12)	3.08	0.00***	4.84 (1.10)	4.41	0.00**
Psychomotor Speed	−11.52 (3.55)	−3.24	0.00***	−5.75 (0.46)	−12.17	0.00***
Reaction Time	−9.34 (1.11)	−8.44	0.00***	−6.85 (0.92)	−7.43	0.00***
Complex Attention	−17.68 (1.29)	−13.67	0.00***	−22.06 (1.32)	−5.05	0.00***
Cognitive Flexibility	−15.93 (0.93)	−17.13	0.00***	−16.17 (0.79)	−20.51	0.00***
Verbal Memory Test						
Correct Hits-immediate	0.07 (0.39)	0.17	0.87	−0.20 (0.24)	−1.16	0.24
Correct Passes-immediate	0.47 (0.11)	4.36	0.00***	0.44 (0.11)	3.78	0.00***
Correct Hits-delay	0.19 (0.21)	0.89	0.37	0.35 (0.18)	1.94	0.05
Correct Passes-delay	1.17 (0.13)	8.90	0.00***	1.06 (0.14)	7.66	0.00***
Visual Memory Test						
Correct Hits-immediate	0.03 (0.15)	0.21	0.83	0.21 (0.15)	1.46	0.15
Correct Passes-immediate	−0.34 (0.15)	−2.28	0.02*	−0.10 (0.17)	−0.60	0.55
Correct Hits-delay	−0.08 (0.16)	−0.47	0.64	0.09 (0.57)	0.57	0.57
Correct Passes-delay	3.44 (2.94)	1.17	0.21	0.68 (0.18)	3.67	0.00***
Finger Tapping Test						
Right Taps Average	−1.86 (0.40)	−4.62	0.00***	−2.04 (0.34)	−6.05	0.00***
Left Taps Average	−1.34 (0.33)	−4.04	0.00***	−1.31 (0.31)	−4.22	0.00***
Symbol Digit Coding						
Correct Response	−7.64 (0.48)	−15.74	0.00***	−7.16 (0.40)	−17.87	0.00***
Errors	−0.12 (0.22)	−0.56	0.57	1.92 (2.06)	0.94	0.35
Stroop Test						
Simple Reaction Time	4.28 (12.28)	0.35	.73	16.49 (7.20)	2.29	0.02*
Complex Reaction Time Correct	50.55 (8.12)	6.23	0.00***	35.91 (7.70)	4.66	0.00***
Stroop Reaction Time Correct	71.82 (7.16)	10.03	0.00***	63.37 (7.76)	8.16	0.00***
Stroop Comission Errors	1.05 (0.18)	5.77	0.00***	1.40 (0.16)	8.73	0.00***
SAT						
Correct Responses	−8.03 (0.44)	−18.31	0.00***	−8.41 (0.43)	−19.47	0.00***
Errors	6.99 (0.84)	8.30	0.00***	9.61 (2.55)	3.77	0.00***
Correct Reaction Time	35.67 (9.86)	3.62	0.00***	21.82 (12.39)	1.76	0.04*
CPT						
Correct Responses	−1.30 (0.20)	−6.65	0.00***	−1.60 (0.20)	−8.08	0.00***
Omission Errors	1.18 (0.16)	7.53	0.00***	1.78 (0.23)	7.72	0.00**
Commission Errors	2.09 (0.36)	5.86	0.00***	5.77 (2.26)	2.55	0.01*
Choice Reaction Time Correct	25.50 (3.10)	8.38	0.00***	43.53 (11.43)	3.81	0.00***

* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.

Table 5
Differences in CNSVS Domain Scores Between the Groups with/without comorbidity pre- and post-MPH Administration.

	ADHD-IMean (SD)			ADHD-CMean (SD)		
	None	Comorbidity	p	None	Comorbidity	p
Baseline measurement						
Neurocognition Index	85.98 (14.93)	85.36 (19.14)	0.77	86.65 (15.83)	83.37 (15.13)	0.04*
Memory	87.91 (19.97)	86.41 (22.48)	0.55	85.96 (23.23)	83.01 (22.49)	0.23
Psychomotor Speed	92.27 (13.14)	91.26 (16.46)	0.56	94.84 (13.68)	91.65 (12.67)	0.02*
Reaction Time	79.27 (23.80)	82.31 (21.83)	0.28	81.40 (22.10)	80.14 (20.61)	0.58
Complex Attention	84.22 (28.19)	83.62 (29.74)	0.86	80.87 (31.14)	77.20 (30.85)	0.27
Cognitive Flexibility	87.01 (18.24)	86.68 (22.74)	0.89	89.05 (18.71)	85.43 (17.70)	0.06
Post-MPH Administration						
Neurocognition Index	95.51 (13.36)	95.16 (14.55)	0.83	95.69 (14.74)	92.79 (13.93)	0.06
Memory	84.50 (20.15)	82.79 (23.38)	0.51	81.53 (24.03)	78.03 (22.63)	0.16
Psychomotor Speed	102.21 (54.91)	106.0 (76.68)	0.62	99.90 (13.48)	97.76 (11.53)	0.12
Reaction Time	88.82 (18.59)	91.17 (21.04)	0.32	86.33 (21.56)	88.55 (17.27)	0.29
Complex Attention	102.27 (26.47)	100.45 (23.35)	0.56	102.78 (21.95)	99.44 (22.75)	0.16
Cognitive Flexibility	103.10 (17.41)	102.24 (18.93)	0.69	104.61 (19.84)	102.22 (17.01)	0.23

* $p<0.05$.

analysis. Regarding the limitations, the participants were recruited from a single center. Therefore, the present results highlight the need for more research in this area with multicenter sampling. In addition, this study was not able to determine the effects of individual comorbidities. Therefore, analyses should be conducted to determine the individual effects of comorbidities in future studies.

5. Clinical significance

ADHD is a complex syndrome of developmental impairments in EF. These impairments are variable and chronic, and they significantly interfere with functioning in many aspects of an individual's daily life. In addition, comorbidities are a rule and not an exception in individuals with ADHD. Furthermore, EF deficits are not specific to ADHD but are

also associated with other psychiatric conditions. Therefore, increased awareness of methods to improve EF in children with ADHD is needed. Moreover, this study is one of the largest to date to investigate the effects of MPH on neurocognitive test battery scores in participants with various presentations of ADHD and the effects of comorbidities on EF.

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CRediT authorship contribution statement

Sevim Berrin Inci Izmir: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Melis Ipci:** Conceptualization, Methodology, Funding acquisition, Writing – review & editing. **Eyüp Sabri Ercan:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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