Article

The Effect of Methylphenidate Treatment on Olfactory Function in Children and Adolescents With ADHD

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Abstract

Objective: This study aimed to research whether there is an olfactory disorder in ADHD, and if so, what is the effect of methylphenidate on this condition. **Method:** This is a cross-sectional study aiming to evaluate olfactory threshold, identification, discrimination and threshold, discrimination, and identification (TDI) scores in 109 children and adolescents, 33 of whom have ADHD without medication, 29 with ADHD with medication and 47 control groups. **Result:** In the post hoc tests, the mean odor discrimination test, the mean odor identification test, and the mean TDI scores of the unmedicated ADHD group were significantly lower than those of the other two groups, and that the mean odor threshold test scores of the medicated ADHD group were significantly lower than those of the control and unmedicated groups. **Conclusion:** Olfactory function could be a useful tool to monitor treatment effects and may be a promising candidate as a biomarker in ADHD. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

Keywords

child/adolescent, ADHD, methylphenidate, odor function, sniffin' sticks

Introduction

ADHD is defined as a persistent pattern of inattentiveness and/or hyperactivity-impulsivity that usually impairs functioning or development (Albayrak et al., 2008; American Psychiatric Association, 2013; Biederman & Faraone, 2005; Stockhorst & Pietrowsky, 2004). Evidence suggests that ADHD has multiple etiologies, including genetic, environmental, neurobiological, and neurochemical factors, catecholamine dysfunction, and including that dopaminergic and noradrenergic neurotransmission, is an important underlying cause (Albayrak et al., 2008; Biederman & Faraone, 2005). Alterations in dopaminergic pathways are considered involved in the underlying pathology that leads to both symptoms of inattention and/or hyperactivity and alterations in the olfactory process (American Psychiatric Association, 2013). Moreover, children with ADHD often experience symptoms of a sensory processing disorder in various areas (Miller et al., 2012). Individuals with ADHD have problems with sensory seeking, auditory filtering, and sensitivity to tactile, auditory, visual, taste, and olfactory stimulants (Mangeot et al., 2011).

The olfactory system consists of the occuring orbitofrontal cortex (OFC), amygdala, hippocampus, and pyrifomal cortex (PIR; Benarroch, 2010). Activations in the orbitofrontal cortex have been found in many olfactory imaging studies, and this area contributes to the identification and differentiation of odors (Albrecht et al., 2006). The association between dopamine and orbitofrontal cortex dysfunction and ADHD has also been well documented. These are also mechanisms that affect olfaction processes (Schecklmann, Schenk et al., 2011).

To understand the relationship between olfaction and neuropsychiatric disorders, it is necessary to understand the olfactory pathway. The signals from the olfactory receptors converge via the olfactory nerve in the glomeruli of the olfactory bulb, where there are a large number of inhibitory interneurons (mainly gamma aminobutyric acid [GABA] and dopamine) (Brand, 2006). The task of these interneurons is to filter and amplify the olfactory signals. Dopamine

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Table 1. Psychostimulants and Other Medications in the Treatment of Children and Adolescents with ADHD.

Psychostimulants	Generic name
Methylphenidate immediate release	Ritalin
Methylphenidate sustained release	Concerta
	Medikinet Retard
	Ritalin LA
Amphetamine Liquid	
Lisdexamphetamine	
Other medications	
Atomoxetine	
Guanfacine extended release	

appears to play an important role in mediating the inhibitory effects of bulbar interneurons on olfactory neurotransmission (Cave & Baker, 2009).

It is associated with significant changes in olfactory function in neuropsychiatric diseases where the effect of dopaminergic neurotransmission is strong. This is the case in typical adult diseases such as Parkinson's disease or schizophrenia and childhood diseases such as ADHD (Kamath et al., 2012). Olfactory functioning is most frequently assessed by three parameters: olfactory sensitivity (the smell detection threshold) and smell identification and discrimination ability. The smell discrimination test measures the ability to discriminate one smell quality from another, while the odor identification test examines the retrieval of an odor that has previously been sniffed and stored in memory.

Methylphenidate (MPH) is considered first-line therapy in ADHD and second-line drugs are lisdexamfetamine, atomoxetine, and guanfacine (Table 1; Drechsler et al., 2020). Methylphenidate blocks dopamine re-uptake in the mesolimbic system and prefrontal cortex (PFC), thereby increasing dopamine neurotransmission in the prefrontal cortex, striatum, and various other brain regions and norepinephrine transmission in the locus coeruleus, raphe nuclei, thalamus, and thalamic subnuclei (Hannestad et al., 2010). Considering the pathways affected by methylphenidate, the relationship between methylphenidate and odor function cannot be ignored.

There are only two studies in the literature that have investigated the effect of methylphenidate treatment on olfactory function. First, in the study conducted by Romanos et al. children with unmedicated ADHD were found to have higher odor sensitivity compared to the healthy control group, but not medicated ADHD. However, no difference was determined in odor identification and discrimination (Romanos et al., 2008). In the second study, Schecklmann et al. reported that the ability for smell discrimination in children with ADHD was better than that of the control group. In the same study, no difference was found in odor sensitivity and odor identification tests. Furthermore, that study demonstrated that the odor discrimination ability of the patients receiving drug treatment was similar to that of the control group (Schecklmann, Schaldecker et al., 2011). However, as mentioned above, the number of studies on this subject is insufficient and their results need to be expanded. When the results of the studies conducted in ADHD groups that received and did not receive methylphenidate treatment similar to the current study were examined, the results can be seen to be contradictory.

In addition, changes in odor parameters in ADHD subtypes were investigated. There have been no previous studies evaluating odor parameters according to subtypes. This study aimed to research whether there is an olfactory disorder in ADHD, and if so, what is the effect of methylphenidate on this condition.

Materials and Methods

The prevalence of ADHD is known to be 2% to 7% to form the study group (Sayal et al., 2018). From this starting point, when it was planned to have a group of at least 45 subjects to form a data set, the power of the study was calculated as 92%. The study included 109 children, aged 6 to 16 years, with ADHD (29 children with treatment, 33 children without treatment), and 47 healthy control subjects matched for age, gender, intelligence quotient (IQ), educational attainment, and sociocultural characteristics to the ADHD group. The study was conducted between April 2019 and December 2019 at the outpatient clinic of the Pediatric and Adolescent Psychiatry Department. Healthy control subjects were recruited from various schools. The ADHD patients were categorized into two groups: ADHD-unmedicated group (not receiving any medication) and ADHD-medicated group (using continuous methylphenidate at a sufficient and effective dosage) for at least 3 months before the olfactory tests. All children were evaluated by two certified child and adolescent psychiatrists using a semistructured psychiatric interview to determine the presence of any psychiatric disorder, and only patients with "pure" ADHD were included in the study. The Wechsler Intelligence Scale for Children IV (WISC-IV) was used to evaluate IQ. The participants who were eligible to participate in the study were examined by an otorhinolaryngologist. Seven children with acute and chronic oto-rhino-laryngological diseases and other medical illnesses, those with a history of otorhinolaryngology, surgery or head injury, drug or alcohol abuse, or smoking habits were excluded from the study. Five children who used ADHD medications (such as atomoxetine) other than methylphenidate were also excluded from the study.

Data Collection Tools

Conners' Parent Rating Scale Revised Short Form (CPRS-RS): The CPRS-RS was applied to measure the severity of ADHD. The CPRS-RS, which includes 27 items

in total, consists of three subscales (hyperactivity, cognitive problems/inattention, and oppositional subscale) and an auxiliary scale (ADHD-Index) (Kumar & Steer, 2003). Each scale item is answered on a 4-point Likert scale and assigned 0, 1, 2, or 3 points according to the severity of the symptoms. A high score indicates more severe problematic behavior. The Turkish validity and reliability study was conducted by Kaner et al. (2013).

The Stroop TBAG form (ST-TBAG): The Stroop test TBAG form (ST-TBAG), which has proven reliability and validity, was employed to measure the severity of attention deficit (selective attention) and basic cognitive speed (Karakas et al., 1999; Stroop, 1935). The ST-TBAG, which consists of five subtests, was applied to assess the severity of attention problems and basic cognitive tempo. The scale was adapted to Turkish children by Karakas et al. (1999). When evaluating the scale score, errors, corrections, and the duration for completion of each subtest are taken into account. In this study, only Stroop total time, total error, and total correction scores were calculated. Higher points of total error and correction, and/or longer completion duration are considered indicative of more severe attention deficits and greater impairment in cognitive function.

Wechsler Intelligence Scale for Children IV (WISC-IV): WISC-IV is an intelligence test established to measure the intellectual skills of individuals between the ages of 6 to 16 years (Wechsler, 2004). The test has 15 subtests and each subtest is divided into four subscales. Each subscale has a standardized mean and SD of 100 and 15, respectively. The WISC-IV was adapted to Turkish by Öktem et al. in 2011 (Öktem et al., 2011).

Two otorhinolaryngologists performed this test to measure threshold discrimination and identification subtests (Murphy et al., 2001). The participants were asked to wear scent-free clothes and materials on the day of the test and to not eat anything for 1 hr before the test. The subtests were performed in a quiet and well-ventilated room using odorless gloves. First, the participants were asked to estimate their olfactory ability and sensitivity by responding to the question "How would you describe your olfactory ability and sensitivity?." Next, they were told to choose one of the options of normal, reduced, or increased. The participants were blind-folded during the odor detection thresholds and odor discrimination tasks, and no feedback was provided. The Sniffin' Sticks Extended Test consists of three subtests: Threshold, Discrimination, and Identification (TDI score):

Olfactory Assessment: The evaluation of threshold, discrimination, and identification subtests was conducted using the Sniffin' Stick Extended Test (SSET) (Burghart GmbH, Wedel, Germany) in accordance with the manufacturer's instructions (Hummel et al., 2007). The SSET consists of three subtests; olfactory threshold (OT) test, odor discrimination (OD) test, and odor identification (OI) test and has a total score (threshold, discrimination, and identification [TDI]).

Olfactory Threshold (OT) Test: Odor Threshold (OT) Test: In the OT test, 16 triplet pens containing 4% *n*-butanol solution at different concentrations are smelled in increasing concentration. Two of the 16 triplet pens are fragrance-free, one contains fragrance, and the participant is asked to identify the BUT/PEA pen among the three pen sets offered (Öktem et al., 2011). The test begins with the pen with the most intense odor (highest /PEA concentration). Thirty seconds later, the subject is presented with two other items, which should theoretically report that they are odorless. Participant's responses are marked in the grid presented in Figure 1. as correctly defined (+) or undefined (−). The turning point of the test is the concentration at which the patient gives two consecutive correct answers. With two consecutive correct identifications, another set of triads with lower concentration were sniffed. A higher concentration is then presented until two correct responses are obtained. The test continues in this way seven times. The threshold is considered the arithmetic mean of the last four of the seven stages. The OT score ranges from 1 to 16, with higher scores indicating a lower (better) participant's threshold (Rumeau et al., 2016).

Odor Discrimination (OD) Test: The OD test were performed using 16 triplets of odorants. Two of the sixteen triplets contain the same odor, the other third contains a different odor, and the participant is requested to identify the sample that has a different smell. The score of the test is calculated as the total of correctly identified pens, ranging from 0 to 16.

Odor Identification (OI) Test: The OI test consists of 16 odor sticks. These 16 pens are presented one by one to the participant, who is asked to choose the most appropriate of the four written options written for that odor. Each correct answer is scored as "1" and each incorrect answer as "0," to give a total score ranging from 0 to 16.

Threshold, Discrimination, and Identification (TDI) score: The TDI score is derived from the total of the mean scores of the three subtests. The lowest score is 1, and the maximum score is 48. Scores above 30 indicate normal olfactory function, while 15 to 30 points show reduced odor performance. A score below 15 is defined as a loss of olfactory function.

Statistical analysis: For statistical analysis, IBM SPSS 23.0 software was used. Group differences for categorical and numerical variables were analyzed using the Kruskal-Wallis *H* test or the Chi-square test. When a difference was found as a result of the Kruskal-Wallis *H* test, the reason for the difference was examined with the Mann-Whitney *U* test. The relationship of the CPRS-RS and Stroop scores with the olfactory test scores was investigated with Spearman correlation analysis. A value of $p \leq .05$ was considered statistically significant.

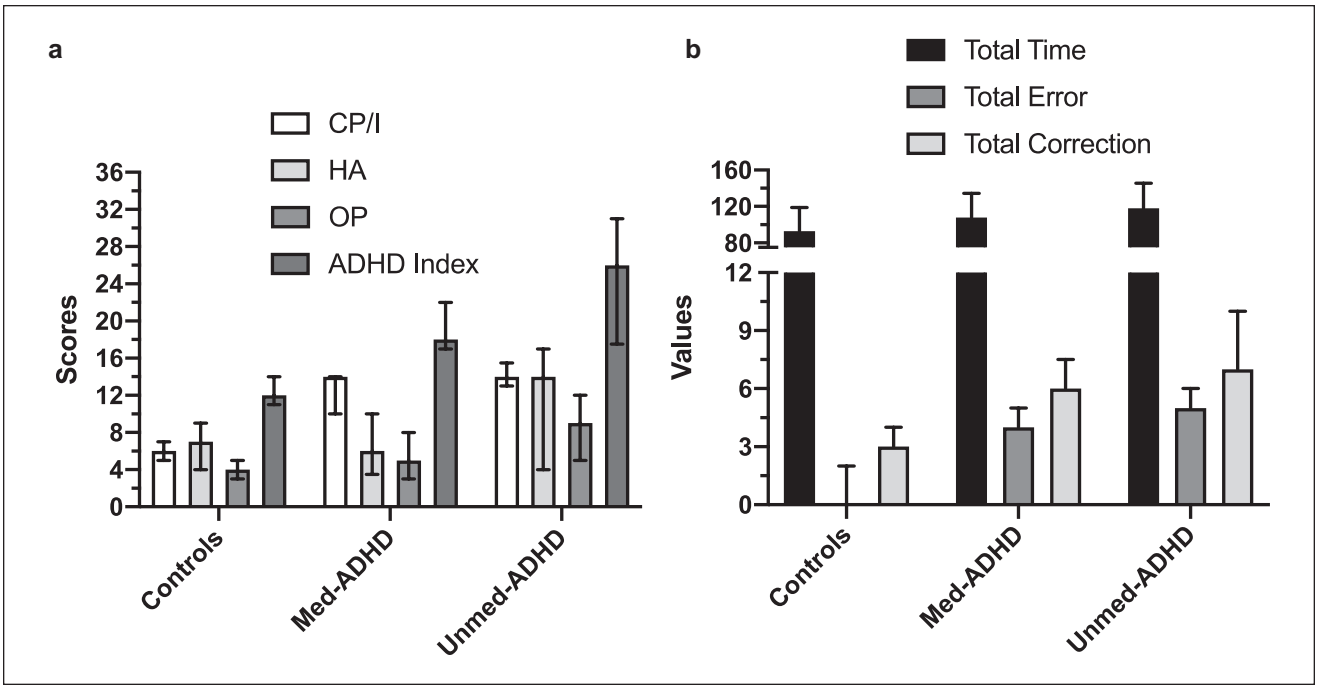

Figure 1. (a) Scores of CPRS-RS in the participants. CPRS-RS, Conners' Parent Rating Scale-Revised-Short Form, CP/I, Cognitive Problems/Inattention Scores, HA, Hyperactivity Scores, OP, Oppositional Scores, Unmed-ADHD, unmedicated ADHD; med-ADHD, and medicated ADHD. The mean of the scores of CPRS-RS performed on the patient and control groups is shown in Figure 1a. Controls $p \leq .005$ compared to med-ADHD and unmed-ADHD, unmed-ADHD $p \leq .005$ compared to med-ADHD. (b) Scores of Stroop test in the participants. Unmed-ADHD, unmedicated ADHD; med-ADHD, and medicated ADHD. The mean of the scores of the Stroop test performed on the patient and control groups is shown in Figure 1b. Controls $p \leq .005$ compared to med-ADHD and unmed-ADHD, unmed-ADHD $p \leq .005$ compared to med-ADHD.

Results

Clinical Characteristics and Demographic Variables of the Participants

This study was completed with 62 ADHD children and 47 control subjects. There were no significant differences between the groups regarding age, gender, place of residence, level of family income, levels of education of mothers and fathers, and type of ADHD presentation ($p \geq .05$ for all) Considering the sociodemographic data, it was homogeneously distributed in both groups. There was no evidence that any demographic characteristics confounded the outcomes. The mean clinical characteristics and demographic variables of the participants are given in Table 2.

CPRS-RS and Stroop Test Scores by Groups

CPRS-RS and Stroop scores of the participants (control $n=47$, unmedicated ADHD $n=33$, and medicated ADHD $n=29$) are shown in Figure 1a and b. As expected, the cognitive problems/inattention, hyperactivity, oppositional scores, and ADHD index scores on the CPRS-RS of children in the unmedicated ADHD group were significantly higher than those of the other two groups, and these scores of the medicated ADHD group were significantly higher compared to the control group ($p \leq .05$ for all). Statistically significant differences were determined in the Stroop Test-total time, total error, and total correction scores. These three scores of the unmedicated ADHD group were significantly higher than those of the other two groups, and the scores of the medicated ADHD group were significantly higher than those of the control group ($p \leq .05$ for all). The mean of CPRS-RS test scores and ST-TBAG form scores are given in Figure 1a and b.

Olfactory Assessment Results

Figure 2 displays the scores of odor threshold, odor discrimination, odor identification, and Threshold Discrimination, and Identification (TDI) obtained by Sniffin' Stick Extended Test in Control ($n=47$), unmedicated ADHD ($n=33$), and medicated ADHD ($n=29$) groups. The mean olfactory processing scores were found to be significantly different among the groups. In post hoc tests, the mean odor discrimination test, the mean odor identification test, and the mean TDI scores of the unmedicated ADHD group were determined to be significantly

Table 2. Socio-Demographic and Clinical Characteristics of Participants.

	Unmedicated ADHD ($n=33$)	Medicated ADHD ($n=29$)	HC ($n=47$)	p-Value
Age (mean-years ± *SD*)	11.21 ± 2.21	11.03 ± 2.27	11.40 ± 2.35	.770*
Age groups, years (*n*, %)				.930**
6–10	14 (42.4)	11 (37.9)	21 (44.7)	
11–14	13 (39.4)	14 (48.3)	18 (38.3)	
>14	6 (13.8)	4 (13.8)	8 (17)	
Gender (*n*, %)				.896**
Male	20 (60.6)	17 (58.6)	30 (63.8)	
Female	13 (39.4)	12 (41.4)	17 (36.2)	
Place of residence (*n*, %)				.824**
Province	19 (57.6)	13 (44.8)	26 (55.3)	
County	10 (30.3)	10 (34.5)	13 (27.7)	
Village	4 (12.1)	6 (20.7)	8 (17)	
Family Income Level (*n*, %)[a]				.776**
Low	13 (39.4)	8 (27.6)	18 (38.3)	
Middle	8 (24.2)	8 (27.6)	14 (29.8)	
High	12 (36.4)	13 (44.8)	15 (31.9)	
Maternal education level (*n*, %)				.735**
Primary school	11 (33.3)	7 (24.1)	16 (34)	
Middle School	8 (24.2)	10 (34.5)	13 (27.7)	
High school	8 (24.2)	10 (34.5)	13 (27.7)	
University	6 (18.2)	2 (6.9)	5 (10.6)	
Paternal education level (*n*, %)				.902**
Primary school	7 (21.2)	5 (17.2)	9 (19.1)	
Middle School	5 (15.2)	6 (20.7)	7 (14.9)	
High school	12 (36.4)	9 (31)	21 (44.7)	
University	9 (27.3)	9 (31)	10 (21.3)	
ADHD Presentations (*n*, %)				
Predominantly inattentive	12 (36.4)	18 (62.10)	-	
Predominantly hyperactive/impulsive	3 (9.10)	2 (6.9)	-	.125**
Combined	18 (54.5)	9 (31)	-	

Note. ADHD = Attention Deficit Hyperactive Disorder; HC = healthy controls; SD = Standard Deviation.
*ANOVA test. **χ^2 test. Statistical significance: $p \leq .05$.
[a]The level of income was determined by the minimum wage value on the date of the study for the workers in our country.

lower compared to the other two groups and the mean odor threshold test scores of the medicated ADHD group were significantly lower than those of the control group and unmedicated group. No significant difference was determined between the the medicated ADHD group and control group in respect of the mean odor identification test, the mean odor discrimination test, and the mean TDI scores. The mean values of the olfactory functions are given in Figure 2.

Olfactory Function According to ADHD Presentation

Figure 3 shows the odor threshold, odor discrimination, odor identification, and Threshold Discrimination and Identification (TDI) scores obtained from the ADHD subgroups (Predominantly inattentive $n=30$, Predominantly hyperactive/impulsive $n=5$, Combined $n=27$ and Controls $n=47$). When the odor threshold score, odor discrimination score, odor identification score, and TDI score were examined between the ADHD subgroups and the control group, there was a statistically significant difference between at least the two groups (Figure 3). The control group was found to be significantly different from the ADHD subgroup. The predominantly inattentive type and other ADHD subgroups differed from each other.

Correlations

Correlation analyses revealed that there were significant minimal to moderate and high positive or negative correlations between the results of odor tests and CPRS-RS and

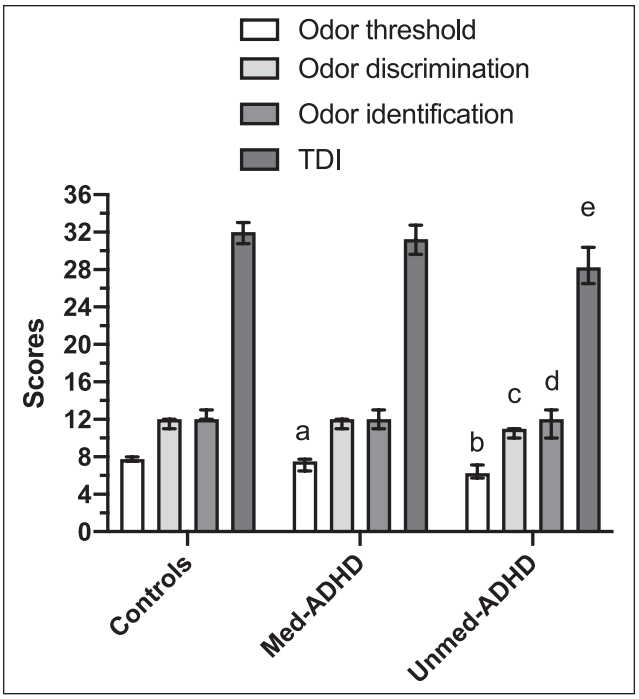

Figure 2. Scores of odor threshold, odor discrimination, odor identification, and Threshold, Discrimination, and Identification (TDI) obtained by Sniffin' Sticks Extended Test. ADHD, attention deficit hyperactive disorder; Unmed-ADHD, unmedicated ADHD; med-ADHD, and medicated ADHD. $aP \leq 0.001$ compared to unmed-ADHD and controls, b,c,eP med-ADHD and controls, $dP = 0.010$ compared to controls.

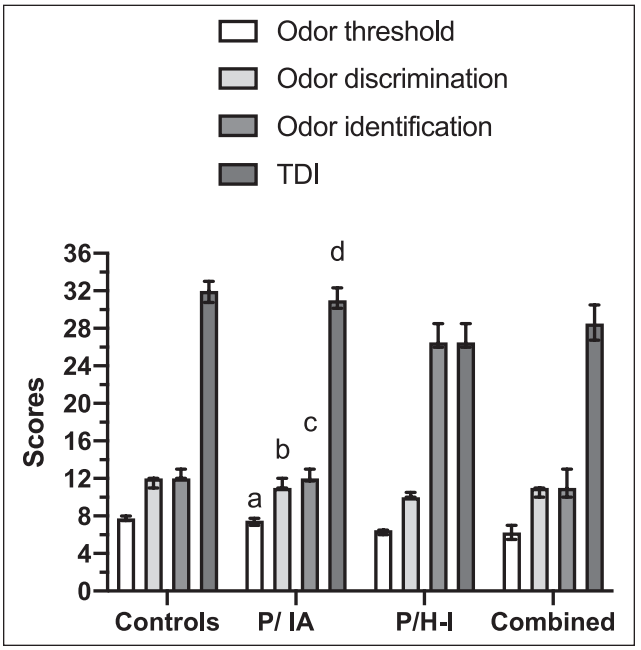

Figure 3. Scores of odor threshold, odor discrimination, odor identification, and Threshold, Discrimination, and Identification (TDI) obtained by Sniffin' Sticks Extended Testi in the ADHD subgroups. P/IA, Predominantly inattentive, P/H-I, Predominantly hyperactive/impulsive. Controls $p \leq 0.005$ compared to others group. a,b,$dP < 0.005$ compared to P/H-I and combined, c < 0.005 compared to combined.

Stroop tests (Table 3). There were significant, moderate, and negative correlations between the CPRS-RS-Hyperactivity and CPRS-RS-Oppositional scores and OTT value of ADHD children ($r = -.58$ and -0.67, respectively; $p \leq .05$). There was a significant, high, and negative correlation between the CPRS-RS-ADHD Index score and OTT value of ADHD children ($r = -.72$; $p \leq .05$). There were significant, moderate, and negative correlations between the CPRS-RS-ADHD Index score and ODT and TDI values of ADHD children ($r = -.51$ and $r = -.6$, respectively; $p \leq .05$). There were significant, moderate, and negative correlations between the CPRS-RS-Oppositional and Stroop Test-Total Time scores and TDI value of ADHD children ($r = -.52$ and -0.52, respectively; $p \leq .05$).

Discussion

In this study, the olfactory functions of children and adolescents with ADHD taking and not taking medication were compared with those of healthy control subjects. Olfactory function was measured using the Sniffin' Sticks test. Accordingly, the children in the unmedicated ADHD group showed significantly poorer performance in the Sniffin' Sticks test compared to the children in the medicated ADHD group and the healthy control group. The children in the medicated ADHD group had poorer odor threshold test and odor identification test scores than the control group, whereas the odor discrimination test scores and the mean TDI scores of these children were similar to those of the control group. This finding suggests that the ADHD medication (methylphenidate) has less effect on odor threshold and odor identification than odor discrimination. When the odor threshold score, odor discrimination score, odor identification score, and TDI score were examined between the ADHD subgroups and the control group, the control group was found to be significantly different from the ADHD subgroup. The predominantly inattentive type and other ADHD subgroups differed from each other. The study results also showed a significant association between the scores of the CPRS-RS and Stroop test and olfactory processing, suggesting that lower olfactory performance is related to the severity of ADHD. Since the methylphenidate doses of the patients were not known, only the relationship between disease severity and odor parameters was investigated.

Previous studies regarding olfactory function in children with ADHD have yielded conflicting findings. In five studies, no changes in odor identification were found (Murphy et al., 2001; Romanos et al., 2008; Sari & Taskintuna, 2015;

Table 3. The Relationship Between Values of Odor Tests and CPRS-RS and Stroop Tests.

	OTT	ODT	OIT	TDI
Parameters	*r*	*r*	*r*	*r*
CPRS-RS-Cognitive Problems/Inattention Scores	−0.497	−0.428		−0.428
CPRS-RS-Hyperactivity Scores	−0.583	−0.317	−0.363	−0.486
CPRS-RS-Oppositional Scores	−0.675	−0.389	−0.312	−0.527
CPRS-RS-ADHD Index Scores	−0.728	−0.512	−0.345	−0.601
Stroop Test-Total Time Scores	−0.421	−0.447	−0.411	−0.529
Stroop Test-Total Error Scores	−0.427	−0.367	−0.176	−0.379
Stroop Test-Total Correction Scores	−0.421	−0.447	−0.363	−0.495

Note. CPRS-RS = Conners' Parent Rating Scale-Revised-Short Form; ODT = Odor discrimination test; OIT = Odor identification test; OTT = Odor threshold test; TDI = Threshold, Discrimination, and Identification. Statistically significant correlations are shown in the table. Correlation coefficient values were interpreted as minimal, low, moderate, and high when *r* values were up to .3, .5, .7, and more than .7.

Schecklmann, Schaldecker et al., 2011; Schecklmann, Schenk et al., 2011), while others have reported a decreased identification ability (Ellison-Wright et al., 2008; Filipek et al., 1997). Some studies have shown that odor discrimination increases in ADHD and returns to normal with treatment (Schecklmann, Schaldecker et al., 2011; Schecklmann, Schenk et al., 2011). Romanos et al. reported an increase in the odor sensitivity of children with unmedicated ADHD (Romanos et al., 2008). The findings of the present study are consistent with studies showing a decrease in olfactory functioning in ADHD.

For the scent test, it should be borne in mind that scents are presented in series. Accordingly, short-term and working memory processes and cortical areas such as the prefrontal cortex seem to be related to discrimination and identification. It has been demonstrated that all brain lobes are affected, and especially the prefrontal area of the frontal lobe in individuals with ADHD (Biederman & Faraone, 2005). Studies have shown that the effects can occur not only in cortical areas but also in the corpus callosum, cerebellum, and striatal areas (Arnsten, 2007; Filipek et al., 1997). In a meta-analysis examining brain imaging studies performed on individuals with ADHD, it was revealed that the decrease in gray matter volume was most prominently observed in basal ganglion structures such as the right putamen and globus pallidus (Ellison-Wright et al., 2008). In addition, the activity between the PFC, cerebellum, and striatum is very sensitive to the neurochemical environment and is provided by neurotransmitters (NTs), dopamine (DA), and norepinephrine (NE) interacting with each other via multiple receptors (Arnsten, 2007; Robbins, 2003), which may be either presynaptic or postsynaptic (Bowton et al., 2010; Wang et al., 2007). Some studies have shown that ADHD patients have lower than normal amounts of DA receptors in several brain regions (Wang et al., 2007). Olfaction is interceded by neurotransmitters such as dopamine, delivering a potential link to the pathophysiology of ADHD (Halász & Shepherd, 1983; Hsia et al., 1999). In particular, dopamine appears to play an important role in olfactory bulbs, which interferes with their inhibitory effects on bulbar interneurons in olfactory neurotransmission (Cave & Baker, 2009). In general, the relevant neurotransmitters and related central regions have led to the introduction of the idea of olfaction as a possible biomarker for ADHD and neuropsychiatric disorders (Atanasova et al., 2008; Romanos et al., 2008).

It can be said that the methods of the current study were similar to the study by Romanos et al. because the sample group was formed of subjects with and without medication. However, an interesting finding of the current study was that children with ADHD had lower performance in all odor parameters, and only odor discrimination was normalized with methylphenidate treatment, and while the other two parameters increased with methylphenidate treatment they were not normalized. The exact mechanism of methylphenidate is not fully understood, although it has been detected to inhibit presynaptic noradrenaline and dopamine reuptake (Berridge et al., 2006). Thus, dopaminergic dysregulation can be thought to play a role in poorer olfactory function in ADHD, because dopaminergic interneurons affect olfactory receptor neurons in the olfactory bulb. Dopamine is also thought to act as a neuroprotective molecule for olfactory neurons, as it reduces excitatory glutamatergic neurotransmission (Hegg & Lucero, 2004). Moreover, previous studies have reported that the odor identification ability of patients with lesions in the orbitofrontal cortex or the dorsomedial nucleus of the thalamus is impaired, while the threshold ability is maintained (Jones-Gotman & Zatorre, 1988; Martzke et al., 1997; Potter & Butters, 1980). The olfactory function is divided into two processes; first, the odor threshold, also termed as olfactory sensitivity, is labeled as "peripheral," and the second is identification, discrimination, and memory, labeled as "central." Deficits in odor identification, discrimination, and memory might correspond to central impairment (changes in cortical and limbic processing), while deficits in odor threshold could be

thought to reflect impairment in peripheral (failure in processing at the level of the nasal epithelium) (Jones-Gotman & Zatorre, 1988; Lötsch et al., 2016; Martzke et al., 1997; Potter & Butters, 1980). Another possible explanation for the lower olfactory performance of children with ADHD compared to healthy controls may be that these children have attention problems during the olfactory task. The increase in all odor test scores with treatment may also be due to the decrease in attention deficits with methylphenidate use.

The study findings showed that there was a negative correlation between ADHD severity and olfactory test results, and there were differences between ADHD subtypes in at least two groups. A recent study examining the olfactory function in children with ADHD determined no relationship between presentation and severity of ADHD and all olfactory parameters (i.e., odor threshold, identification, and discrimination; Sari & Taskintuna, 2015). The contradictory results of previous studies can be attributed to methodological differences including the heterogeneity of study settings, methodologies used, age groups, and case definitions and the source of cases, gender, or sociodemographic status of the population.

There are several limitations to this study which must be considered. First, the sample size was small. Second, additional instruments such as brain imaging techniques and electrophysiological measures were not used as an adjunct to olfactory testing. Third, our study was a cross-sectional study, so findings on the effects of methylphenidate have consistently been interrupted. Fourth, no examination was made according to the methylphenidate doses used by the patients. Despite these limitations, to the best of our knowledge, this is one of the limited number of studies evaluating olfactory dysfunction in ADHD. Also, as far as we know, it is the first study to examine the effects of methylphenidate on odor parameters in ADHD and ADHD subtypes, and the relationship between ADHD severity and odor parameters. The findings provide considerable information about the individual olfactory parameters and overall olfactory functioning in children with ADHD.

Conclusion

In conclusion, the findings of this study suggest that the results of the odor threshold test increase with methylphenidate medication, whereas the odor identification test scores, discrimination test scores, and the mean TDI scores return to normal with methylphenidate treatment. In addition, the predominantly inattentive type and other ADHD subgroups differed from each other. In other words, it was found that the predominantly inattentive type had lower odor sensitivity than the other groups. The study results also showed a significant association between the scores of the CPRS-RS and Stroop test and olfactory processing, suggesting that lower olfactory performance is related to the severity of ADHD. Given the improvement with methylphenidate treatment, changes in olfactory functioning can be said to be most likely associated with modulation of the dopaminergic system, and therefore, from the results of this study it can be considered that the decrease in olfactory function may be a noninvasive state marker for ADHD. Considering the outcome between ADHD subtypes and the relationship between ADHD severity and odor performance, it can be used to illuminate the etiology of ADHD with the comments made from our study. However our results need confirmation by larger sample sizes and future longitudinal studies that include additional neuroimaging techniques and electrophysiological measurements.

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Authors' Contributions

The study was planned by C. M. I., A. U. C., E. E. A., and A. B., and the experiments were done by A. U. C. and A. B. A. U. C., A. B. and S. A. S. contributed to the collection, analysis, and interpretation of the data. A. U. C. and A. B. drafted the article and revised it. E. E. A. gave final approval of the version to be published. All authors reviewed the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval and Consent to Participate

Approval of the study protocol was obtained from the local Human Ethics Committee (Date: 20.03.2019, No: 2019-03/08). After a full verbal explanation regarding the study, all children accepted to participate in the study, and written and verbal informed consent was provided by the parents.

Human and Animal Rights

No animals were used for studies that are basis of this research. The study on children are in accordance with Helsinki Declaration of 1975, as revised in 2013.

Consent for Publication

Not applicable.

The Standard for Reporting

STROBE guidelines and methodology were followed.

Availability of Data and Materials

The data supporting the findings of the article are available within the article.They are available on request from the corresponding author and not publicly available due to privacy or ethical restrictions.

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