

# Association of Age and Response to Methylphenidate HCL Treatment in Adult ADHD: A Proton Magnetic Resonance Spectroscopy Study

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**Purpose:** This study investigated the age-dependent effects of methylphenidate (MPH) on brain metabolites including choline (Cho), N-acetyl aspartate (NAA) and creatine (Cr) levels in the dorsolateral prefrontal cortex (DLPFC), striatum, cerebellum, and anterior cingulate cortex (ACC) regions of the brain in adult patients with attention deficit hyperactivity disorder (ADHD).

**Patients and Methods:** The study was included 60 patients with ADHD between the ages of 18 and 60 years. The patients were grouped with respect to their ages as follows: 18–24 years, 25–30 years, and 31 and over years. Levels of NAA, Cr and Cho in DLPFC, ACC, cerebellum and striatum were measured with magnetic resonance spectroscopy (MRS). Subjects were then given 10 mg of oral MPH and the same metabolite levels were measured 30 minutes apart.

**Results:** Twelve (20%) of the cases were female and 48 (80%) were male. The age distribution of the cases is as follows: 15 subjects between the ages of 18–24, 26 subjects between the ages of 25–30 and 19 subjects over the age of 30. NAA levels were higher after MPH in the DLPFC of the 18–24 age group ( $p = 0.016$ ) and in the cerebellum of the 25–30 age group ( $p = 0.041$ ). No increase in Cho and Cr levels was observed after treatment compared to before ( $p > 0.05$ ).

**Conclusion:** It is thought that treatment of MPH can be effective on metabolites in different brain regions and this effect can vary upon age adult ADHD patients. After MPH treatment, both the 18–24 age group (in the DLPFC) and the 25–30 age group (in the cerebellum) was detected significantly higher NAA levels compared to pre-treatment levels. This increase in NAA levels suggested that pharmacotherapy, especially at early ages, may be effective on neuronal damage.

**Keywords:** adult, attention deficit hyperactivity disorder, magnetic resonance spectroscopy, methylphenidate, age

## Introduction

Neuroimaging techniques have been crucial to understanding the functional and structural changes in brain regions associated with attention deficit hyperactivity disorder (ADHD). Recent advances in these techniques also enable such further research into brain structures and functions in response to psychostimulant drug treatments. In structural neuroimaging studies; volume reduction has been reported in brain regions such as the frontal lobe, cerebellum, corpus callosum, total and right brain, and caudate nucleus.<sup>1</sup> In functional neuroimaging studies; It has been reported that regional blood circulation and glucose metabolism decrease in the prefrontal cortex (PFC) and cerebellar regions, but increase in the parietooccipital cortex at rest, and symptoms regress after psychostimulant drug treatment.<sup>2</sup> Magnetic resonance spectroscopy (MRS) is used in the differential diagnosis of diseases with neurodegenerative activity. N-acetyl aspartate (NAA) as an indicator of overall neuronal integrity, low NAA/creatine (Cr) ratio is associated with neuronal loss or damage. Choline (Cho) reflects membrane integrity and higher choline levels or Cho/Cr ratio indicate higher cellular destruction, myelin degradation, gliosis and inflammation. Creatine is an invariable member of cellular energy metabolism.<sup>3</sup>

A meta-analysis of 16 MRS studies analyzed the effect of age on neurochemical abnormality in both children and adults with ADHD.<sup>4</sup> Eleven studies included children with ADHD, while five involved adults with ADHD.<sup>5–9</sup> All five studies

included drug-free adults with ADHD. In this meta-analysis, it was reported that the NAA level in the PFC of children with ADHD was higher than normal, but there was no difference in the striatum and cerebellum. No difference in metabolite levels was found at any other site in adults with ADHD. In addition, it has been reported that there is a negative correlation between high NAA levels in PFC and the mean age of the patients. It has been suggested that the age-related abnormality of the NAA level in the PFC is a potential neural basis for the age-related variation of ADHD symptoms.<sup>4</sup>

Most neuroimaging studies have supported disruption in the frontostriatal cerebellar circuit. Methylphenidate (MPH) has been shown to affect frontostriato-thalamic circuit functions related to the pathophysiology of ADHD.<sup>10</sup> It has been reported that blood flow velocity increased in caudate, bilateral prefrontal and thalamic regions after MPH application.<sup>2</sup> Methylphenidate is effective in maintaining adequate attention through the dopamine and serotonin system in the neocortex and filtering out unnecessary sensory stimuli by normalizing hyperexcitability in the somatosensory cortex.<sup>2</sup>

Studies examining treatment-related metabolic changes in adults with ADHD are very few.<sup>11</sup> In the literature, MRS studies investigating the effect of stimulant treatment was available only thirteen studies.<sup>11</sup> Five of these studies were conducted in adult ADHD.<sup>11–15</sup> In these studies, changes in the brain were examined before and after MPH. Different results have been reported.

There is no study in the English literature investigating the effects of MPH on the age-related brain. This study aimed to evaluate the age-related effects of MPH on NAA, Cr and Cho levels in the dorsolateral prefrontal cortex (DLPFC), striatum, cerebellum, and anterior cingulate cortex (ACC) in adult ADHD patients.

## Patients and Methods

### Study Design

Sixty patients aged 18–60 years who met the criteria for adult ADHD according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) were included in the study. Patients with concomitant neurological disease, mental retardation and psychiatric disorders were excluded from the study. Wender Utah Rating Scale (WURS) and Adult ADHD Diagnosis and Rating Scale were used to evaluate patients.

### Wender–Utah Rating Scale (WURS)

This scale can be used to assess adults for attention deficit hyperactivity disorder with a subset of 25 questions associated with that diagnosis. A validity and reliability study of WURS was conducted for Turkish individuals with a cut-off score of 36.<sup>16</sup>

### Adult ADD/ADHD DSM IV- Based Diagnostic Screening and Rating Scale

This scale is a self assessment scale and patients can complete the questionnaire after being duly informed. When developing adult ADD/ADHD Scale, 18 symptoms of the diagnostic criteria in DSM-IV were reframed, so patients can understand them. The first part of this scale had 9 inattention questions and the second part had 9 hyperactivity/impulsivity questions. The Adult ADD/ADHD DSM-IV Based Diagnostic Screening and Rating Scale has a validity and reliability study for Turkish individuals.<sup>17</sup>

Patients who scored 36 points or more on the WURS and gave an answer of 2 or 3 points to at least six of the nine questions in the first and/or second parts of the Adult ADHD Diagnosis and Evaluation Scale were diagnosed with ADHD.

Levels of NAA, Cr and Cho in DLPFC, ACC, cerebellum and striatum were measured via proton MRS. Subjects were then given 10 mg of oral MPH and the same metabolite levels were measured 30 minutes apart. The patients were grouped with respect to their ages as follows: 18–24 years, 25–30 years, and  $\geq 31$  years. The study was conducted in line with the principles of the Declaration of Helsinki and was approved by the Pamukkale University Faculty of Medicine Ethics Committee (date:25/03/2011 no:52). Informed written consent was obtained from all patients included in the study.

## Proton Magnetic Resonance Spectroscopy

1.5 Tesla MR device (GE Medical System, Milwaukee, WI, USA) used with a standard head coil. The MRS protocol was as follows: horizontal plane, 10 mm thickness; TR/TE, 3000/88.2; Angle of View, 10; matrix, 512 × 512; Then 1. T2 weighted fast spin echo sequences were obtained using these parameters. MRS was performed using the single voxel (<sup>1</sup>H-voxel)

technique inserted into each of the DLPF, ACC, cerebellum and striatum. A volume of interest was manually placed in each area of the appropriate brain tissue. The chemical shift selective pulse (CHESS) method was used to suppress water-borne signals. Following this, point-resolved spectroscopy (PRESS) technique was used to localize the spectroscopy volume (TR/TE: 3000–35). As a result, short TE time spectra were obtained from the VOI in the ACC, striatum, DLPFC and cerebellum regions, and the metabolite ratios obtained with the “General Electric software spectral analysis program” were evaluated. H1 MRS analyzes were performed by the radiologist and NAA, Cho, Cr values were measured in the DLPFC, ACC, cerebellum and striatum areas. Patients were given 10 mg oral methylphenidate and after a 30-minute waiting period, NAA, Cho, Cr values were measured again.

## Statistical Analysis

Statistical Package for the Social Sciences version 16 (SPSS, Inc., Chicago, IL, USA) was used for data analysis. The change from before in brain metabolite levels after MPH administration was analyzed with a paired *t*-test. The Kruskal–Wallis test was used to compare brain metabolite levels before and after MPH administration between age groups. A *p*-value <0.05 was considered statistically significant. Mann Whitney *U*-test was used to determine the group that caused the difference. Bonferroni correction for multiple comparisons using the Mann–Whitney *U*-test was performed ( $0.05/3 = 0.017$ ) to analyze the nonparametric Kruskal–Wallis test results. Therefore, the *p* value was considered significant as  $0.05/3=0.017$  since there were three groups.

## Results

The study included 60 patients (20% of them were female) with a mean age of  $28.98 \pm 7.66$  years (range, 18–59 years). The distribution of the patients regarding ADHD subtype groups was as follows: 21 (35.0%) were predominantly inattentive, 11 (18.3%) were predominantly hyperactive/impulsive and 28 (46.7%) were combined type.

In the 18–24 years age group, the increase in the NAA levels in the DLPFC region of the patients after MPH treatment was significant compared to their pretreatment levels ( $p = 0.016$ ). In the 25–30 years age group, the increase in the NAA levels in the cerebellum region of the patients after MPH treatment was significant compared to their pretreatment levels ( $p = 0.041$ ).

Table 1 shows the NAA levels of the patients measured in the ACC, striatum, cerebellum, and DLPFC regions before and after MPH treatment between the age groups. There was a significant difference in NAA levels between the age groups before MPH treatment in the striatum ( $p = 0.005$ ). Accordingly, NAA levels of the patients in the 18–24 years age group were significantly higher than that of the 25–30 years and  $\geq 31$  years age groups (respectively Mann Whitney  $U = 82,500$ ;  $p = 0.002 < 0.017 (0.05/3)$ ), Mann Whitney  $U = 66,000$ ;  $p = 0.008 < 0.017 (0.05/3)$ ). In other brain regions, before and after MPH treatment, there were no significant differences in NAA levels between age groups ( $p > 0.05$ ).

Table 2 outlines the Cr levels of the patients measured in the ACC, striatum, cerebellum, and DLPFC regions before and after MPH treatment regarding age groups. In striatum, before MPH treatment, there was significant difference in Cr levels between age groups ( $p = 0.001$ ). According to data, Cr levels of the patients in the 18–24 years age group were significantly higher than that of the 25–30 years and  $\geq 31$  years age groups (respectively Mann Whitney  $U = 76,000$ ;  $p = 0.001 < 0.017 (0.05/3)$ , Mann Whitney  $U = 44,500$ ;  $p = 0.001 < 0.017 (0.05/3)$ ). Additionally, there was a significant difference between age groups in Cr levels after MPH treatment in the striatum ( $p = 0.047$ ). Accordingly, the Cr levels of the patients in the 18–24 years age group were significantly higher than that of the 25–30 years age group (Mann Whitney  $U = 107,000$ ;  $p = 0.017 (0.05/3)$ ). There was no significant difference in Cr levels between the age groups before and after MPH treatment in other parts of the brain ( $p > 0.05$ ).

Table 3 displays the Cho levels of the patients measured in the ACC, striatum, cerebellum, and DLPFC regions before and after MPH treatment regarding age groups. In striatum, before MPH treatment, there was significant difference in Cho levels between age groups ( $p = 0.041$ ). Accordingly, Cho levels of the patients in the 18–24 years age group were significantly higher than that of the 25–30 years age group (Mann Whitney  $U = 106,000$ ;  $p = 0.016 < 0.017 (0.05/3)$ ). There was no significant difference between age groups in Cho levels before and after MPH treatment in other brain regions ( $p > 0.05$ ).

**Table 1** Age-Dependent Distribution of N-Acetyl Aspartate Levels Before and After Methylphenidate Treatment

Brain Region	Age Groups, Years			p*
	18–24 N=15 Mean±SD	25–30 N=26 Mean±SD	≥ 31 N=19 Mean±SD	
Prefrontal cortex				
Before MPH	67.200±17.164	66.385±12.400	71.158±13.688	0.607
After MPH	75.200±15.223	65.269±12.035	68.842±17.134	0.098
Anterior cingulate cortex				
Before MPH	69.933±19.506	63.269±13.669	61.316±9.165	0.469
After MPH	74.133±16.698	63.731±9.523	64.895±9.110	0.084
Cerebellum				
Before MPH	64.800±12.243	58.654±14.656	58.105±10.832	0.140
After MPH	67.133±9.999	60.269±11.241	61.263±11.165	0.094
Striatum				
Before MPH	71.467±12.311	60.462±8.654	60.684±9.405	0.005**
After MPH	68.800±13.127	60.538±8.787	62.000±14.682	0.078

Notes: \*Kruskal–Wallis test was used. \*\*p < 0.05.

Abbreviations: SD, standard deviation; MPH, Methylphenidate HCl.

**Table 2** Age-Dependent Distribution of Creatine Levels Before and After Methylphenidate Treatment

Brain Region	Age Groups, Years			p*
	18–24 N=15 Mean±SD	25–30 N=26 Mean±SD	≥31 N=19 Mean±SD	
Prefrontal cortex				
Before MPH	43.267±9.122	38.500±6.114	41.474±5.243	0.214
After MPH	42.800±9.792	40.654±7.261	41.526±8.208	0.968
Anterior cingulate cortex				
Before MPH	42.533±10.575	42.423±7.500	41.789±6.365	0.848
After MPH	45.067±8.198	41.962±7.113	43.895±5.537	0.300
Cerebellum				
Before MPH	51.933±11.132	48.885±10.109	50.789±10.358	0.695
After MPH	55.000±8.071	51.538±10.331	52.737±9.643	0.773
Striatum				
Before MPH	52.133±8.618	42.731±7.175	42.684±4.911	0.001**
After MPH	48.667±8.217	42.500±6.941	44.053±7.870	0.047**

Notes: \*Kruskal–Wallis test was used. \*\*p < 0.05.

Abbreviations: SD, standard deviation; MPH, Methylphenidate HCl.

## Discussion

The current study results demonstrated that there were significant differences in the brain metabolite levels between different age groups of ADHD patients prior to the MPH treatment. Following MPH treatment, there were significant differences both between age groups and within the same age groups compared to their pretreatment levels.

In a meta-analysis including sixteen MRS studies, it was analyzed that the effect of age on neurochemical abnormality in both children and adult with ADHD.<sup>4</sup> Five of these studies was on adult ADHD.<sup>5–9</sup> In this meta-analysis, increased NAA levels were found in the medial prefrontal cortex of children with ADHD but no abnormal data in adults with ADHD.<sup>4</sup> In adults with ADHD, no difference in metabolite levels was found in any other region. In

**Table 3** Age-Dependent Distribution of Choline Levels Before and After Methylphenidate Treatment

Brain Region	Age Groups, Years			p*
	18–24 N=15 Mean±SD	25–30 N=26 Mean±SD	≥ 31 N=19 Mean±SD	
Prefrontal cortex				
Before MPH	40.200±9.836	41.538±8.401	42.316±10.034	0.724
After MPH	41.867±10.035	39.731±9.293	41.474±9.300	0.690
Anterior cingulate cortex				
Before MPH	39.467±12.727	38.692±6.834	36.579±9.131	0.684
After MPH	39.467±9.054	36.000±6.505	38.737±6.959	0.208
Cerebellum				
Before MPH	44.933±8.058	39.577±7.834	40.947±8.052	0.207
After MPH	43.467±11.096	40.962±7.942	44.211±9.784	0.707
Striatum				
Before MPH	38.800±6.689	33.308±7.064	34.842±5.718	0.041**
After MPH	38.333±8.077	35.923±7.889	38.000±7.461	0.400

Notes: \*Kruskal–Wallis test was used. \*\*p< 0.05.

Abbreviations: SD, standard deviation; MPH, Methylphenidate HCl.

addition, it was revealed a negative correlation between heightened NAA levels and mean age of patients in PFC.<sup>4</sup> In a previous study, significantly lower concentrations of NAA were measured in the left DLPFC in unmedicated ADHD patients compared to healthy controls and they emphasized that NAA levels have a particular importance in brain metabolite studies because a decrease in NAA levels implies a reversible stage of severe neuronal dysfunction in the patients.<sup>18</sup> In this study, before MPH treatment, in the striatum region, NAA levels of the patients in the 18–24 years age group were significantly higher than the other age groups and in the same region. Additionally, considering that age and NAA levels are negatively correlated in the literature, and NAA levels decrease as the brain develops, higher NAA levels were found at earlier ages in accordance with the literature in our study.<sup>19</sup>

In this study, after MPH treatment, both the 18–24 years age group (in the DLPFC) and the 25–30 years age group (in the cerebellum) displayed significantly increased NAA levels compared to their pretreatment levels. In a study conducted by Bertolino et al<sup>20</sup> on schizophrenic patients; After 4 weeks of atypical antipsychotic use, an increase in the NAA/Cr ratio was observed in DLPFC and it was suggested that pharmacotherapy may be effective on brain metabolites. NAA is an indicator of overall neuronal integrity, and a decrease in NAA levels indicates a reversible phase of severe neuronal dysfunction.<sup>18</sup> In light of this information, this increase in NAA levels suggested that the treatment of MPH may be effective on neuronal damage, especially at early ages. Additionally, the study suggests that ongoing neuronal plasticity, which is likely to be the case before more than half of our patients were also receiving treatment, continues after a single dose of MPH treatment.

Before MPH treatment, in the striatum region, Cr levels of the patients in the 18–24 years age group were significantly higher than the other age groups and in the same region. In normal people, Cr increases with age. On the other hand, it decreases in hypoxia and hypoperfusion.<sup>21</sup> In a study examining the effects of long-term use of MPH on cerebral blood flow in ADHD patients, a decrease in regional cerebral blood flow was found in the right hemisphere orbitofrontal cortex and anterior part of the middle PFC compared to the control group before treatment.<sup>22</sup> This abnormal decrease in the right PFC returned to normal after treatment. Regional cerebral blood flow in the right striatum decreased with MPH treatment. However, the treatment resulted in increased blood flow in the upper PFC regions. Striatal activity may have been inhibited by MPH-induced prefrontal activation. Because inhibitory signals are sent to the striatum by cortical dopamine activity in the prefrontal region via the frontostriatal circuit. These comments support the view that the main pathology in ADHD is PFC dysfunction and subsequent striatal hyperactivation.<sup>22</sup> In our study, increased striatal blood flow and Cr values were found before MPH, which was consistent with this study. Higher Cr levels at early ages



may be related to the fact that ADHD symptoms are more severe at these ages and that striatal hyperactivation is more common at this age.

In addition, after MPH treatment, Cr levels in the striatum region of the patients in the 18–24 years age group were significantly higher than that of the 25–30 years age group. Similarly, Cr level, which is higher in early-aged ADHD patients, is thought to decrease relatively at the same rate due to a single dose of 10 mg MPH in each age group, but it is a possible finding that it is still higher after MPH. It is speculated that the increase in Cr levels after MPH treatment as in the current study, may be resulting from the normalization of cerebral blood flow and glucose metabolism following psychostimulant administration in ADHD.<sup>4</sup> At the same time, in studies evaluating MRS findings, it is stated that the findings about Cr level are contradictory and show less reliability.<sup>23</sup>

In another meta-analysis, researchers found an increase in the Cho signal in the striatum of children with ADHD and the bilateral pregenual ACC of adults with ADHD.<sup>3,24</sup> Similarly, in a meta-analysis including both child and adult ADHD patients, significant changes of Cho levels in the right frontal lobe and left striatum were observed in children and the variations in Cho levels were significant in the left and right ACC in adults.<sup>24</sup> Before MPH treatment, in the striatum region, Cho levels of the patients in the 18–24 years age were significantly higher than that of 25–30 years age group. The fact that Cho, which is one of the indicators of cell destruction, is high at early ages, and that ADHD symptoms and neuronal damage are more severe at that age, suggests that it may be associated with a decrease in symptoms and/or severity in adulthood.

Contrary to these studies reporting variations in the brain metabolites, another study showed no significant difference in NAA, Cho and Cr concentration compared to the healthy control group which may be due to the study patients using distinct medication protocols.<sup>25</sup> In line with this study, a double-blind, placebo-controlled MRS study among adult ADHD patients documented that 12-week MPH treatment did not significantly affect Cr, Cho or NAA levels in the cerebellar hemisphere and ACC.<sup>11</sup>

The heterogeneity and conflict in the results of the ADHD studies concerning brain metabolites might be related to many varying factors in the patient populations such as being different ages, using different medications, being in different subtypes of ADHD, and having comorbidities. In addition, some other studies are claiming that genetic diversity in ADHD patients can also influence the levels of brain metabolites in specific regions. In a study among patients with ADHD, after MPH treatment, there were significant differences in the NAA, Cho, and Cr levels in different genotype carriers suggesting that polymorphisms of the catechol-O-methyltransferase gene in ADHD patients can explain individual differences in neurochemical responses to MPH.<sup>26</sup> Another study by the current group concerning genetic polymorphism in ADHD patients reported that patients with the 10/10 genotype DAT1 gene showed increased Cr levels after MPH uptake in the cerebellum and in patients with the SNAP-25 MnlI polymorphism G/G genotype and Ddel polymorphism T/T genotype, NAA levels were significantly increased after MPH treatment compared with pretreatment levels in the ACC.<sup>27,28</sup>

There are several limitations of the current study. Lack of control groups, the inevitable effects of other stimulants on the patients such as smoking, low-field MR imaging and the unilateral area evaluating can be considered as limitations. This is the first study to investigate brain metabolites from the age-related effects of MPH perspective in ADHD.

## Conclusion

The current study findings show that there might be an association between age groups and dynamics of brain metabolites before/after MPH treatment in adult ADHD patients which supports the literature on neuro-metabolite associations with ADHD symptoms. In this study, after MPH treatment, both the 18–24 age group (in the DLPFC) and the 25–30 age group (in the cerebellum) was detected significantly higher NAA levels compared to pre-treatment levels. This increase in NAA levels suggested that pharmacotherapy, especially at early ages, may be effective on neuronal damage. Although the research field of ADHD is rapidly developing, it is still mostly focused on pediatric patients. Further developments may lead to novel strategies in spectroscopic investigations of ADHD and further studies focusing on specific brain regions in the course of different age groups may help better clinical understanding of ADHD.

## Abbreviations

ADHD, attention deficit hyperactivity disorder; PFC, prefrontal cortex; MRS, Magnetic resonance spectroscopy; NAA, N-acetyl aspartate; Cr, creatine; Cho, Choline; MPH, Methylphenidate; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders; WURS, Wender Utah Rating Scale.

## Data Sharing Statement

The data associated with the paper are available from the corresponding author upon reasonable request.

## Ethics Approval

The study was conducted in line with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Faculty of Medicine, Pamukkale University (date:25/03/2011 approval number:52). All patients included in the study provided written informed consent.

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## Author Contributions

Gonca Ayse Unal and Ayse Nur Inci Kenar made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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