

CLINICAL STUDY

Correlations of ADHD symptoms with neurometabolites measured by ¹H magnetic resonance spectroscopy

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Abstract: *Objectives:* Despite the number of studies on neurometabolite changes in ADHD (Attention deficit/hyperactivity disorder), there is lack of evidence on neurometabolite associations with ADHD symptoms.

Background: We aimed to find the correlations of neurometabolites with ADHD symptoms.

Methods: Twenty ADHD children were examined by means of ¹H-MRS. The spectra were taken from dorsolateral prefrontal cortex (DLPFC) and white matter behind DLPFC, bilaterally. Neurometabolites were correlated with ADHD-RS-IV (ADHD-Rating Scales IV), CPRS (Conners Parent rating Scale) and DPREMB (Daily Parent Rating of Evening and Morning Behavior) scores.

Results: NAA/Cr (N-acetylaspartate/creatine) in the right DLPFC positively correlated with CPRS subscale IV learning problems and negatively correlated in the left white matter with DPREMB morning behavior subscale and ADHD-RS-IV score. Glx/Cr (glutamate + glutamine/creatine) positively correlated in the right white matter with ADHD-RS-IV and negatively correlated in the left white matter with DPREMB morning behavior subscale score. Cho/Cr (choline/creatine) in the left white matter negatively correlated with DPREMB morning behavior subscale and ADHD-RS-IV score.

Conclusion: ADHD symptoms could result from different activities of the left- and right-hemisphere prefrontal circuits. In consequence to impulses to novel task searching the increased right prefrontal circuit activity could be mediated by different motivational control (Fig. 9, Ref. 73). Text in PDF www.elis.sk.

Key words: N-acetylaspartate, glutamate, choline, prefrontal cortex.

ADHD (Attention Deficit Hyperactivity Disorder) is the most common neuropsychiatric disorder in childhood with worldwide prevalence of 4–12 % in children population (1). Symptoms of this diagnosis are categorized into three clusters, namely hyperactivity, impulsivity and inattention affecting children during all their daily activities (2). The diagnosis is connected with a high rate of comorbidities. The most frequent is the oppositional defiant disorder (40–60 %), anxiety disorders (34 %), conduct disorders (14 %), tics (11 %) and affective disorders (6 %) (3).

Volumetric and functional neuroimaging methods have discovered various morphological and neurophysiological correlates in different brain areas in ADHD (4–17). Extensive and consistent findings are the alterations of prefrontal cortex volume and thickness (18–31), as well as hypoperfusion of frontal areas during resting state (32–36) and performance tests (37–48).

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The frontal neural circuits are connected with integration and analysis of signals from other cortical areas, motor activity regulation, attention and working memory functions (49, 50), which are altered in ADHD children (51).

The method which shed new light on brain *in vivo* neurobiochemical processes is that of magnetic resonance spectroscopy, which is able to detect the defined metabolites (N-acetylaspartate, creatine, choline, glutamate/glutamine, myoinositol and lactate) in a particular brain area. Several studies have found the differences in the frontal lobe neurometabolites between healthy subjects and those with ADHD (both children and adults). When compared to healthy subjects, the right prefrontal cortex (52), right frontal lobe (53) and right dorsolateral prefrontal white matter (54) of children with ADHD yielded higher NAA/Cr. Furthermore, NAA/Cr in the right frontal area was strongly associated with regulation of sensorimotor, attentional-executive functions, memory and learning in ADHD children (53). In adults with ADHD however, the left dorsolateral prefrontal cortex yielded decreased NAA when compared to adults with ADD (attention deficit disorder) and healthy subjects (55). When compared to healthy controls, children with ADHD yielded higher Glx/Cr in both frontal lobes (53), and right prefrontal cortex (54), as well as higher Cho/Cr in the right frontal lobe (53).

In spite of the fact that studies using magnetic resonance spectroscopy method provided evidence that brain biochemistry in frontal areas in ADHD and non-ADHD subjects differ, there is a lack of evidence on the associations of particular neurome-

tabolites with core or comorbid ADHD symptoms. To our best knowledge, no study has so far investigated the associations of neurometabolites within the prefrontal neural circuits with ADHD symptoms assessed by clinicians or parents in medication-naive children. The aim of our study was to find out the correlations of particular metabolites in dorsolateral prefrontal areas (grey and white matter) with core and comorbid ADHD symptoms. We chose dorsolateral prefrontal cortex (DLPFC) due to its role in attention sustain, working memory, planning and organization of tasks (56). White matter behind DLPFC includes fibers leading to and from DLPFC (49) which are a part of neural circuits responsible for motivation, as well as for executive and emotional responses (57).

Methods

Subjects

Based on clinical interview according to DSM-IV criteria, we examined 20 children (males = 16, females = 4; at age of 11.4 ± 1.27 years) with the diagnosis of ADHD assessed by experienced senior consultant psychiatrist and trainee in child and adolescent psychiatry specialization. All patients fulfilled the criteria for ADHD combined subtype, 7 children have a comorbid diagnosis of oppositional defiant disorder. Children were medication-naive. All patients were right-handed. Written informed consent was obtained from the participating children and their parents. The protocol was approved by the local Ethics Committee. The study conformed to the code of ethics stated in the Declaration of Helsinki.

Exclusion criteria included current or past pharmacotherapy for ADHD, anxiety disorder, current major depressive episode or diagnosis of recurrent depressive disorder in the past, current or past bipolar or psychotic disorder, serious medical or neurological illness, active drug abuse or previous history of drug abuse, history of significant medical disorder or head trauma, mental retardation, specific developmental learning disorders, tic disorders, metallic devices precluding magnetic resonance imaging, and presence of structural MRI abnormalities.

Symptom assessment

Clinical assessment of the core ADHD symptoms was quantified by 18-item ADHD-Rating Scale-IV (ADHD-RS-IV) (58). The scale includes questions revealing the symptoms of hyperactivity, impulsivity and inattention in a four-point scale from 0 to 3 (not at all – very much). The total score was taken into the statistical evaluation.

Parents of children fulfilled the 93-item Conners Parent Rating Scale (CPRS) (59) which apart from hyperactivity and impulsivity symptoms assesses a number of comorbid symptoms ranging from behavioral problems to anxiety and psychosomatics. Each item is rated by parent by means of a four-point scale from 0 to 3 (not at all – very much). The scale includes 8 subscales: I – conduct problems, II – anxiety, III – hyperactivity/impulsivity, IV – learning problems, V – psychosomatics, VI – perfectionism, VII – antisocial behavior, and VIII – muscle tension. This instrument was used to research the connections of neurometabolites with potential comorbid conditions which do not fulfill the crite-

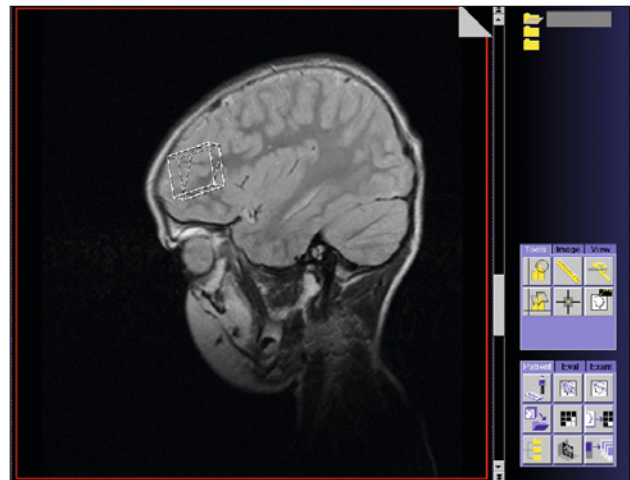


Fig. 1. Display of image-guided volume of interest (VOI) selection on sagittal slice – dorsolateral prefrontal cortex.

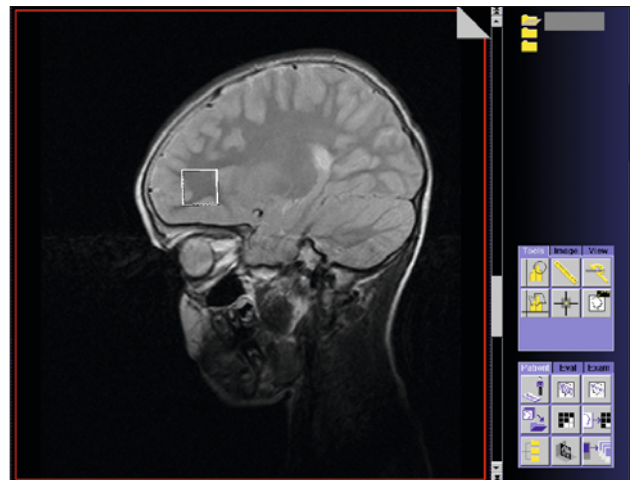


Fig. 2. Display of image-guided volume of interest (VOI) selection on sagittal slice – white matter behind dorsolateral prefrontal cortex.

ria of particular diagnoses, i.e. anxiety disorders, as these were within exclusion criteria.

Evening and morning patterns of behavior were evaluated by parents completing the 11-item Daily Parent Rating of Evening and Morning Behavior (DPREMB) (60). The scale specifically evaluates the evening and morning patterns of behavior in children by means of two subscales of four-point scale from 0 to 3 (not at all – very much). This instrument was used to assess the possible associations of neurometabolites with the behavior of ADHD children in these two critical periods of the day, in which significant differences have been found in parent reports evaluating all daily challenges of their children (43 % ADHD vs 12 % non-ADHD, $p < 0.05$ in the morning; 33 % ADHD vs 8 % non-ADHD, $p < 0.05$ late in the evening) (2).

Magnetic resonance spectroscopy

The single-voxel ^1H magnetic resonance spectroscopy examination and the assessment of clinician and parents were performed

on the same day. We examined the dorsolateral prefrontal cortex (DLPFC) (volume = 8 ml) and white matter behind dorsolateral prefrontal cortex (anterior semioval center; volume = 7.5 ml) in four single-voxel MRS measurements using a clinical 1.5 Tesla MR – scanner Siemens Symphony (Siemens, Erlangen) with parameters as follows: PRESS sequence with water suppression (CHES), TE/TR = 30/3000 ms, 128 averages. Manual shimming was performed for every voxel separately. MR spectra were processed using LCModel and quantified relatively to the water signal acquired for each voxel in a separate measurement (PRESS with no water suppression, TE/TR = 30/10000 ms, 2 averages) (Figs 1 and 2). The basic set of metabolite signals for LCModel comprised N-acetyl aspartate (NAA), NAA-glutamate (NAAG), creatine (Cr), choline (Cho), glutamine and glutamine (Glx), and myo-inositol (mI). Lactate (Lac) and a few other metabolites were also included in the basic set, but their values were not used in the statistical evaluation. The whole MR session took approximately 45 minutes. All children were examined at the same time of day, at approximately 4:00 pm.

Statistical analysis

The score of ADHD-RS-IV and that of all subscales of CPRS and DPREMB were correlated with neurometabolite ratios to creatine in four examined areas. Ratios to creatine were used for correction of possible effects of cerebrospinal fluid volume in voxels. For statistical evaluation we used Spearman correlation coefficient. Significance level was set at $p < 0.05$.

Results

We found several significant correlations of metabolites with the score of scales/subscales. NAA/Cr in the right DLPFC positively correlated with the score of CPRS subscale IV – learning problems ($r = 0.517$; $p = 0.020$) (Fig. 3). NAA/Cr in the left white matter behind DLPFC negatively correlated with the total score of ADHD-RS-IV ($r = -0.498$, $p = 0.025$) (Fig. 4) and DPREMB subscale of morning behavior score ($r = -0.536$, $p = 0.015$) (Fig. 5).

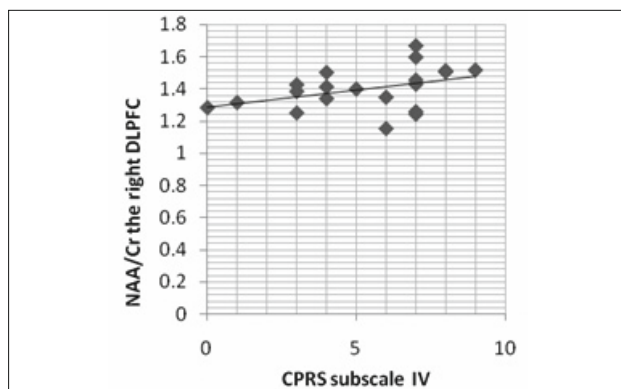


Fig. 3. Positive correlation of NAA/Cr in the right DLPFC with CPRS subscale IV – learning problems score; NAA – N-acetylaspartate, Cr – creatine, DLPFC – dorsolateral prefrontal cortex, CPRS – Conners Parent Rating Scale.

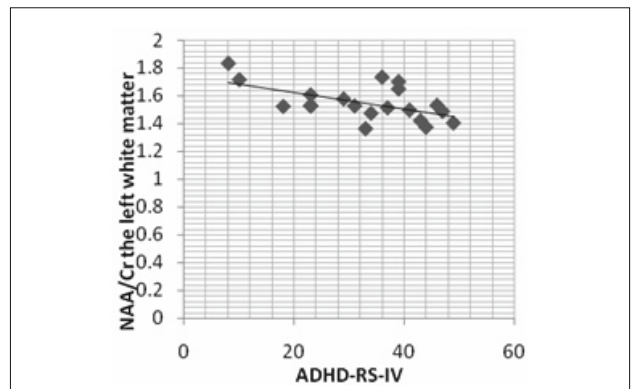


Fig. 4. Negative correlation of NAA/Cr in the left white matter with the total score of ADHD-RS-IV score; NAA – N-acetylaspartate, Cr – creatine, ADHD-RS-IV – ADHD Rating scale IV.

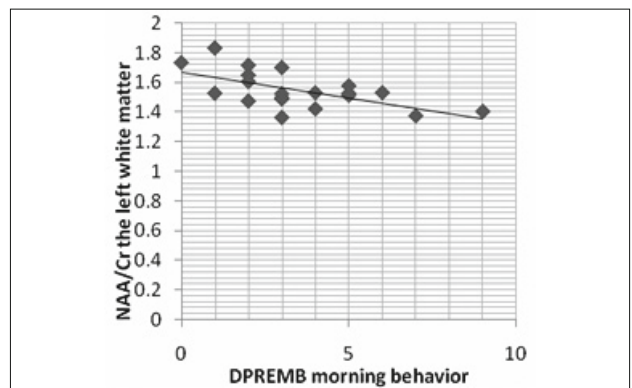


Fig. 5. Negative correlation of NAA/Cr in the left white matter with DPREMB morning behavior subscale score; NAA – N-acetylaspartate, Cr – creatine, DPREMB – Daily Parent Rating of Evening and Morning Behavior.

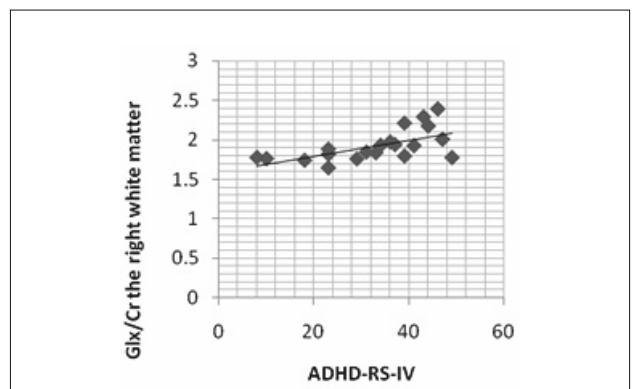


Fig. 6. Positive correlation of Glx/Cr in the right white matter with the total score of ADHD-RS-IV; Glx – glutamate/glutamine/GABA, Cr – creatine, ADHD-RS-IV – ADHD Rating scale IV.

Glx/Cr in the right white matter positively correlated with the score of ADHD-RS-IV ($r = 0.655$, $p = 0.002$) (Fig. 6) while in the left white matter it negatively correlated with the subscale of morning behavior score of DPREMB ($r = -0.596$, $p = 0.006$) (Fig. 7).

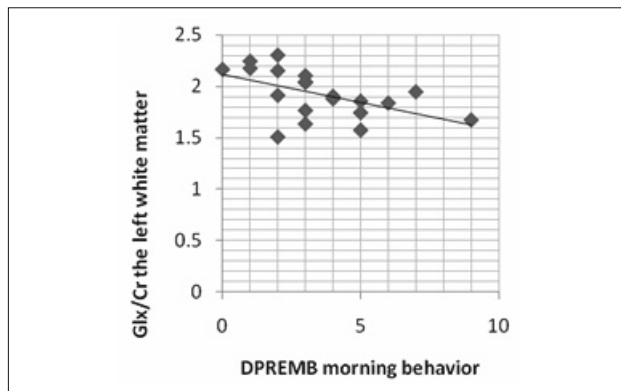


Fig. 7. Negative correlation of Glx/Cr in the left white matter with the subscale of morning behavior score of DPREMB; Glx – glutamate/ glutamine/GABA, Cr – creatine, DPREMB – Daily Parent Rating of Evening and Morning Behavior.

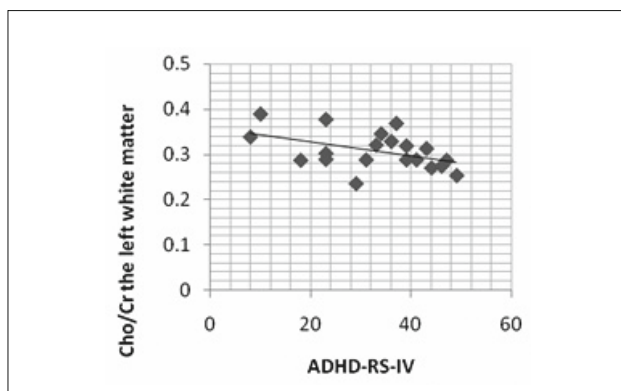


Fig. 8. Negative correlation of Cho/Cr in the left white matter with ADHD-RS-IV total score; Cho – choline, Cr – creatine, ADHD-RS-IV – ADHD Rating scale IV.

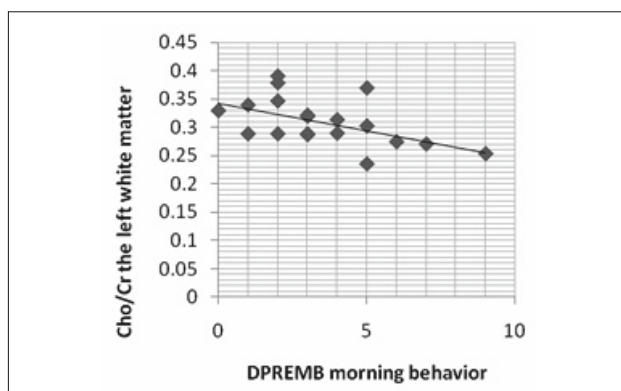


Fig. 9. Negative correlation of Cho/Cr in the left white matter with DPREMB morning behavior subscale score; Cho – choline, Cr – creatine, DPREMB – Daily Parent Rating of Evening and Morning

Cho/Cr in the left white matter negatively correlated with ADHD-RS-IV score ($r = -0.485$, $p = 0.03$) (Fig. 8) and DPREMB morning behavior subscale score ($r = -0.568$, $p = 0.009$) (Fig. 9).

Discussion

Our results of correlations of neurometabolites with symptoms evaluated by clinicians and parents are novel and reveal some important aspects of ADHD pathophysiology.

We found a positive correlation of NAA/Cr in the right DLPFC with the subscale IV – learning problems of CPRS. NAA is a neurometabolite present exclusively in neurons and is considered to be a biomarker of neural viability and metabolic health, a sensitive indicator of neuronal damage (61), and mitochondrial source of energy (62). NAA changes as manifestations of brain neuroplasticity are discussed (63). Compared to healthy subjects, NAA/Cr was higher in the right prefrontal cortex (52) and right frontal lobe (53). Moreover the study was connected with memory, learning, and regulation of sensorimotor and attentional-executive functions in children with ADHD. Our results support the hypothesis of cortico-striatal hyperactivity (64) based on hypercatecholaminergic state leading to increased mitochondrial metabolism (52) with an effect on increased NAA in prefrontal cortex, which could be at the basis of attentional deficits leading to problems with learning (subscale IV of CPRS includes global school problems which are rather the consequence of ADHD symptoms rather than specific developmental learning disorders).

We found a positive correlation of Glx/Cr in the right white matter with the score of ADHD-RS-IV. White matter behind DLPFC includes projections leading to and from DLPFC (49). The peak of Glx includes the signals of glutamate and glutamine (65, 66). This is the first study on finding the association of Glx resonance in the white matter with ADHD symptoms. The reason for the presence of the neurotransmitter in the white matter is questionable. Based on the findings of studies on rat and mouse brain, in which the propagation of action potential lead to rapid vesicular release of glutamate from discrete sites along axons in white matter (67, 68), our finding indicates the presence of glutamate released from glutamatergic projections from prefrontal cortex, which are part of frontal circuits responsible for motivation, as well as for executive and emotional responses (57). Studies evaluating the differences between ADHD and non-ADHD children have found higher Glx/Cr in the left and the right frontal lobes (53) and the right prefrontal cortex (64). Authors hypothesized that neuronal pathways in the frontal lobe could be stimulated easier in children with ADHD due to the increased glutamate level, which could lead to the hyperactive component of ADHD (53). Our results support this hypothesis indicating that the activity of glutamatergic fibers in the right hemisphere is directly connected with the severity of ADHD symptoms. As these fibers are activated in executions controlled by emotional motivation (57), the changes in their activity could be at the basis of the motivation/reward system differences in people with ADHD (69), and are discussed later.

Both NAA/Cr and Cho/Cr in the left white matter were negatively correlated with the total score of ADHD-RS-IV. Choline-containing compounds present inside the tCho (total choline) peak, phosphocholine and glycerophosphocholine, are involved in the metabolism of membrane lipids, namely phosphatidylcho-

line and sphingomyelin. Thus the peak of choline is considered to be an indicator of membrane metabolism and provides the information about the increased membrane degradation or synthesis (61). In the right frontal lobe, higher choline resonances have been found in children with ADHD compared to healthy subjects (53). Increased choline levels have been also found in adults with ADHD in the anterior cingulate cortex bilaterally; furthermore choline was highly correlated with reaction time in Continuous Performance Test (70). To our best knowledge, no study has shown so far the choline changes in the white matter in ADHD children, however higher NAA/Cr in the left semi-oval center has been shown in children with ADHD compared to control subjects (52). We previously hypothesized that the increased glutamate level could lead to hyperactivation of prefrontal circuits with the increase in membrane and mitochondrial metabolism in children with ADHD (71). However, according to our results, glutamate does not seem to be associated with NAA and choline concerning either ADHD symptoms severity or the brain area. Our results indicate that higher mitochondrial and membrane metabolism in the left white matter is connected with lower ADHD symptoms, which is contradictory to our previous hypothesis. These findings brought another questions about ADHD pathophysiology including the possibilities of different roles of opposite hemispheres in ADHD symptoms representation. While the ADHD symptoms could be associated with the glutamate-induced hyperactivity in the right-hemisphere prefrontal circuits, the left-hemisphere prefrontal circuits could be hypoactivated leading to the decreased neuronal activity and membrane metabolism.

The negative correlations of DPREMB morning behavior subscale score with NAA/Cr, Glx/Cr and Cho/Cr only in the left white matter are related findings. Our results indicate that the difference in activity of the left- and right-hemisphere prefrontal circuits could play an important role in ADHD symptoms representation. Prefrontal lobe is important in new situations and tasks which require the choice of pre-existing cognitive routines to be configured in a new way. Moreover, prefrontal lobes are characterized by a substantial hemisphere specialization. While the left hemisphere processes the tasks which must be solved by routine strategies, the right hemisphere is important to figure out situations that are novel (72). We found only positive correlations of neurometabolites in the right prefrontal areas and only negative correlations in the left prefrontal areas. This indicates that more severe ADHD symptoms are associated with higher activity of the right-hemisphere prefrontal circuits and lower activity of the left-hemisphere prefrontal circuits. Two possible mechanisms could explain these findings. Firstly, the brain of non-ADHD people processes the repeated incoming information by the left hemisphere using familiar cognitive routines, whereas the brain of ADHD people processes the repeated information constantly as novel. Such approach to task solving would allow a different point of view in each process and lead to finding several solutions to one problem. Secondly, people with ADHD have impulses to search for novel information and tasks in order to activate their right prefrontal system. The latter trait is represented in their

temperament as novelty seeking (73). Thus, as previously hypothesized, the ADHD symptoms could result from increased prefrontal circuits activity (52, 64, 71), however the more extensive activation could be either the consequence of attention focused on searching for novel solutions to the defined task or impulses to novel task solving, rather than a primary brain failure. Furthermore, the problem solving could be mediated by different motivational control in people with ADHD. Compared to non-ADHD individuals, adults with ADHD reported themselves to be more self-transcendent (73), which is a character trait associated with experience of being part of something greater than oneself. ADHD people were described as being more judicious, idealistic, faithful and spiritual rather than self-oriented, materialistic and controlling, which are the characteristics of low self-transcendence trait. The authors of this study hypothesized that overreliance on the right hemisphere processing could be the mechanism (73). Thus, considering a different activation and function of their prefrontal circuits, the problems with attention and hyperactivity in children with ADHD in a standard school or home setting could be a consequence of inadequate tasks or efforts to motivate children in inadequate manner.

The negative correlations of DPREMB morning behavior subscale score with NAA/Cr, Glx/Cr and Cho/Cr in the left white matter are remarkable also in the connection of the fact that all children were measured in the afternoon hours. Thus, it seems that the level of morning behavior problems in ADHD is not consequential to the actual state influenced by external conditions, but represents the constant characteristics of a child. In regard to the fact that we found no significant correlations of these metabolites with the evening behavior subscale score, it is possible that the evening behavior of a child with ADHD could be a consequence of daily events processing, rather than of "endogenous mechanisms" like in morning behavior. In the future studies, the correlation of the score of morning behavior and that evaluating the ADHD symptoms severity should be done. In case of a positive finding, the morning behavior could be the indicator of ADHD symptoms severity.

Our results are novel and bring new evidence on ADHD pathophysiology including brain metabolic processes. However, this study has several limitations which must be noted. We evaluated a relatively small sample of subjects and due to the latter fact the females and males were not separated. Gender separation would be crucial especially to confirm the hypothesis of different roles of opposite hemispheres in ADHD symptoms representation. In our study, 1.5T ¹H-MRS was used by which Glx peak including glutamate and glutamine resonances cannot be reliably distinguished. 3T ¹H-MRS would be more adequate to find out the relations between metabolite levels and their clinical representations. Further studies including functional neuroimaging methods are necessary to elucidate the processes leading to ADHD symptoms.

Our study provided evidence that ADHD symptoms are significantly associated with some neurometabolite levels in prefrontal areas. Based on the findings of positive correlations of neurometabolites with ADHD symptoms in the right prefrontal

areas and negative correlations in the left prefrontal areas, we hypothesize that the different activity of the left- and right-hemisphere prefrontal circuits is an important mechanism in ADHD symptoms. The ADHD symptoms could result from the increased right prefrontal circuits' activity as a consequence of either focusing the attention on searching for novel solutions to the defined task, or that of impulses to novel tasks searching. This is probably mediated by motivational control which differs from that of non-ADHD individuals. Considering the different activation and function of their prefrontal circuits, the problems with attention and hyperactivity in children with ADHD in a standard school or home setting could be consequential to inadequate tasks or efforts to motivate children in inadequate manner. Despite the limitations of the study, our results brought new aspects of ADHD neurobiology including brain metabolic processes.

Learning points

- The increased mitochondrial metabolism in prefrontal cortex could be at the basis of attentional deficits leading to problems with learning
- ADHD symptoms could be associated with hyperactivity in prefrontal circuits of the right hemisphere and hypoactivity of prefrontal circuits in the left hemisphere
- Considering the different activation and function of their prefrontal circuits, the problems with attention and hyperactivity in children with ADHD in a standard school or home setting could be the consequence of inadequate tasks or efforts to motivate children in inadequate manner.

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