



Adults with attention-deficit/hyperactivity disorder – a brain magnetic resonance spectroscopy study

Margaretha Dramsdahl^{1,2*}, Lars Ersland^{3,4}, Kerstin J. Plessen^{5,6,7}, Jan Haavik^{1,7,8}, Kenneth Hugdahl^{1,7,9} and Karsten Specht^{3,9}

¹ Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

² Department of Clinical Medicine, University of Bergen, Bergen, Norway

³ Department of Clinical Engineering, Haukeland University Hospital, Bergen, Norway

⁴ Section for Radiology, Department of Surgical Sciences, University of Bergen, Bergen, Norway

⁵ Center for Child and Adolescent Psychiatry at Bispebjerg, Copenhagen, Denmark

⁶ Institute for Neurology, Psychiatry, and Sensory Sciences, University of Copenhagen, Copenhagen, Denmark

⁷ K.G. Jebsen Centre for Research on Neuropsychiatric Disorders, University of Bergen, Bergen, Norway

⁸ Department of Biomedicine, University of Bergen, Bergen, Norway

⁹ Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway

Edited by:

Ziad Nahas, Medical University of South Carolina, USA

Reviewed by:

Jarred Younger, Stanford University School of Medicine, USA

Darin Dougherty, Massachusetts General Hospital, USA

*Correspondence:

Margaretha Dramsdahl, Division of Psychiatry, Haukeland University Hospital, Jonas Lies vei 65, N-5021 Bergen, Norway.
e-mail: margaretha.dramsdahl@helse-bergen.no

Background: Impaired cognitive control in individuals with attention-deficit/hyperactivity disorder (ADHD) may be related to a prefrontal cortical glutamatergic deficit. We assessed the glutamate level in the left and the right midfrontal region including the anterior cingulate cortex in adults with ADHD and healthy controls. **Methods:** Twenty-nine adults with ADHD and 38 healthy controls were included. We used Proton Magnetic Resonance Imaging with single voxel point-resolved spectroscopy to measure the ratio of glutamate to creatine (Glu/Cre) in the left and the right midfrontal region in the two groups. **Results:** The ADHD group showed a significant reduction of Glu/Cre in the left midfrontal region compared to the controls. **Conclusion:** The reduction of Glu/Cre in the left midfrontal region in the ADHD group may reflect a glutamatergic deficit in prefrontal neuronal circuitry in adults with ADHD, resulting in problems with cognitive control.

Keywords: ADHD, MR spectroscopy, MRS, glutamate, Glu/Cre, cognitive control, cortex cinguli anterior, ACC

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with three distinct clinical subtypes; the inattentive, the hyperactive/impulsive, and the combined type. The pooled prevalence of children and adolescents with ADHD worldwide is estimated to 5.3% (Polanczyk et al., 2007). Approximately 65% of affected children show persistent symptoms with functional impairment into adulthood (Faraone et al., 2006), whereas some children experience an improvement or even complete elimination of symptoms during adolescence, which may be explained by a delay and later catch-up in cortical maturation (Shaw et al., 2007). Adults with persisting ADHD thus may represent a subgroup with symptoms caused by other neurobiological underpinnings than a mere delay of cortical development.

Although ADHD is regarded as a neuropsychologically heterogeneous disorder (Willcutt, 2005; Doyle, 2006; Sonuga-Barke et al., 2010), deficits in cognitive control are considered key impairments in this disorder. A cognitive control process presumably taps the executive control network (Hugdahl et al., 2009), which is one of the three networks described in the attentional networks model (Fan et al., 2005, 2009). The anterior cingulate cortex (ACC) is part of the executive control network (Posner and Rothbart, 2007) and its function is essential for the exertion of cognitive control (Bush et al., 2000; Carter and Van Veen, 2007). Studies using functional neuroimaging (Bush et al., 2005) suggest that a dysfunction in the dorsal ACC plays a role in the pathophysiology of ADHD.

The ACC has a high density of glutamate receptors (Vogt, 2009), and glutamate may be an important metabolite for cognitive functions (O'Neill and Dix, 2007). Glutamatergic neurotransmission may prove a key target in the treatment of several psychiatric disorders (Javitt, 2004), and growing research on the psychopharmacology of glutamate receptor agonists and antagonists documents an increasing interest for its therapeutic use in psychiatry (Parsons et al., 2005; Krystal et al., 2010; Lesage and Steckler, 2010). A recent study (Ludolph et al., 2010) highlights the role of glutamate in ADHD by demonstrating that the norepinephrine reuptake inhibitor atomoxetine, which is effective against ADHD symptoms, is also an NMDA receptor antagonist.

Magnetic resonance spectroscopy (MRS) is a non-invasive method to measure metabolites in the brain (Graaf, 2007). Earlier MRS studies of persons with ADHD have focused on metabolites like choline compounds, *N*-acetyl aspartate (NAA), glutamate (Glu), and glutamine (Gln; Perlov et al., 2009). A synthesis of Glu and Gln (Glx) has often been used, because the separation of Glu and Gln proves difficult at lower field strengths. The separation of Glu from Gln is, however, possible at field strengths as low as 2 T if using a short echo time (TE) and the linear combination of model (LCModel; Provencher, 1993, 2001). The concentration of total creatine (Cre) is relatively constant, which is why this metabolite has often been used as an internal concentration reference (Graaf, 2007; Dager et al., 2008).

A recent meta-analysis including 16 MRS studies of participants with ADHD concluded with altered Glx/Cre, NAA/Cre, and Choline/Cre ratios (Perlov et al., 2009) in patients relative to controls. However, only three of these studies included adults. To our knowledge, a total of seven MRS studies of adults with ADHD have been published (Hesslinger et al., 2001; Perlov et al., 2007, 2010; Colla et al., 2008; Kronenberg et al., 2008; Ferreira et al., 2009; Rusch et al., 2010), of which the ACC has been examined specifically in four studies. Although a significantly reduced Glx/Cre ratio in ACC was reported in one study (Perlov et al., 2007), other findings have been inconsistent across studies, possibly explained by heterogeneity of the sample and different spectroscopic methodologies.

In this MRS study we aimed at focusing on the midfrontal region due to the assumed importance of the ACC for cognitive control functions, which in turn are central in the pathophysiology of ADHD. Glutamate is essential in neurotransmission in the ACC and may prove a key metabolite in cognitive functions, and we thus hypothesized that adults with ADHD would show a reduction of the glutamate level in the midfrontal region compared with the controls.

MATERIALS AND METHODS

PARTICIPANTS

The sample of 29 participants with ADHD and 38 healthy controls was recruited from the Norwegian ADHD-project in Bergen. The ADHD group consisted of 15 men and 14 women with mean age 32.9 years (SD = 7.1, age range 21–48 years) and mean Wechsler Abbreviated Scale of Intelligence (WASI) IQ 110.6 (SD = 14.3, IQ range 78–128). The control group consisted of 15 men and 23 women with mean age 29.8 years (SD = 6.5, age range 21–41 years) and mean WASI-IQ 116.3 (SD = 9.4, IQ range 96–136). The groups did not differ significantly neither in their composition of sex ($\chi^2 = 1.00$; $df = 1$; $p = 0.32$), nor with respect of means of age [$t(65) = 1.84$; $p = 0.07$] or means of IQ [$t(65) = -1.97$; $p = 0.053$].

All patients had been diagnosed according to ICD-10 or DSM-IV criteria for hyperkinetic disorder/ADHD by a psychiatrist or psychologist before the inclusion in the Norwegian ADHD-project in Bergen. Controls were randomly selected from the comparison group in the Norwegian ADHD-project in Bergen (Halmoy et al., 2009), recruited from the database of the Medical Birth Registry of Norway. Details concerning the recruitment procedure are described in recent publications by the Bergen group (Johansson et al., 2008; Halleland et al., 2009; Halmoy et al., 2009). All participants in both groups were interviewed with the ADHD module of K-SADS (Kaufman et al., 1997) adjusted to adults, administered by an experienced psychiatrist (Margaretha Dramsdaahl). Based on symptoms reported in childhood, the participants were categorized into the following subgroups: seven with inattentive type, three with hyperactive/impulsive type and 19 participants with combined type. According to the present symptoms, however, nine participants had an inattentive type, one had symptoms of the hyperactive/impulsive type and 19 participants had a combined type. The Adult ADHD Self-Report Scale (ASRS-18; Kessler et al., 2005) was used to determine current ADHD symptoms in both groups. It consists of two subscales, one

scale measuring inattentive symptoms, the other scale measuring hyperactive/impulsive symptoms.

The ADHD group included both medication naïve as well as medicated participants. The 16 patients medicated with stimulants ($n = 15$) or atomoxetine ($n = 1$) were instructed to withhold medication 48 h prior to testing to reduce the possible influence of medication. Nine participants followed this instruction, whereas five reduced the dosage during the last 48 h (including the sole participant on atomoxetine), and two participants continued their ordinary medication. Thirteen of the participants in the ADHD group had not used stimulants or atomoxetine during the past 6 months.

Participants with ADHD consisted of 23 right-handed and 6 left-handed participants, whereas 33 right-handed and 5 left-handed controls were included. Handedness was determined by the hand that the subject preferred to draw and write with.

Exclusion criteria for both groups were current severe psychiatric axis I disorder or substance abuse, epilepsy, or other neurological or physical disease with cognitive impairment. Participants with a lifetime history of developmental delay, premature birth before 34 weeks of gestational age, or IQ below 70 were neither included. To ensure as representative ADHD sample as possible, we included participants with current mild psychiatric comorbidity (anxiety disorders and mild depressive symptoms). Eleven of the ADHD participants had diagnosis of an anxiety disorder (panic disorder, agoraphobia, social phobia, and/or specific phobia), two had a depressive disorder or dysthymia, and three ADHD participants had diagnosis of both anxiety and depressive disorder. No participant, however, reported ongoing, severe symptoms at the time for the MR scanning. Further exclusion criteria for the controls were lifetime history of ADHD, current ADHD symptoms (score >36 on ASRS-18, or >20 on one of the two subscales), or first-degree relatives (parents, children, siblings) with ADHD. Three of the controls had diagnosed specific phobia, but none had ongoing symptoms at the time of scanning.

Written informed consent was obtained from all participants after receiving detailed information about the procedure. The study was approved by the Norwegian Regional Medical Research Ethics Committee West IRB #3 (FWA00009490, IRB00001872).

MR SPECTROSCOPY

^1H -MR scanning was performed with a 3.0-T GE Signa HDx scanner, using an eight-channel head coil. Single voxel point-resolved spectroscopy (PROBE-PRESS) was used with the following parameters: TE = 35 ms, TR = 1500 ms. Line-width was less than 8 Hz and water suppression level at least 94%.

A T_1 -weighted image using a 3D Fast Spoiled Gradient Recall sequence (TE = 14 ms, TR = 400 ms, TI = 500 ms; scan matrix: 256×256 ; field of view of $256 \text{ mm} \times 256 \text{ mm}$, 188 sagittal slices of 1 mm thickness) was acquired to position the slices parallel to the line connecting the lowest edge of the splenium and the rostrum of the CC. In addition to the T_1 -weighted image an axial T_2 -weighted image was acquired prior to the proton MRS imaging sequences. The T_2 -weighted image was used as reference for cerebrospinal fluid (CSF) within the area of interest to avoid CSF contamination of the MRS voxel.

Voxel size was 20 mm × 20 mm × 20 mm localized in the left and the right midfrontal region including the dorsal ACC. The position of the MRS voxel was parallel to the CC, midway between the upper part of the mid-body of the CC, and the most anterior part of the genu, close against the edge of the white matter in the CC (**Figure 1**). Scanning was performed with the MRS voxel localized first in the left and then in the right midfrontal region.

DATA ANALYSIS

The ratio of Glu to Cre were estimated by LCModel software version 6.2-1A using a simulated basis-set for a TE of 35 ms, delivered by Provencher (2011). LCModel automatically quantifies *in vivo* spectra, avoiding analyses of individual peaks or use of any subjective-influenced model. Estimated SD (Cramér–Rao lower bounds) below 20% were accepted, which is a rough criterion for estimates of acceptable reliability (Provencher, 2011).



FIGURE 1 | The position of the 20-mm × 20-mm × 20-mm voxel in the midfrontal region.

All statistical analyses were made by general linear model (GLM) using the Statistica 8 software (<http://www.statsoft.com/>). Group comparisons were made between the ADHD and control group and between the left and right side in a multivariate analysis of variance (MANOVA) including Glu/Cre left and Glu/Cre right as dependent variables and group as categorical variable. In order to control for any effect of covariates, the data were reanalyzed with multivariate analysis of covariance (MANCOVA) including Glu/Cre left and Glu/Cre right as dependent factors, group, sex, and handedness as categorical predictors, and age and IQ as continuous predictors. Since none of the interactions were significant, we removed the interaction terms before re-running the analysis twice with Glu/Cre left and Glu/Cre right, respectively, as dependent variables, group as categorical predictor, and sex, handedness, age, and IQ as covariates. Medication and comorbidity were not included as covariates in the GLM analyses, since these variables had implications mainly for the ADHD group, and some of the subgroups would be very small or even give empty cells in the statistical design. Thus, to investigate the effect of comorbidity and medication we did independent *t*-tests of the ADHD group with Glu/Cre ratio left side as dependent variable and comorbidity and medication, respectively, as grouping variables. As a last analysis we correlated the value of Glu/Cre in the left midfrontal region and scores of the two ASRS subscales to explore a possible association.

RESULTS

All spectra of the 67 included participants were of good quality (see **Figure 2** for a representative spectrum).

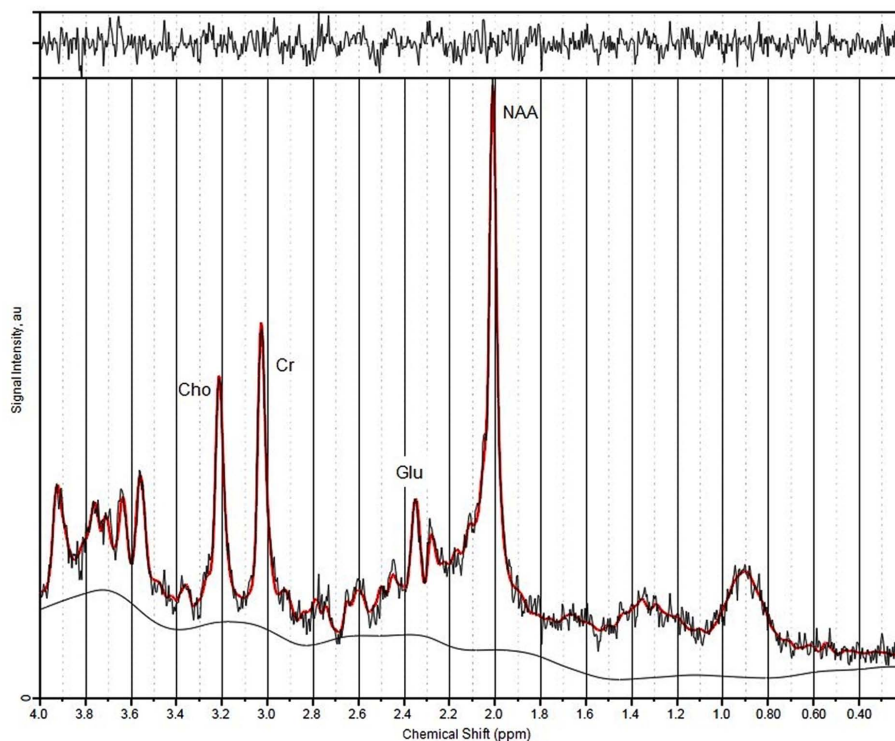


FIGURE 2 | A representative spectrum indicating position of peaks and calculation of signal-to-noise ratios.

The MANOVA including Glu/Cre left and Glu/Cre right as dependent variables and group as categorical variable revealed significant main effects of group and of side (Table 1; Figure 3). The mean Glu/Cre ratio was reduced in the ADHD group compared to the control group and the difference was only significant in the left midfrontal area. The mean Glu/Cre ratio was significantly lower in left midfrontal region compared to right midfrontal region in both groups. The MANCOVA including Glu/Cre left and Glu/Cre right as dependent factors, group, sex, and handedness as categorical predictors, and age and IQ as continuous predictors, revealed a significant main effect of group, but no longer any significant side effect (Table 2). Age and IQ had each a significant main effect, but, more importantly, no interactions between the factors became significant.

The ANCOVAs with Glu/Cre left and Glu/Cre right, respectively, as dependent variables, group as categorical predictor, and sex, handedness, age, and IQ as covariates confirmed a main effect of group at the left side, but not at the right (see Table A2 in Appendix).

In order to further elaborate the significant group effect in the left midfrontal area, detected by the MANOVA, follow up statistics were performed for this region, only. The *t*-test of the ADHD group with Glu/Cre ratio left side as dependent variable and comorbidity as grouping variable revealed significant

lower Glu/Cre value in the ADHD group without comorbidity compared to the ADHD group with comorbidity (see Table A1 in Appendix). The *t*-test of the ADHD group including medication as grouping variable showed no significant difference in Glu/Cre ratio at left side between the medicated and non-medicated ADHD participants (see Table A1 in Appendix).

The correlation between the symptoms of severity (ASRS scores) and the value of Glu/Cre in the left midfrontal region of the ADHD participants revealed no significant correlation. When including the controls and thus increasing the statistical power, a significant negative correlation between inattentive symptoms and Glu/Cre level was revealed ($r = -0.274, p = 0.025$). There was no significant correlation between the hyperactive/impulsive scores and the level of Glu/Cre in left midfrontal region ($r = -0.107, p = 0.39$).

DISCUSSION

The main finding of a reduced ratio of Glu/Cre in the left midfrontal region in participants with ADHD supports the hypothesis of ADHD as a hypoglutamatergic condition (Carlsson, 2001). Glutamate is an important neurotransmitter in cognitive processes (Van Wageningen et al., 2009, 2010) and seems to have a central role in neurotransmission in the ACC (Bozkurt et al., 2005; Yang et al., 2006). The dorsal ACC, in turn, plays a crucial role in the exertion of cognitive control (Bush et al., 2000; Carter and Van Veen, 2007), and a glutamatergic deficit in the midfrontal region including the dorsal ACC, may contribute to the impaired cognitive control in persons with ADHD.

The hypothesis that a dysregulation of catecholaminergic neurotransmission contributes to the development of symptoms typical for ADHD has been supported from different research areas, notably from pharmacological studies of psychostimulants (Staller and Faraone, 2007; Genro et al., 2010). The exact modes of action of human ADHD-medication, however, are still unknown (Solanto, 1998; Challman and Lipsky, 2000; Cornforth et al., 2010). Although changes in dopamine or norepinephrine levels may primarily mediate the effect of psychostimulants, the putative monoamine dysfunction in ADHD may also derive from an impaired glutamatergic transmission (Carlsson, 2001).

Our results partially replicate and extend previous studies of brain glutamate levels in persons with ADHD, but comparisons between studies may be difficult because of methodological and/or

Table 1 | Main and interaction effects of general linear model including glutamate/creatine ratios at left and right side as dependent variables and group (ADHD, control) as categorical predictors.

	SS	df	MS	F	p
Group	0.269	1	0.269	8.34	0.005*
Side	0.288	1	0.288	13.48	0.000*
Side × group	0.009	1	0.009	0.43	0.513

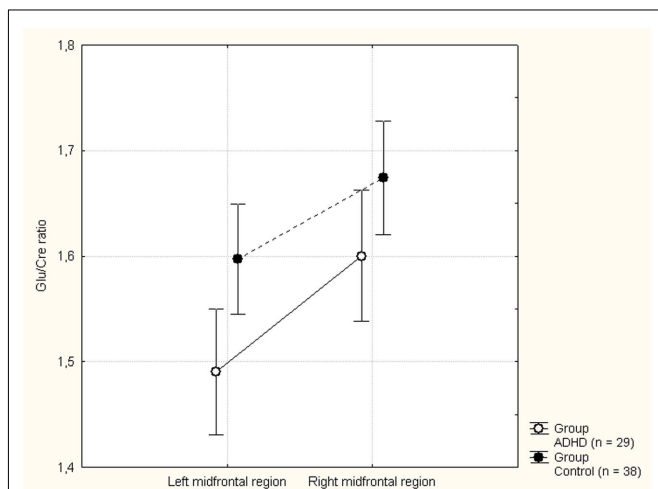


FIGURE 3 | Mean glutamate to creatine (Glu/Cre) ratio in the left and right midfrontal region in the attention-deficit/hyperactivity disorder (ADHD) and control groups. Vertical bars denotes 95% confidence intervals.

Table 2 | Main effects of general linear model including glutamate/creatine ratios at left and right side as dependent variables, group (ADHD, control), sex (man, woman), and handedness (left, right) as categorical predictors, and age and IQ as continuous predictors.

	SS	df	MS	F	p
Group	0.108	1	0.108	4.484	0.039*
Side	0.005	1	0.005	0.246	0.622
Sex	0.009	1	0.009	0.358	0.552
Age	0.175	1	0.175	7.264	0.009*
IQ	0.219	1	0.219	9.097	0.004*
Handedness	0.074	1	0.074	3.084	0.084

positional differences. One study concluding with significantly reduced Glx/Cre in the right ACC (Perlov et al., 2007) used multi-voxel chemical shift imaging (CSI) instead of single voxel spectroscopy. A recent single voxel MRS study reported increased glutamate concentration in the left ACC (Rusch et al., 2010), with the voxel of measurement positioned in the rostral part of ACC, anterior to the genu of the CC, and not in the dorsal, “cognitive” part. Furthermore, women were only included when ADHD was comorbid with a borderline personality disorder, making it difficult to draw conclusions about the specific impact of ADHD.

In addition to the diagnostic effect, we also revealed a significant main effect of side with reduced Glu/Cre in the left mid-frontal area. A difference in Glu/Cre value between the left and the right side may indicate a lateralization of the frontal region including the dorsal part of the ACC. Reports of morphological differences between left and right midfrontal regions support this hypothesis, with the paracingulate sulcus more commonly found pronounced in the left compared to the right hemisphere (Huster et al., 2007; Fornito et al., 2008). The significant difference between the Glu/Cre in left and right midfrontal region disappeared, however, after correction for the covariates sex, handedness, age, and IQ (see Table 2).

The re-analysis showed a significant main effect of age. This finding is in accordance with earlier report of a slight decrease of Glu concentration in the ACC with increasing age (Schubert et al., 2004).

The exploratory finding of a significant negative correlation between inattentive symptoms and Glu/Cre level may support the presumption of glutamate in the midfrontal region as an important factor of cognitive control.

This study has several limitations. First, our sample is small with seven predictive variables (group, sex, handedness, age, IQ, medication, and comorbidity), and replication studies are thus necessary. We here present a representative ADHD sample, which increased the numbers of variables and possible confounding factors. The mean IQ value was lower in the ADHD group compared to the control group, but not significantly different. Cognitive difficulties in neurodevelopmental disorders like ADHD are, however, of such pervasive nature that matching fully for IQ is likely to reduce the representativeness of the ADHD group (Dennis et al., 2009). Likewise, any correction for comorbidity would result in a non-representative ADHD group. The significant lower Glu/Cre value in the ADHD group without comorbidity compared to the ADHD group with comorbidity support the presumption that

comorbidity cannot explain the main finding of reduced Glu/Cre ratio at left side in the ADHD group.

Second, the participants were on different medication regimes, and even if medication did not seem to have any significant influence in our study (see Table A1 in Appendix), it may have an influence on the neurochemistry and the neuronal activity. Inclusion of only medication naïve participants would be a way to eliminate a possible confounding effect of medication.

Third, changes in the Glu/Cre ratio may be a result of changes in the concentration of Cre. As an internal reference the concentration of Cre is supposed to be constant, and no changes have been reported with age, at least not before the age of 60 years (Saunders et al., 1999). The concentration of Cre, however, may vary in pathological conditions, such as mood disorders (Capizzano et al., 2007), brain tumors (Yerli et al., 2007), or ischemia (Karaszewski et al., 2010), and even small changes in the Cre value may influence the ratio of Glu to Cre. However, we analyzed the Glu/Cre ratio, because the ratio is less sensitive to relaxation and partial volume effects than the absolute concentrations of metabolites (Provencher, 2011). Unknown units of the absolute concentrations were another reason for using the ratios.

A last limitation is the possible confounding factors of offsets of the chemical shifts, as well as different distribution of CSF and gray and white matter in the voxels. We consider, however, the voxel size large enough to minimize these effects, but cannot eliminate a contribution of these factors to the differences between the sides, as well as the groups.

In conclusion, our results reflect a hypoglutamatergic condition in the midfrontal regions of adults with ADHD, which may cause impaired cognitive control and a dysfunctional top-down regulation. More studies mapping the glutamatergic pathways and their interaction with other transmitters in persons with ADHD would help to further reveal the underlying neurobiology of the disorder.

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APPENDIX

Table A1 | Independent *t*-tests of the ADHD group (*n* = 29) with glutamate/creatine ratio left side as dependent variable, and comorbidity and medication, respectively, as grouping variables.

	Glu/Cre left	<i>t</i> -value	df	<i>p</i>
Mean – Comorb. Yes (<i>n</i> = 16)	1.548	2.167	27	0.039*
Mean – Comorb. No (<i>n</i> = 13)	1.419			
Mean – Medic. Yes (<i>n</i> = 16)	1.469	−0.753	27	0.458
Mean – Medic. No (<i>n</i> = 13)	1.517			

Table A2 | Main effects of general linear model including glutamate/creatine ratios at left side and right side, respectively, as dependent variables, group (ADHD, control) as categorical predictor, and sex (man, woman), handedness (left, right), age, and IQ as covariates.

	Glu/Cre left					Glu/Cre right				
	SS	df	MS	<i>F</i>	<i>p</i>	SS	df	MS	<i>F</i>	<i>p</i>
Group	0.150	1	0.150	7.469	0.008*	0.085	1	0.085	3.279	0.075
Sex	0.002	1	0.002	0.093	0.761	0.022	1	0.022	0.845	0.362
Age	0.165	1	0.165	8.215	0.006*	0.085	1	0.085	3.279	0.075
IQ	0.153	1	0.153	7.602	0.008*	0.097	1	0.097	3.737	0.058
Handedness	0.091	1	0.091	4.523	0.038*	0.029	1	0.029	1.122	0.294