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ORIGINAL INVESTIGATION

Hyperactivity and impulsivity in adult attention-deficit/hyperactivity disorder is related to glutamatergic dysfunction in the anterior cingulate cortex

Jochen Bauer[a], Anne Werner[b], Waldemar Kohl[b], Harald Kugel[a], Anna Shushakova[c], Anya Pedersen[c]* and Patricia Ohrmann[b]*

[a]Institute for Clinical Radiology, School of Medicine, University of Muenster, Germany; [b]Department of Psychiatry, School of Medicine, University of Muenster, Germany; [c]Clinical Psychology and Psychotherapy, Institute of Psychology, University of Kiel, Germany

ABSTRACT

Objectives: Attention-deficit/hyperactivity disorder (ADHD) is closely linked to the dysregulation of dopaminergic and noradrenergic neurotransmission in the fronto-striatal neural network, including the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC). Additionally, increasing evidence supports the involvement of the glutamatergic system in the pathophysiology of ADHD. Impulsivity, a core symptom in patients with ADHD, has been repeatedly associated with glutamatergic neurotransmission, and pharmacological treatment of ADHD has been shown to reduce glutamate levels in the prefrontal cortex.

Methods: We investigated glutamate levels in the ACC and the DLPFC in 30 adults with ADHD and 30 healthy controls using single-voxel proton magnetic resonance spectroscopy on a 3T scanner.

Results: The ADHD group showed a significant increase in glutamate in the ACC compared to controls, no significant differences in metabolites were observed in the DLPFC. Overall, glutamate levels in the ACC were positively correlated with ADHD symptomatology, especially hyperactivity and impulsivity symptoms.

Conclusions: Increased levels of glutamate in the ACC, which were positively correlated with hyperactivity and impulsivity, support the hypothesis that dysfunctional glutamatergic neurotransmission is at least partially responsible for ADHD symptomatology. Modulation of glutamatergic neurotransmission might therefore be a promising avenue for future pharmacological interventions.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a prevalence of approximately 5% in children and adolescents worldwide (Kessler et al. 2006; Polanczyk et al. 2007). Between 40 and 60% of the affected children show persistent symptoms into adulthood (Faraone et al. 2006). Clinically, symptoms of hyperactivity seem to decrease, whereas inattention and impulsivity persist with a high risk for poor socio-economic outcomes and functional impairment (Spira & Fischel 2005; Shaw et al. 2012; Dalsgaard et al. 2013; Chang et al. 2014).

The neurobiological mechanisms through which environmental and genetic factors interact and cause ADHD are still not fully understood. The neurodevelopmental character of ADHD implies the concept of a perturbed cortical trajectory as the fundamental deficit. The model of delayed maturation with respect to functional and structural connectivities fits the overall time course of synaptic pruning and myelination in the prefrontal cortex (PFC) during adolescence, as improvements in cortical network wiring lead to improved executive functioning. Abnormal pruning of neuronal connections might stall brain maturation, resulting in reduced brain connectivity and impairments in cognitive and emotional control systems (Liston et al. 2011).

A cingulo-frontal-parietal network, comprising the anterior cingulate cortex (ACC), dorsolateral and ventrolateral PFC, and parietal cortex working smoothly and in concert with subcortical and cerebellar regions has been associated with unperturbed motor, emotional and cognitive processes (Bush 2011). However, each of these brain regions displays functional and structural abnormalities in ADHD (Arnsten & Rubia 2012).

CONTACT Patricia Ohrmann ohrmann@uni-muenster.de Department of Psychiatry, University of Muenster, Albert-Schweitzer-Campus 1, A9, D-48149 Muenster, Germany
*Shared last authorship.

Functional imaging studies in patients with ADHD have also implicated dysfunctions in attentional and executive brain circuits, including the ventrolateral and dorsolateral PFC, ACC, parietal cortex, cerebellum and nucleus accumbens (Cherkasova & Hechtman 2009; McCarthy et al. 2014). A recent meta-analysis of functional imaging data obtained from studies of inhibition and attention in ADHD patients revealed abnormalities in two distinct brain networks. Impaired inhibition was related to reduced activation in the right inferior frontal cortex, supplementary motor area and ACC, whereas attention tasks revealed reduced activation in the dorsolateral prefrontal cortex (DLPFC), parietal cortex and cerebellum in patients compared to controls (Hart et al. 2013).

Dysfunctions in fronto-striatal emotional and cognitive control networks are closely related to dopaminergic and noradrenergic dysfunctions (Fineberg et al. 2010). Methylphenidate is the most effective medical treatment in children and adults with ADHD. Methylphenidate blocks dopamine and norepinephrine transporters and consequently increases dopamine and norepinephrine levels at the synaptic cleft. Interestingly, methylphenidate also lowers glutamate levels in ADHD children (Hammerness et al. 2012; Wiguna et al. 2014), and memantine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist improved ADHD symptoms in both children and adults (Findling et al. 2007; Surman et al. 2013; Biederman et al. 2014). As was shown in animal models, the ACC has a high density of glutamate receptors (Bozkurt et al. 2005), and a hypofunctional dopaminergic system and an increased release of glutamate in the fronto-striatal system was found in the spontaneously hypertensive rat, an animal model of ADHD symptomatology (Miller et al. 2014). A recent in vitro study reported that atomoxetine, an approved ADHD treatment that is supposed to bind to the presynaptic noradrenaline transporter (NET), blocks NMDA receptors in micromolar concentrations that are equivalent to those found in plasma of treated patients (Ludolph et al. 2010).

In vivo data on glutamate neurotransmission in patients with ADHD have been inconsistent so far. Proton MR spectroscopy (MRS) allows the in vivo quantification of glutamate (Glu) or the combined signal of glutamate and glutamine (Glx) in localised brain areas, e.g., the ACC. Spectroscopic data support the hypothesis of increased levels of Glu or Glx in different brain regions of children and adolescents, especially the ACC, the posterior cingulate cortex and the striatum, whereas no changes or decreased levels of Glx in prefrontal brain areas have been reported in adult patients (Endres et al. 2015; see for review: Perlov et al. 2007; Dramsdahl et al. 2011; Altabella et al. 2014; Spencer et al. 2014). To the best of our knowledge, only one study has examined glutamate in the PFC of adult ADHD patients. The authors found no difference between ADHD patients and controls in glutamate concentrations in the left DLPFC, but they found an increase in GABA concentrations in a subcortical volume of ADHD patients (Bollmann et al. 2015).

In our study, we used ^{1}H-MRS to investigate glutamate levels in the ACC and DLPFC, which are two key brain regions for executive functioning. In regard to the literature on dysfunctional neural networks and on previous MRS studies in ADHD we hypothesised that increased glutamate levels in these brain areas are related to the psychopathology of ADHD, especially impulsivity and hyperactivity.

Methods

Participants

Thirty patients with ADHD who were admitted to the outpatient clinic of the Department of Psychiatry and the outpatient clinic of the Institute of Psychology at the University of Muenster were included in our study. All patients fulfilled DSM-IV criteria for ADHD (Diagnostic Interview for ADHD in adults 2.0 (DIVA)) (Kooij 2012) and were diagnosed by an experienced psychiatrist (PO) and two clinical psychologists (AP and AS). Thirty age-matched healthy controls were recruited through advertisements in local newspapers. Exclusion criteria for both groups were severe neurological disorders, head injury, substance abuse or dependence (except nicotine), and lifetime diagnoses of psychotic or bipolar disorders (Structured Clinical Interview for DSM-IV-TR (SCID-I)) (Wittchen et al. 1997). One ADHD patient suffered from a comorbid mild major depressive episode and two patients had a specific phobia. Control participants with current psychiatric disorders (except for three controls with specific phobias) were excluded.

We excluded two patients with ADHD and two controls because of technical or methodological reasons. In two patients with ADHD and one control subject acquisition of spectra could not be completed and subjects had to be taken out of the scanner due to technical MR problems during acquisition. In one control subject acquisition of both spectra was not possible due to shortness of time (scanning started delayed). Additionally, one patient did not complete the study, and one control subject reported use of cannabis the day before scanning. Thus, the final sample consisted of 27 patients with ADHD and

27 controls. Fifteen patients with ADHD were diagnosed according to the criteria of DSM-IV as the combined subtype, and 12 were diagnosed as the predominantly inattentive subtype. As expected, symptoms of hyperactivity and impulsivity were significantly higher in patients with the combined subtype than those with the inattentive subtype ($t(25) = 3.046$, $P = 0.006$), whereas symptoms of inattention did not differ between groups ($t(25)=0.0619$, $P = 0.542$). Moreover, none of the clinical variables (age, sex, years of education, vocabulary or reasoning; in all cases $P > 0.05$) differed between ADHD subtypes. Sixteen patients with ADHD had never been treated with methylphenidate, whereas 11 patients were on stimulant medication. However, all patients were medication free for at least 24 h prior to the experiment. All participants provided written informed consent prior to participation in the study, which was approved by the local Ethics Committee according to the Declaration of Helsinki. Healthy subjects received financial compensation of 10€ per hour.

All participants completed the 22-item ADHD self-report scale (ADHD-SR) (Roesler et al. 2004) to quantify the severity of ADHD symptoms in adulthood. Childhood symptoms were evaluated by retrospective self-ratings using the Wender Utah Rating Scale (WURS-K, German short version) (Retz-Junginger et al. 2002). To estimate intelligence, the multiple choice vocabulary (MWT-B) (Lehrl 2005) and the subtest 'reasoning' of the Achievement Measurement System (AMS) (Horn 1983) were used. The demographic and clinical characteristics of patients and controls are summarised in Table 1.

^{1}H-MR spectroscopy

^{1}H-MRS data were acquired using a 3T-scanner (Gyroscan Intera 3T, Philips Medical Systems, Best, the Netherlands) with a transmit/receive head coil. T1-weighted 3D high-resolution anatomical images of the whole brain were acquired using a 3D fast-gradient echo sequence (Turbo Field Echo, TFE): TR =7.5 ms, TE 3.4 ms, FA =9°, two signal averages, and an inversion prepulse every 814.5 ms. These images were reconstructed into cubic voxels with a 0.5-mm edge length. From this dataset, slices in three orthogonal planes were displayed using multiplanar reconstruction for localisation of the spectroscopic volumes of interest (VOIs; 15 × 15 × 15 mm). The location of the VOI in the ACC was chosen to cover the rostral ACC bilaterally (BA 24, Figure 1(A)). Axially, the voxel was positioned directly at the most anterior part of the genu of the corpus callosum. In the sagittal slices, the inferior border of the VOI was placed parallel to the line connecting the anterior and posterior commissures. The VOI in the left DLPFC was chosen to cover BA 9, 10 and 46 (Figure 1(B)) according to coordinates described by Rajkowska and Goldman-Rakic (1995).

Spectral data were acquired with a point-resolved spectroscopy sequence using the following parameters: TE 32 ms, TR 2000 ms, bandwidth 2000 Hz, 2048 data points and 128 signal averages. A short echo time was chosen to obtain the optimal selectivity for glutamate and sufficient quality for glutamate and glutamine (Mullins et al. 2008; Hancu 2009). Example spectra for both regions of interest are presented in Figure 1. For quality control, a phantom with a concentration of 50 mM creatine was measured before each MRS session using the standard study protocol. The overall scanner variance caused by external factors during the acquisition of all data was 1.6%. Quantification of the spectra was based on LCModel spectral fitting (Provencher 1993, 2001). All concentration values were normalised to the unsuppressed water signal from the same VOI and expressed in institutional units (IU). The following metabolites were quantified: *N*-acetyl-aspartate with *N*-acetyl-aspartyl-glutamate (tNAA), glycerophosphocholine and phosphocholine (tCho), creatine and phosphocreatine (tCr); glutamate (Glu), and the combined signal of glutamine and glutamate (Glx). To correct metabolite concentrations for CSF, a procedure developed in-house based

Table 1. Demographic and clinical characteristics of patients with ADHD and healthy controls.

	Healthy controls	Patients with ADHD	Statistics	*P*
Age (years)	29.0 (8.90)	31.1 (8.90)	$t(52)=-0.871$	0.388
Age range (years)	19–49	19-48		
Sex (male:female)	17:10	15:12	$X^2 = 0.307$	0.580
Education (years)	11.44 (1.67)	11.26 (1.68)	$t(52) = 0.406$	0.686
Vocabulary	29.33 (3.57)	29.07 (3.73)	$t(52) = 0.261$	0.795
AMS Reasoning	27.67 (5.73)	27.85 (4.86)	$t(52)=-0.128$	0.899
ADHD-SR sum	7.12 (4.13)	30.10 (8.76)	$t(52)=-010.625$	0.001
ADHD-SR inattention	3.04 (2.25)	16.54 (4.68)	$t(52)=-13.038$	0.001
ADHD-SR hyperactivity/impulsivity	3.83 (2.68)	13.38 (6.10)	$t(52)=-11.93$	0.001
WURS-K sum	14.28 (12.11)	35.19 (13.08)	$t(52)=-5.917$	0.001

AMS, Achievement Measure System, subtest Reasoning; ADHD-SR, ADHD self-report scale; vocabulary, MWT-B; WURS-K, Wender Utah Rating Scale - German Short Version.

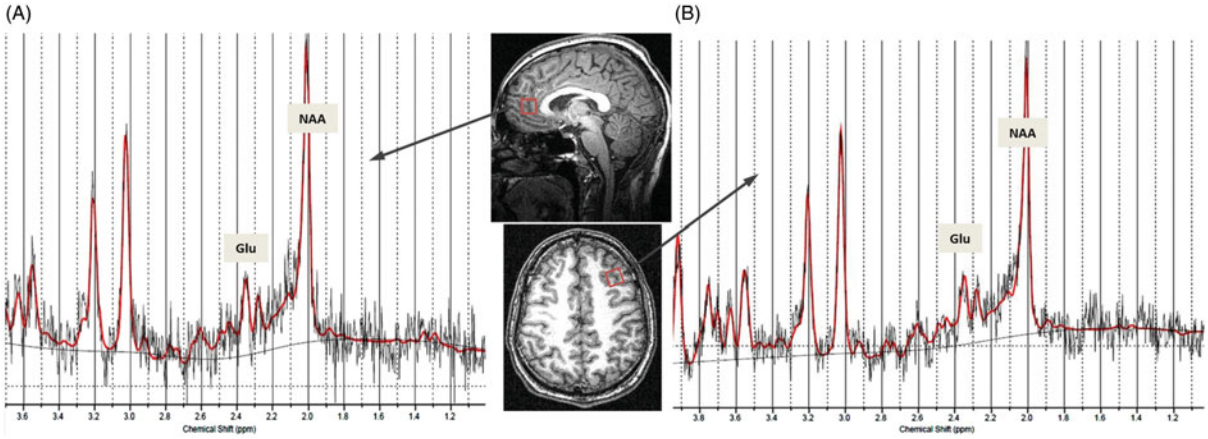

Figure 1. Localisation of the volumes of interest in the rostral anterior cingulate cortex bilaterally (A) and in the left dorsolateral prefrontal cortex (B) with the representative spectrum of one patient with ADHD.

on the VBM5 algorithm (VBM5, http://dbm.neuro.uni-jena.de/vbm/) was used to segment the T1-weighted datasets. In both VOIs, the amount of grey (GM) and white matter (WM) did not differ significantly between patients and controls (ACC GM ($t(52) = 0.416$, $P = 0.679$; ACC WM ($t(52) = 0.138$, $P = 0.891$; DLPFC GM ($t(51) = 0.043$, $P = 0.966$; DLPFC WM ($t(51) = -0.697$, $P = 0.489$). Moreover, WM and GM correlated highly significantly (ACC: $r = 0.840$, $P < 0.001$; DLPFC: $r = 0.989$, $P < 0.001$). Only metabolite signals with Cramér-Rao lower bounds (CRLBs) below 20% were accepted and used for the following analyses. As recent literature has shown that strict quality filtering based on relative CRLBs might cause a bias in mean concentrations, we also looked at all metabolite signals with absolute CRLB distribution and did not find differences in means and SDs in both groups (Kreis 2016).

Statistics

Analyses of metabolites were carried out using SPSS (SPSS 22.0 for Windows, SPSS, Inc., Chicago, IL). Group differences in metabolite levels between patients and controls and between the two patient subgroups were tested with Student's t-tests and ANCOVAs with the covariates age, gender and GM. Pearson's correlation coefficients were computed to determine correlations between metabolites and the demographic and clinical characteristics. R^2 values are the coefficients of determination for each subgroup calculated from Pearson's correlation coefficient (r). In accordance with our hypotheses, we were primarily interested in the correlation between glutamate levels and symptom severity in ADHD. Significance was assumed for P values <0.05 (two-tailed). After Bonferroni-corrections for multiple comparisons in each VOI, between-group differences were significant for P values <0.01 (two-tailed).

Table 2. Mean and SD of metabolite levels in the ACC and DLPFC of patients with ADHD and healthy controls.

	Healthy controls	Patients	t	P
(A) Mean metabolite concentrations in the ACC				
ACC				
tNAA [IU]	10.89 (1.26)	11.23 (1.16)	−1.040	0.303
Glutamate [IU]	10.90 (1.61)	12.19 (1.69)	−2.856	**0.006**
Glx [IU]	16.69 (2.32)[1]	17.65 (2.25)	−1.510	0.137
tCho [IU]	2.24 (0.33)	2.39 (0.47)	−1.298	0.200
tCr [IU]	8.20 (0.95)	8.30 (1.14)	−0.352	0.726
(B) Mean metabolite concentrations in the left DLPFC				
DLPFC				
tNAA [IU]	10.62 (1.54)	10.72 (0.80)	−0.280	0.781
Glutamate [IU]	9.39 (1.62)	9.75 (2.03)	−0.638	0.527
Glx[IU]	13.55 (2.59)	13.58 (2.54)	−0.050	0.961
tCho [IU]	1.73 (0.38)	1.89 (0.33)	−1.593	0.118
tCr [IU]	6.29 (0.82)	6.85 (1.06)	−2.091	0.042

ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; SD, standard deviation; t, Bonferroni-corrected two-sample t-test significant for P values <0.01; tNAA, NAA + NAAG; tCho, glycerophosphocholine and phosphocholine; tCr, total creatine; Glx, glutamate and glutamine; IU, institutional units. Significant results ($P < 0.01$) are shown in bold.

Results

^{1}H-MR spectroscopy in the ACC

The mean metabolite concentrations in the ACC are displayed in Table 2(A). The group comparisons revealed significantly higher glutamate levels in the ACC in patients with ADHD compared to controls. ($t(52) = -2.856$, $P = 0.006$). Comparisons of metabolite levels in ADHD subtypes with those in controls revealed significantly higher levels of glutamate in the combined ($t(40) = -3.163$, $P = 0.003$), but not in the inattentive subtype ($t(37) = -1.418$, $P = 0.165$). All other metabolites did not differ significantly between patients and controls. The difference in glutamate levels stayed significant after including GM, age and

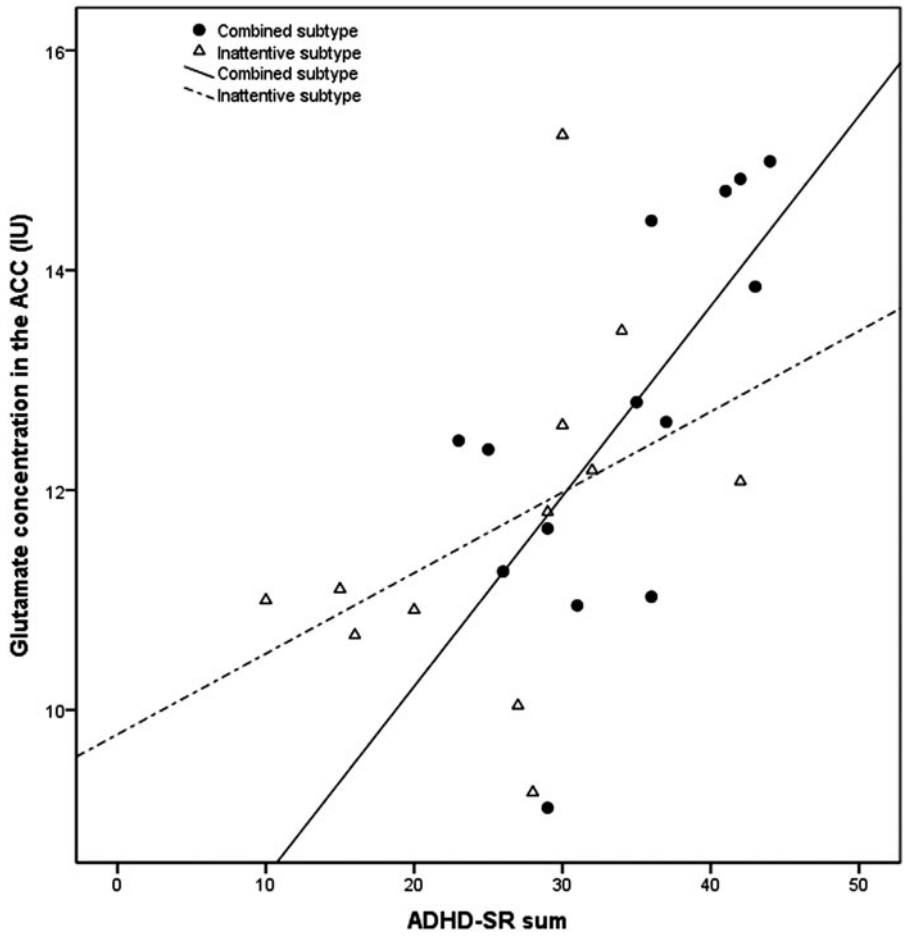

Figure 2. Correlation between glutamate (IU) and the ADHD self-report scale sum score in patients with combined and inattentive subtypes of ADHD.

gender as covariates (healthy controls: Glu [IU] = 10.94 (SD = 1.603); ADHD patients: Glu [IU] = 12.19 (SD = 1.726); F(1, 49) = 7.177; $P = 0.010$).

There were no significant differences between never-medicated patients and patients treated with methylphenidate (in all cases $P > 0.05$). This was also the case for glutamate levels in the ACC (never-medicated patients: Glu [IU] = 12.41 (SD = 1.86); patients treated with methylphenidate Glu [IU] = 11.87 (SD =1.44); $t(52) = 0.810$, $P = 0.426$).

Glutamate levels correlated significantly with ADHD symptomatology as measured with the ADHD-SR in patients (sum score: $r = 0.594$, $P < 0.001$) as well as in the total sample (sum score: $r = 0.553$, $P < 0.001$).

Positive correlations with glutamate levels were found for the combined subtype ($r = 0.688$, $P = 0.007$), but not for the inattentive subtype ($r = 0.420$, $P = 0.174$, see Figure 2). In addition, the ADHD-SR hyperactivity/impulsivity subscale ($r = 0.571$, $P = 0.002$), but not the inattention subscale ($r = 0.350$, $P = 0.080$), correlated significantly with glutamate levels in the ACC. Moreover, glutamate levels in the ACC correlated moderately with retrospectively reported childhood symptoms in ADHD patients (WURS-K: $r = 0.400$, $P = 0.043$).

^{1}H-MR spectroscopy in the DLPFC

The mean metabolite concentrations in the left DLPFC are displayed in Table 2(B). There were no significant between-group differences with respect to metabolite levels. Again, there were no significant differences between never-medicated and medicated patients. There were no significant correlations between metabolite levels and clinical or demographic characteristics in patients and healthy controls.

Discussion

There are two important findings in our study. The first was a significant increase in glutamate in the ACC of patients with ADHD compared to that in healthy controls. The second was a positive correlation between this glutamatergic dysregulation and clinical

symptomatology in ADHD patients, especially impulsivity and hyperactivity. Thus, our data extend previous studies of glutamate in children and adolescents with ADHD (Altabella et al. 2014; Spencer et al. 2014).

Only a few studies of ADHD using spectroscopy have investigated glutamate separately; most studies have quantified the combined signal of glutamate and glutamine. Additionally, in most previous studies, ratios of glutamate to creatine were reported (Perlov et al. 2009; Dramsdahl et al. 2011). However, alterations in the Cr pool, as found in the absolute quantitative studies, imply that this metabolite is not a stable reference. Increased, as well as decreased, levels of Cr have been found in children and adolescents with ADHD (Carrey et al. 2007; Yang et al. 2010).

Increased levels of glutamate and Glx have been reported in the ACC of children and adolescents with ADHD (Altabella et al. 2014), whereas the only study on glutamate in the PFC in adults with ADHD, which investigated the DLPFC, found no difference between patients and controls (Bollmann et al. 2015). Interestingly, Rüsch et al. (2010) reported increased glutamate levels in the ACC in patients with borderline personality disorder (BPD) and comorbid ADHD.

Our results are in line with the data reported by Ende et al. (2015), who compared metabolites in ADHD and BPD patients. The authors observed a positive relationship between impulsivity and glutamate/tCr in the ACC and an inverse relationship between impulsivity and GABA levels in both patient groups. GABA is the main inhibitory neurotransmitter in the cerebral cortex and plays an important role in regulating cortical excitability. The GABAergic system matures during adolescence, with prefrontal GABA receptors reaching adult levels during late adolescence. Imbalances leading to increased excitability cause clinical symptoms, such as seizures, cognitive impairment or behavioural disturbances. Increasing evidence supports the relevance of GABAergic neurotransmission for impulsive and aggressive behaviour. Silveri et al. (2013) reported a negative relationship between impulsivity and impaired response inhibition and GABA levels in the ACC of healthy men. Boy et al. (2011) related GABA levels in the DLPFC of healthy men with urgency, one facet of impulsivity, and described a negative relationship implicating GABA-mediated inhibitory mechanisms in emotional control. Thus, our data and those from the study of Ende et al. (2015) are consistent with the hypothesis of a disturbed excitatory/inhibitory neurotransmission, which is related to impulsive behaviour in ADHD.

There was no significant difference in the Glx levels in the ACC in the present study which is in line with data from Endres et al. (2015) who also reported no differences in a large group of well-characterised patients with ADHD and healthy controls. Thus, the overall pool of glutamate and glutamine was not significantly different between patients and controls. Glu is regarded as the major component of the Glx signal. Glu found in neuronal synaptic vesicles is the primary source of extracellular Glu and is released from the vesicles into the synaptic cleft to induce excitatory neurotransmission. Glu is then rapidly cleared from the synaptic cleft via high-affinity amino acid transporters in neurons and astrocytes. To prevent excitotoxicity, these transporters can rapidly reduce the extracellular Glu concentration to nanomolar levels (Moussawi et al. 2011). In astrocytes, Glu is metabolised into Gln and subsequently transported back into neurons, where it is converted into Glu and used to refill the synaptic vesicles. Spectroscopy cannot differentiate between these various Glu pools; however, the Glu and Glx signals detected by ^{1}H spectroscopy are very closely related to the results for Glu/Gln cycling reported by ^{13}C MRS (Rothman et al. 2011).

Imbalances in glutamatergic neurotransmission in the ACC have been reported in a variety of neuropsychiatric disorders. In OCD patients glutamate levels in the ACC were found to be increased, whereas in schizophrenia Glx and glutamate levels were reduced (Ohrmann et al. 2005; O'Neill et al. 2016; Wijtenburg et al. 2016). In affective disorders, disturbed glutamatergic neurotransmission in the ACC has been related to decreased levels of Glx in depressive episodes, whereas in mania Glx levels seem to be increased (Jun et al. 2014). Thus, imbalanced prefrontal glutamatergic neurotransmission might be transdiagnostically related to emotional and cognitive symptoms in neuropsychiatric disorders. Psychopharmacologically, modulators of the glutamatergic system have been investigated for almost all neuropsychiatric disorders, including OCD, anxiety disorders, bipolar disorders, schizophrenia and major depression, where ketamine which blocks NMDA receptors has repeatedly shown antidepressant efficacy (Pittenger 2015; Rasmussen 2016).

In the DPLFC no metabolite changes were observed, which is consistent with spectroscopy findings from other recent studies (Maltezos et al. 2014; Bollmann et al. 2015).

There are several limitations associated with our study that should be discussed. Firstly, the sample size was small and did not allow sophisticated analyses of subgroups. Thus, we were unable to investigate the effects of sex on metabolite levels. So far, data have not suggested different metabolite levels between

male and female ADHD patients. In our study, male and female ADHD patients also did not differ in regard to the severity of symptoms or subtype distribution. Secondly, it should be noted that 11 patients were medicated with methylphenidate, although these patients withdrew from stimulants 24 h before MR spectroscopy. As several studies have shown a positive effect of psychopharmacology on structural brain pathology in ADHD, e.g., cortical thinning, the medication also might have affected the metabolites (Frodl & Skokauskas 2012; Schweren et al. 2013). In our study, metabolite levels in patients with and without medication did not differ in either brain region. Maltezos et al. (2014) also found no effect of stimulant medication on metabolite levels in a large group of adult ADHD patients.

Our ACC volume was located in the rostral ACC, i.e., the 'affective' subdivision of the anterior cingulate (Bush et al. 2000), although functional and structural studies have also suggested alterations in the dorsal ACC in ADHD. Concepts of ACC organisation and function are still a matter of debate, and dorsal and ventral parts of the ACC have partly overlapping patterns of connectivity with limbic regions, e.g., the amygdala. Additionally, Etkin et al. (2011) very convincingly showed that both dorsal and ventral-rostral subdivisions are involved in emotional processing, with ventral-rostral portions of the ACC and medial PFC having a regulatory role with respect to limbic regions. In the future, spectroscopic imaging that allows coverage of large brain volumes might be an efficient way to obtain a comprehensive picture of glutamatergic transmission in the ACC. Nevertheless, current methodological limitations do no not allow quantification of glutamate with 3T-MR spectroscopic imaging.

Overall, our findings support the notion of a dysregulated excitatory glutamatergic neurotransmission that is closely related to hypofunctional dopaminergic transmission in fronto-striatal networks of emotion regulation and cognitive control in ADHD. Because progress in MR spectroscopy in recent years has enabled investigation of both the GABAergic and glutamatergic transmitter systems in distinct brain areas of patient populations, future studies should implement GABA and glutamate acquisition methodology. Additionally, longitudinal studies that simultaneously investigate metabolites and functional networks, as well as structural changes from childhood until adulthood, will enable an improved understanding of transmitter dysfunctions and the interactions of catecholaminergic stimulants and glutamate/GABA neurotransmission in ADHD.

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