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Impulsivity and Aggression in Female BPD and ADHD Patients: Association with ACC Glutamate and GABA Concentrations

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Borderline personality disorder (BPD) and attention-deficit-hyperactivity disorder (ADHD) are both characterized by high impulsivity and difficulties in controlling anger and aggression. In BPD, comorbid ADHD may further increase impulsivity. For both disorders, altered MR spectroscopy levels of the neurotransmitters glutamate and GABA as well as some correlations with impulsivity were previously reported. The objective of this study was to investigate the neurotransmitters glutamate and GABA in relation to impulsivity and aggression as expressed in the anterior cingulate cortex (ACC) in groups of female patients with BPD and ADHD, respectively. Associations of glutamate and GABA levels with further BPD (symptom severity) and ADHD aspects (hyperactivity and inattention) were exploratively evaluated. 1H MR spectra were acquired at 3T to determine glutamate to total creatine ratios (Glu/tCr) and GABA levels from the ACC in a BPD group ($n = 26$), an ADHD group ($n = 22$), and a healthy control (HC) group ($n = 30$); all participants were females. Both patient groups showed higher scores on self-reported impulsivity, anger, and aggression compared with HCs. ACC GABA levels were significantly lower in ADHD than HC. Although measures of impulsivity were positively related to glutamate and negatively to GABA, for aggression only a negative correlation with GABA could be demonstrated. These data provide human *in vivo* evidence for the role of ACC Glu/tCr and GABA in impulsivity and aggression. If distinct associations of Glu/tCr and GABA for BPD and ADHD can be confirmed in future studies, this might yield implications for more specific pharmacological treatments.
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INTRODUCTION

Impulsivity and reactive aggression are major behavioral problems and part of the psychopathology of a variety of psychiatric disorders, such as borderline personality disorder (BPD) or attention-deficit-hyperactivity disorder (ADHD). Impulsivity consists of different components including personality traits (eg, tendency to act on the spur of the moment), deficits in executive functions (eg, attention, interference inhibition, information sampling, decision making, delay of gratification), and behavioral inhibition (Sebastian *et al*, 2013, 2014). Aggressive behavior frequently displayed by patients with BPD (Latalova and Prasko, 2010) and ADHD (Connor *et al*, 2010) is usually of two different kinds: reactive (or impulsive) aggression and instrumental aggression. Impulsive aggression refers to uncontrolled outbursts of anger in reaction to goal blocking, provocation, or frustration, whereas instrumental aggression is a relatively non-emotional behavior to further one's goals of power, money, or other external gains (Berkowitz, 1993).

Both high impulsivity and difficulties in controlling anger and aggression are characteristic of affective and behavioral dysregulation in BPD and may lead to severe social and interpersonal problems in patients' lives. On a neural level, these symptoms have been associated with abnormalities in fronto-limbic networks, including the anterior cingulate cortex (ACC) (Mancke *et al*, in press; Sacchetti and Lefler, 2014; Sebastian *et al*, 2014). In previous research, altered ACC structure and function have been demonstrated in BPD (Rusch *et al*, 2010b). On a neurochemical level, glutamate and γ-aminobutyric acid (GABA) are considered important regulatory metabolites in this network (Comai *et al*, 2012a, 2012b). In a previous MR spectroscopy (MRS) study, we demonstrated that glutamate concentrations in the ACC correlated with self-reported impulsivity in female BPD patients (Hoerst *et al*, 2010).

ADHD is another disorder marked by impulse and anger control problems, which can lead to impairments in social functioning (Sacchetti and Lefler, 2014; Wender *et al*, 2001). As BPD and ADHD often co-occur, this may further increase the likelihood of increased impulsivity in BPD (Davids and Gastpar, 2005; Krause-Utz *et al*, 2013; Philipsen *et al*, 2008). A recent study (Krause-Utz *et al*, 2013) demonstrated that

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impulsivity is closely related to stress in BPD (Cackowski *et al*, 2014); whereas in ADHD impulsivity is already present under non-stress conditions.

Although GABA is the major inhibitory neurotransmitter in the brain, glutamate is the major excitatory neurotransmitter. Both relate to several psychological functions. In a study of children with ADHD, lower GABA levels in a region including parts of the primary somatosensory and motor cortices have been reported (Edden *et al*, 2012). In healthy adolescents and adults, two recent studies showed a negative association of GABA levels in the dorsolateral prefrontal cortex with impulsivity (Boy *et al*, 2011; Silveri *et al*, 2013). Despite these studies, Hayes argues that there is still a lack of research on GABA in the general context of impulsivity (Hayes *et al*, 2014). In rodents, Murphy *et al* recently reported implications for glutamatergic and GABAergic mechanisms in the infralimbic cortex in the expression of impulsivity (Murphy *et al*, 2012).

So far, the evidence that both glutamate and GABA influence impulsivity and aggression is scarce. Therefore, the aim of the present study was to investigate the relation of glutamate and GABA levels in the ACC to impulsivity and aggression in female patients with BPD, female ADHD patients, and female healthy controls (HCs). First, we hypothesized that, based on previous findings in self-reported impulsivity, anger, and aggression in BPD and ADHD, we would find higher scores on impulsivity in both patient groups compared with HCs. Second, we expected higher anger and aggression ratings and higher motor impulsiveness in ADHD patients compared with BPD patients (Krause-Utz *et al*, 2013; Lampe *et al*, 2007).

Third, we set out to test the reported correlation between ACC glutamate and impulsivity (Hoerst *et al*, 2010) and additionally hypothesized that GABA levels would reveal an opposite pattern from glutamate levels in their relation to self-reported impulsivity scores. Fourth, we hypothesized to find similar associations for aggression, ie, a positive correlation with ACC glutamate and a negative correlation with GABA levels.

Finally, we exploratively evaluated possible associations of glutamate and GABA ACC levels with BPD and ADHD symptoms, assessing general BPD symptom severity and the other core aspects of ADHD besides impulsivity, which are hyperactivity and inattention.

MATERIALS AND METHODS

Sample

Our sample consisted of 78 female participants comprising 26 female patients with BPD according to DSM-IV (APA, 2000), 22 patients with ADHD according to DSM-IV, and 30 female HC matched for age (18–43 years), education and intelligence (see Table 1). Patients were recruited at the Department of Psychosomatic Medicine and Psychotherapy and the Department of Psychiatry and Psychotherapy, Central Institute of Mental Health in Mannheim, Germany. Furthermore, participants were recruited via advertisements in newspapers, on websites, including disorder-specific internet forums, and via flyers for therapists. The study was approved by the local ethics committee and informed written consent was obtained from all participants.

Table 1 Patient's Characteristics

Descriptive statistics		Mean	SD
Age	HC, $N=30$	27.53	6.60
	BPD, $N=26$	27.54	6.53
	ADHD, $N=22$	30.05	6.74
	Total, $N=78$	28.24	6.63
BSL-23 total	HC	2.60	4.11
	BPD	***45.54***,#*	21.39
	ADHD	***18.23***,§*	13.04
ADHD-RS total	HC	6.53	5.45
	BPD	***18.77***,#*	8.28
	ADHD	***35.09***,§*	7.46
BDI	HC	2.24	3.29
	BPD	30.73*,#	12.01
	ADHD	16.41*,§	12.30
STAI	HC	31.97	7.67
	BPD	61.81*,#	10.83
	ADHD	53.96*,§	10.42
CTQ	HC	30.07	5.08
	BPD	72.50*,#	19.88
	ADHD	45.64*,§	17.23
DES	HC	0.25	0.18
	BPD	2.68*,#	1.51
	ADHD	1.15*,§	0.98
CAARS total	HC	31.10	17.59
	BPD	***83.19***,#*	29.38
	ADHD	***125.77***,§*	23.20
BIS-11 total	HC	53.40	7.43
	BPD	***63.69***,#*	10.37
	ADHD	***83.86***,§*	8.13
STAXI trait total	HC	16.23	3.53
	BPD	***28.12****	7.82
	ADHD	***25.59****	7.01
BGLHA total	HC	1.23	1.94
	BPD	***9.50****	7.14
	ADHD	***8.32****	4.67
GABA (i.u.)	HC	1.70	0.27
	BPD	1.65	0.30
	ADHD	***1.50****	0.27
Glu/tCr	HC	1.07	0.08
	BPD	1.07	0.09
	ADHD	1.06	0.07
GM/BM glutamate voxel	HC	0.82	0.03
	BPD	0.84	0.06
	ADHD	0.81	0.04
GM/BM GABA voxel	HC	0.60	0.04
	BPD	0.60	0.04
	ADHD	0.58	0.04

Numbers in bold and italic are significantly different from one or both other groups; the respective groups are marked by the following symbols.
*significantly different from HC.
#significantly different from ADHD.
§significantly different from BPD.

Diagnostic Assessments

All participants underwent diagnostic assessments including the Structured Clinical Interview for DSM-IV Axis-I disorders (SCID-I (First *et al*, 1997)) and the Borderline Section of the International Personality Disorder Examination (IPDE (Loranger, 1999)). In addition, the Standard Progressive Matrices Test (Raven *et al*, 2003) and a German

vocabulary intelligence test (Mehrfach-Wortschatz-Intelligenz-Test, Version B (Lehrl, 2005) were completed by all participants to estimate their intelligence. Inclusion criteria for the BPD group were at least five DSM-IV criteria for BPD (APA, 2000). For exclusion of ADHD diagnosis in BPD patients, three different measurements were applied: (1) the short version of the Wender Utah Rating Scale (WURS-k (Retz-Junginger *et al*, 2003)) to assess childhood ADHD symptoms; (2) the Connor Adult ADHD Rating Scale (Conners *et al*, 2002) was used, based on the DSM-IV criteria for ADHD (APA, 2000); (3) the Wender-Reimherr Adult Attention Deficit Disorder Scale (Rösler *et al,* 2008), which is a clinical interview conceptualized for adult ADHD. For the ADHD group, the same measurements were applied and BPD diagnosis was excluded via the IPDE. Substance use was assessed with the SCID-I (First *et al*, 1997). Furthermore, a urine drug screening was performed on the day of the MR investigation. No physical examinations were performed on the participants in the study. Medical and neurological conditions were gathered before participation in a detailed medical anamnesis. Serious physical and neurological diseases were exclusion criteria in this study. First-degree relatives of patients and controls were not necessarily free of psychiatric disorders.

Further clinical variables were assessed by self-reported measures concerning borderline symptom severity (Borderline Symptom List-23, BSL-23 (Bohus *et al*, 2007)), childhood trauma history (Childhood Trauma Questionnaire, CTQ, (Bernstein *et al*, 2003)), trait dissociation (Dissociative Experience Scale, DES (Bernstein and Putnam, 1986)), the State-Trait Anxiety Inventory, STAI (Spielberger *et al*, 1983), and depression (Bernstein and Putnam, 1986)) Beck Depression Inventory II (Beck *et al*, 1995).

All measurements and interviews were conducted by well-trained clinical psychologists and psychiatrists. Exclusion criteria for all participants were psychotropic medication within 2 weeks prior to the study, significant somatic disorders, pregnancy, and mental deficiency or developmental disorders. Patients were not generally free of medication. Some patients gradually reduced intake of their psychotropic medication (in consultation with their attending physician) and stopped intake 2 weeks before the study took place. Other patients were recruited while consulting a physician to start medication and were investigated before they started with pharmacotherapy. Lifetime history of any co-occurring psychiatric disorder was an exclusion criterion for HC. BPD and ADHD patients were not included if they had a lifetime history of bipolar affective disorder, psychotic disorder, current suicidal crisis, or substance abuse within the last 2 months.

Assessment of Impulsivity and Aggression

For impulsivity and aggression, the following self-rating scales were applied: the Barratt Impulsiveness Scale (BIS-11) (Preuss *et al*, 2008), the State-Trait Anger Expression Inventory (STAXI) (Schwenkmezger and Hodapp, 1991), and the Brown Goodwin Lifetime History of Aggression (BGLHA) (Brown *et al*, 1979). The BIS-11 consists of 30 items, which are answered on a four-point Likert scale (1 = 'rarely/never' to 4 = 'always') and can be divided into the subscales Motor Impulsiveness, Non-Planning Impulsiveness, and Attentional Impulsiveness. The BGLHA assesses different types of aggressive and antisocial behavior (ie, instances of fighting, temper tantrums, antisocial behavior involving the police), where each item is rated on a scale from 0–4, indicating the frequency of these events ranging from 'never' to 'more than four times'. The trait version of the STAXI consists of 10 items assessing the disposition to experience anger. All items are rated on a four-point Likert scale ranging from 1 (almost never) to 4 (almost always). The BGLHA is a measurement of past overt aggressive behavior in contrast to the STAXI, which measures the tendency to feel anger (which may or may not provoke aggressive behavior). As anxiety and anger are both high arousal, negatively valenced emotions, a strong relationship can be expected.

MR Spectroscopy

In vivo, single voxel 1H MRS was performed at a 3.0 T whole-body MR scanner with a 32 channel receive-only head coil (Siemens Magnetom TIM Trio). Two MRS voxels were acquired and both were placed on the ACC based on an isotropic 1 mm^3 MPRAGE data set with reconstructed coronal and transverse planes aligned with the shape of the corpus callosum (see Figure 1). With a MEGA-PRESS sequence for GABA editing, a $40\times\ 30\times\ 20\,mm^3$ voxel was acquired (TE = 68 ms, TR = 3 s, NEX = 96on, 96 off) (Figure 1). The editing pulse (Gauss shape, 20.36 ms length, bandwidth (FWHM): 44 Hz) in the MEGA-PRESS sequence was switched between 1.9 and 1.5 ppm (second editing frequency 1.5 ppm) alternating every excitation. This editing scheme diminishes contamination by nearby MM resonances (Aufhaus *et al*, 2013; Henry *et al*, 2001: Aufhaus, 2013 #13421)

The glutamate signal was analyzed from a smaller and thus more exactly localized voxel of $15\times30\times12\,mm^3$ acquired with a PRESS sequence in the ACC (TE = 80 ms, TR = 3 s, NEX = 96 (Schubert *et al*, 2004)) owing to the higher concentration and thus better Signal to Noise Ratio for glutamate compared with GABA.

For quantification of the (*in vivo*) spectra, the GABA signals were analyzed using the jMRUI-software (Stefan *et al*, 2009). The MEGA-PRESS sequence includes an editing pulse mirrored at 1.7 ppm (1.9 ppm and 1.5 ppm). This editing scheme does not only suppress the MM signals but additionally results in a different spectral pattern for GABA compared with the pulse schemes without macromolecule suppression. The jMRUI procedure included zerofilling to 2048 points, slight apodization (4 Hz, Lorentzian shape), and HLSVD filtering of the residual water peak. Three peaks with Lorentzian shape were used to fit GABA.

For the other metabolites, LCModel (Provencher, 1993) was used with a simulated basis data set (based on Gamma routines) containing the following metabolites: alanine, aspartate, creatine and phosphocreatine (tCr), GABA, glucose, glutamine, glutamate, glycerol-phosphoryl-choline, phosphoryl-choline, myo-Inositol, lactate, *N*-acetylaspartate, *N*-acetylaspartylglutamate, scyllo-Inositol, and taurine. In addition, signals of macromolecules and lipids were directly simulated by LCModel. Glutamate was evaluated as a ratio to total creatine (Glu/tCr). In the edited GABA spectra, the tCr signal is edited out. As we have previously established a quantitation method for GABA (Aufhaus *et al*, 2013) based

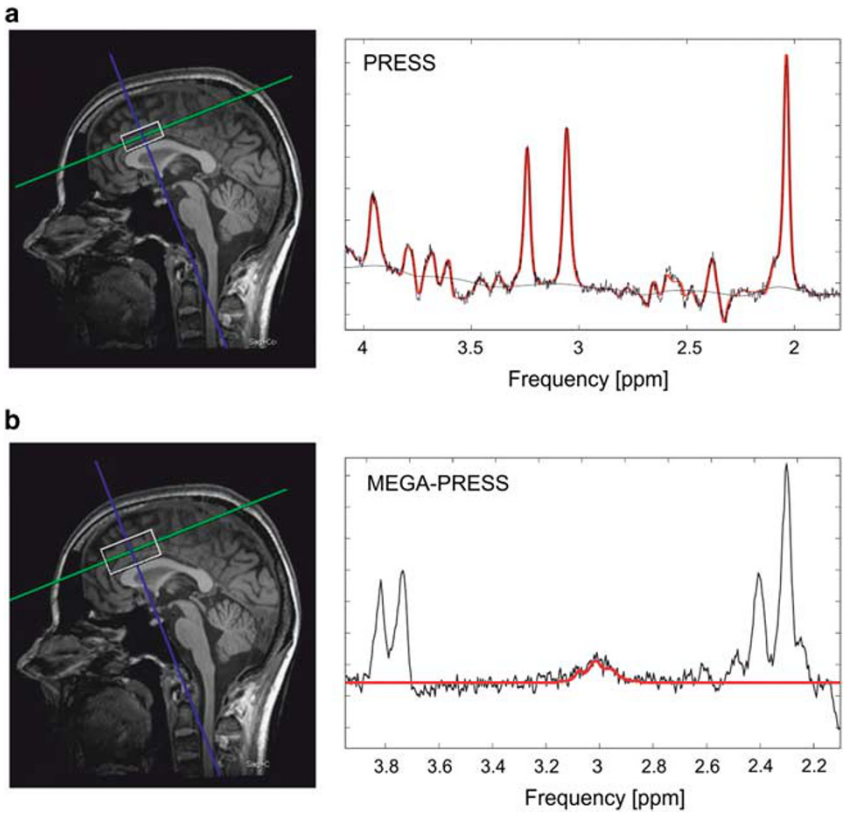

Figure 1 Localizer images with PRESS boxes and exemplary spectra for (a) Glu/tCr detection and (b) GABA detection.

on phantom measurements including correction for the voxel's tissue compartmentation (Weber-Fahr *et al*, 2002), quantitative values for GABA levels are reported. All spectra were of good quality and spectral fits had Cramer rao Lower Bounds below 20 for glutamate and GABA (no subject was excluded).

Statistical Analyses

Statistical analyses were performed using SPSS 21.0 for Microsoft Windows (SPSS). For analyses of group differences in demographic and psychometric variables, a multivariate general linear model analysis was applied. Group differences in GABA and in Glu/tCr were investigated with univariate general linear model analyses. Correlation analyses of GABA and Glu/tCr with psychometrics of impulsivity and aggression were performed as partial correlation for all subjects, controlling for disease state coded as two binary variables. Further correlations were calculated for the individual groups' GABA and Glu/tCr levels with impulsivity additionally controlling for aggression and for anxiety and with aggression additionally controlling for impulsivity and for anxiety. The threshold for statistical significance was set at $P<0.05$.

The ADHD diagnostic score CAARS consists of factor-derived subscales for inattention/memory problems, hyperactivity/restlessness, impulsivity/emotional liability, and problems with self-concept. The behavioral measure 'hyperactivity' is not explicitly covered by the BIS-11, STAXI, and BGLHA scores. Thus, we additionally determined exploratively whether the CAARS subscores and especially the hyperactivity subscore show significant relations to the observed Glu/tCr and/or GABA levels. Further, we tested whether the hyperactivity subscore significantly affects the correlations of impulsivity and aggression with Glu/tCr and GABA.

We additionally performed the correlation analyses group wise. Here, we tested for the difference between two independent correlation coefficients using Fisher's *z*-transformation (Preacher, 2002).

RESULTS

Demographic and Clinical Characteristics

Patient's characteristics are summarized in Table 1. Both patient groups were not free of further comorbid disorders. None of the subjects had been included in our previous study (Hoerst *et al*, 2010). The lifetime and current prevalences of comorbidities in both patient groups are listed in Table 2. The three groups (BPD, ADHD, HC) did not differ in age, intelligence, and education. Disorder-specific symptom ratings were all significantly higher in the patient groups than in the HC group. As expected, BPD patients scored higher in the BSL-23 score than the ADHD group and HC, whereas ADHD patients scored higher in all ADHD measures (WURS-k, CAARS) than BPD patients and HC. The CAARS total score and all its subscores significantly differentiated the ADHD group from the BPD group, but were also significantly higher in BPD than HC. Descriptively, the subscale inattention had the greatest relative difference between BPD (12.0 ± 6.8) and ADHD (23.3 ± 6.9) followed by the subscale hyperactivity (14.7 ± 7.3 in BPD *vs* 22.0 ± 6.1 in ADHD).

Table 2 Lifetime and Current Prevalences of Comorbidities in both Patient Groups

	Lifetime		Current	
Comorbidities	**BPD (*N* = 26)**	**ADHD (*N* = 22)**	**BPD (*N* = 26)**	**ADHD (*N* = 22)**
MDD	20	7	2	0
Anxiety disorder	17	5	11	0
Substance abuse	11	5	3	5
Eating disorder	16	4	7	3
PTSD	13	1	13	1
OCD	13	0	2	0
Individual range	0–5	0–4	0–4	0–2
Mean ± SD	3.2 ± 1.4	1.1 ± 1.2	1.6 ± 1.1	0.4 ± 0.6

Impulsivity and Aggression

Both patient groups displayed elevated self-reported trait impulsivity (BIS total), anger (STAXI), aggression (BGLHA), depression scores (BDI), childhood trauma history (CTQ), and trait dissociation (DES) compared with HCs. As compared with BPD patients, ADHD patients reported higher impulsivity in all BIS-11 facets (non-planning, motor, and attentional impulsivity). No significant differences between patient groups were found in anger (STAXI) and aggression (BGLHA) scores (Table 1).

The aggression scores BGLHA and STAXI for the whole group (controlling for BPD and ADHD) are highly correlated ($r = 0.67$; $P < 0.001$), but only STAXI is significantly correlated with the anxiety score STAI. The impulsivity score BIS-11 total also yields a significant correlation with the STAI score ($r = 0.25$; $P < 0.03$), and shows a trend but no significant correlations with neither BGLHA ($r = 0.17$; $P = 0.13$) nor STAXI ($r = 0.21$; $P = 0.06$). The BDI depression score yields significant correlations with STAXI and STAI ($r > 0.35$, $P < 0.003$) but not with BIS-11 and BGLHA ($r < 0.12$, $P > 0.3$).

MR Spectroscopy

Neither GABA nor Glu/tCr was associated with either age ($r < -0.17$; $P > 0.14$) or the voxel's gray matter content expressed as the gray matter/brain matter (GM/BM) ratio ($r < 0.07$; $P > 0.5$), whereas the GM/BM ratio significantly decreased with age ($r = -0.31$; $P = 0.006$). Thus, age and GM/BM were not used as covariates for the further group comparisons and correlations for GABA and Glu/tCr. In a general linear model, a significant group difference among HC, BPD, and ADHD was observed for GABA. Tukey's *post hoc* test yielded that ADHD patients exhibit significantly lower GABA levels than controls (Table 1). The Glu/tCr ratio was not significantly different between groups (Table 1).

GABA, Glutamate, and Impulsivity

A significant positive partial correlation was observed between the BIS-11 total score and Glu/tCr, controlling for diagnosis with two binary variables. As expected, a significant negative partial correlation between BIS-11 total score and GABA (Table 3 & Figures 2a–d) was found. Although the inclusion of the anxiety and aggression scores as potential confounders in the partial correlation with Glu/tCr did not affect the significance, the negative correlation with GABA was reduced to a trend level (Table 3).

Table 3 GABA and Glu/tCr Correlations with Behavioral Test Scores

Partial correlation controlled for ADHD and BPD, df = 74	**GABA (mM)**		**Glu/tCr**	
	R	***P*-value**	***r***	***P*-value**
BIS-11 total	***−0.25***	***0.03***	***0.32***	***0.005***
Controlled for aggression	*−0.25*	*0.08*	***0.30***	***0.01***
Controlled for anxiety	−0.18	0.12	***0.28***	***0.01***
BGLHA total	***−0.27***	***0.02***	0.10	0.39
Controlled for impulsivity	***−0.24***	***0.04***	0.10	0.41
Controlled for anxiety	***−0.23***	***0.04***	0.12	0.32
Explorative analyses				
CAARS total	***−0.33***	***0.004***	***0.41***	***<0.001***
CAARS inattention	***−0.29***	***0.01***	***0.38***	***0.001***
CAARS hyperactivity	−0.19	0.1	0.19	0.1
BSL-23 total	***−0.25***	***0.03***	0.12	0.3

Numbers in bold and italic indicate significant correlation coefficients and respective *p*-values.

GABA, Glutamate, and Aggression

A significant negative partial correlation controlling for diagnosis with two binary variables between the BGLHA aggression score and GABA, but no positive correlation with Glu/tCr was found. Neither controlling for impulsivity, nor BDI nor STAI scores in a partial correlation explained the negative correlation of BGLHA with GABA significant (Table 3).

Explorative Analysis of the BSL Score and CAARS Scores in Relation to GABA and Glutamate Levels

The BSL score assessed in our study is significantly correlated with the aggression score ($r = 0.29$, $P = 0.009$) but not the BIS-11 impulsivity score ($P = 0.25$). Accordingly, we observe a significant negative correlation of the BSL score with GABA ($r = -0.25$, $P = 0.03$). The CAARS total scores assessed in our study are highly correlated with both the BIS-11 total scores ($r = 0.59$, $P < 0.001$) and the aggression scores BGLHA and STAXI ($r > 0.35$, $P < 0.001$). It further yields significant, equally directed correlations with Glu/tCr ($r = 0.40$, $P < 0.001$) and GABA ($r = -0.27$, $P = 0.02$) as observed for the impulsivity and aggressions scores. Neither Glu/tCr ($r = 0.19$, $P = 0.09$) nor GABA ($r = -0.19$, $P = 0.10$) yielded a significant association with the subscore hyperactivity. The partial correlations with the hyperactivity score used as a control variable still yielded significant results for impulsivity and Glu/tCr ($r = -0.28$, $P = 0.01$) as well as for aggression and GABA ($r = -0.23$, $P = 0.05$).

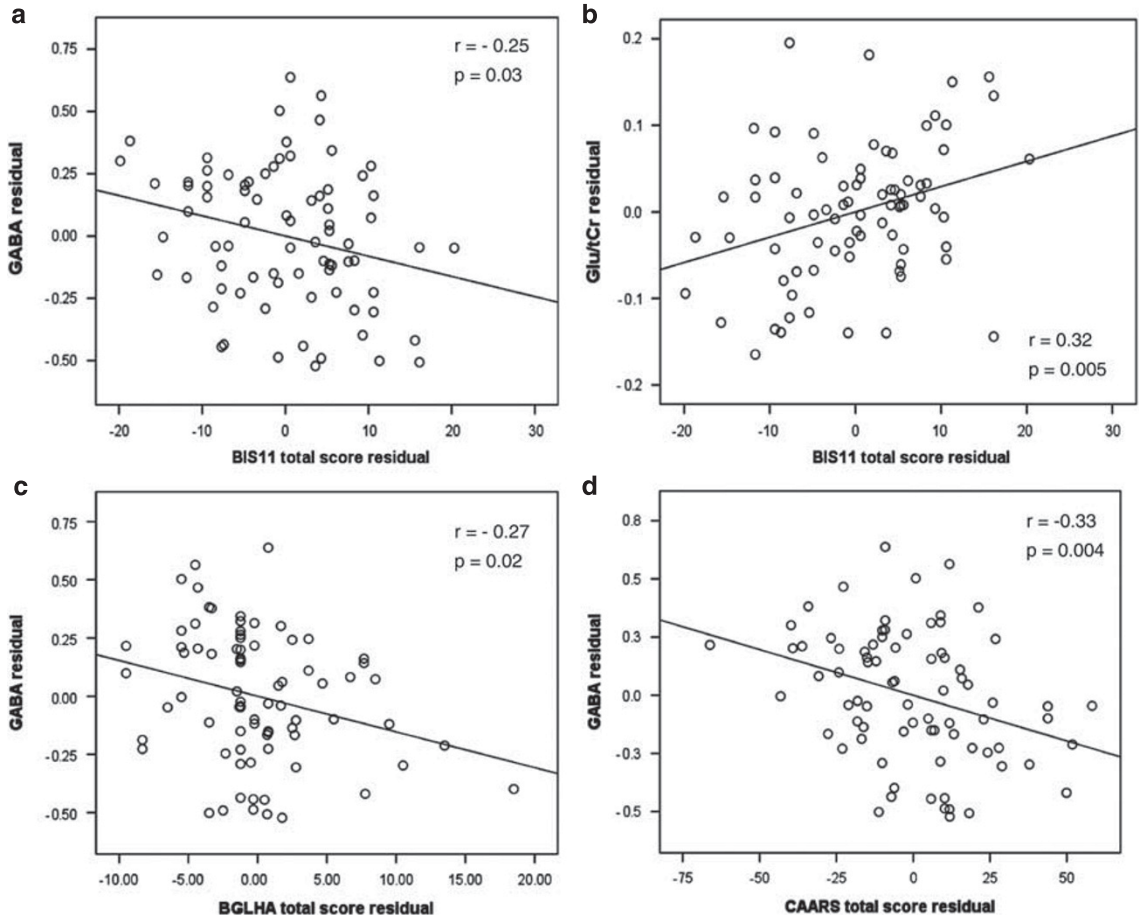

Figure 2 Scatter plot representations of the partial correlations (controlled for BPD and ADHD thus all variables expressed as residuals) of (a) GABA and the BIS-11 total impulsivity score, (b) Glu/tCr and the BIS-11 total impulsivity score; (c) GABA and the BGLHA score, and (d) GABA and the CAARS inattention score.

Group-Wise Correlation Analyses

Group-wise correlation analyses yielded for the BPD, a significant positive correlation, of Glu/tCr with BIS-11 total (BPD: $r = 0.46$, $P = 0.02$) and a negative correlation for the BPD and the HC group for the aggression score BGLHA with GABA ($r < -0.41$, $P < 0.025$) but neither correlation was significant for the ADHD group ($P > 0.7$).

The explorative correlation analyses with the CAARS subscores yielded a strong correlation for GABA with CAARS inattention for the ADHD group ($r = -0.57$, $P = 0.006$) but not the BPD group ($r = -0.07$, $P = 0.7$). For CAARS inattention but none of the other group-wise evaluations, the correlation coefficients for the two groups were significantly different in a fisher z-transformation test (Z-score = 1.84, $P = 0.03$).

DISCUSSION

This study provides evidence that in the ACC levels of Glu/tCr and GABA are related to self-reported impulsivity. We observed a positive correlation of BIS-11 scores with Glu/tCr and an inverse correlation of the BIS-11 score with GABA levels. The latter is reduced to trend level if the correlation is controlled for aggression and/or anxiety. For aggression, significant correlations were only found for GABA, which is negatively correlated with the BGLHA aggression measure.

Regarding impulsivity, anger, and aggression, we found higher scores in BPD and ADHD patients compared with HCs, which are in line with our previous studies in independent patient cohorts (Cackowski *et al*, 2014; Krause-Utz *et al*, 2013). Further, BPD and ADHD patients differed in every aspect of impulsivity, but not in anger and aggression. ADHD patients reported generally elevated impulsivity (BIS-11 total score), stronger tendencies to act without thinking (motor impulsivity), more deficits in planning and future-orientation (non-planning impulsivity), and more problems maintaining attention on a task/being more distractible (attentional impulsivity).

On the neurochemical level, we found evidence for disorder-specific GABA associations: the group of ADHD patients, but not BPD patients, exhibited lower GABA levels in the ACC in comparison with the HC group. In contrast to two previous studies in ADHD where a reduced Glu/tCr level in ADHD was found in a prefrontal voxel (Dramsdahl *et al*, 2011) and the posterior cingulate cortex (Arcos-Burgos *et al*, 2012), we did not find group differences for Glu/tCr in the ACC. As hypothesized, our previous observations of a significant positive correlation of glutamate with self-reported impulsivity in the ACC were substantiated. Furthermore, a trend for an

opposite association of impulsivity scores with GABA was observed. For the BGLHA aggression score, a negative relation was found with GABA levels. Analyzing each group separately, significant associations of Glu/tCr with impulsivity were detected in BPD patients, and of GABA with aggression in BPD and HC, but neither correlation was significant for the ADHD patient group. Whether this was a problem of insufficient group size and thus power or truly related to the distinguished disorders needs to be explored in future studies.

Finally, especially in the ADHD group, low ACC GABA was strongly associated with high inattention scores, whereas hyperactivity did neither correlate with ACC GABA nor Glu/tCr levels. Together with the significantly lower GABA level in the ADHD group compared with the HC group, which was also found in ADHD children in another brain region (Edden *et al*, 2012), this hints toward an important role of ACC GABA in attention regulation.

Our findings of positive correlations of the BIS-11 total impulsivity score with Glu/tCr and a trend for a negative correlation with GABA adds further support for the involvement of glutamatergic and GABAergic mechanisms in the expression of impulsivity (Hayes *et al*, 2014; Jupp *et al*, 2013; Murphy *et al*, 2012). In a group-wise correlation analyses, the Glu/tCr correlations hold for the BPD group. In the ADHD group, only a relation of GABA to the CAARS inattention subscale reached significance. One could speculate that the mechanisms for elevated impulsivity are distinct in BPD and ADHD patients. An interpretation of these disorder-specific associations still needs some caution given the small sample size of the ADHD group and the fact that all correlation coefficients with the exception of the CAARS inattention subscore were not found significantly different in a test using the Fisher's *z*-transformation. Furthermore, hyperactivity scores were neither associated with Glu/tCr nor with GABA levels, neither in the total group nor in the subgroups. Recently, distinct striatal regions have been implicated as possible core regions for ADHD (Ikeda *et al*, 2013) and its relation to GABA in animal models (Caprioli *et al*, 2014). If distinct neurochemical mechanisms for impulsivity and aggression can be confirmed in future studies, these mechanisms may yield important implications for more specific pharmacological treatments.

A potential limitation of this study could be that the individual groups of BPD ($n=26$) and ADHD ($n=22$) patients may not have been large enough to find all existing disorder-specific associations with impulsivity, aggression, and inattention. Some effects, especially in the ADHD group, might have stayed undetected owing to power issues. Although we excluded ADHD as comorbidity for the BPD group and vice versa, other comorbidities might have diluted disorder-specific findings. Comorbidities were somewhat less frequent in the ADHD group. Nevertheless, ADHD, as recently described by Karalunas *et al*, 2014, is not a uniform disorder but can further be divided into three subtypes by a biologically informed temperament-based typology, thus impulsivity and aggression might not be equally expressed in these three subtypes, which we did not differentiate. Furthermore, our MRS findings are not yet linked to other imaging parameters such as default mode network connectivity or task-related functional activation. The use of the Glu/tCr ratio assumes that there is no significant alteration of tCr in BPD and ADHD. In our own study of BPD patients (Hoerst *et al*, 2010) and in the study by Rusch *et al*, 2010a of BPD patients with comorbid ADHD, no ACC tCr changes have been observed. Another limitation is the lack of a control region for the MRS data that preclude statements regarding regional specificity of neurochemistry in the ACC in the behaviors measured. Future studies should combine the potential of various imaging methods to ultimately derive imaging markers for psychopathological traits such as impulsivity, aggression, and inattention, which are important for the understanding and treatment of a variety of psychiatric disorders including BPD and ADHD.

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The authors declare no conflict of interest.

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