ORIGINAL ARTICLE

Correlation of Glutamate Levels in the Anterior Cingulate Cortex With Self-reported Impulsivity in Patients With Borderline Personality Disorder and Healthy Controls

Mareen Hoerst, Dr.sc.hum; Wolfgang Weber-Fahr, Dr.rer.nat; Nuran Tunc-Skarka, Dr.sc.hum; Matthias Ruf, MA; Martin Bohus, MD; Christian Schmahl, MD; Gabriele Ende, Dr.rer.nat

Context: Dysfunction and deficits in the structure of the anterior cingulate cortex have been reported in borderline personality disorder (BPD). To our knowledge, there is only 1 published study to date investigating anterior cingulate cortex metabolism in subjects with BPD and co-occurring attention-deficit/hyperactivity disorder using proton magnetic resonance spectroscopy. Impulsivity is a key feature of BPD and can be related to anterior cingulate cortex function.

Objective: To investigate whether anterior cingulate cortex metabolism may be altered in BPD and correlates with BPD pathology.

Design: Cross-sectional proton magnetic resonance spectroscopy study.

Setting: Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, Mannheim, Germany.

Participants and Patients: Thirty unmedicated female subjects meeting *DSM-IV* criteria for BPD and 31 age-matched healthy female control participants.

Main Outcome Measures: Neurometabolite concentrations in the anterior cingulate cortex and correlation of glutamate levels with self-reported measures of impulsivity and severity of borderline symptoms.

Results: Significantly higher levels of glutamate in the anterior cingulate cortex were found in subjects with BPD as compared with healthy controls. A positive correlation between glutamate concentration and the Barratt Impulsiveness Scale total score as well as between glutamate concentration and the subscore for cognitive impulsivity were observed irrespective of diagnosis. We also found a positive correlation between glutamate concentrations and dissociation as well as between glutamate concentration and subscores of the Borderline Symptom List in the patient group.

Conclusions: Our results support the hypothesis that higher glutamate concentration in the anterior cingulate cortex is associated with both severity of BPD symptoms and subjective impulsivity ratings, the latter independent of BPD. Further studies should confirm the association between enhanced glutamate concentration in the anterior cingulate cortex and behavioral measures of impulsivity.

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Author Affiliations: Departments of Neuroimaging (Drs Hoerst, Weber-Fahr, Tunc-Skarka, and Ende and Mr Ruf) and Psychosomatic Medicine and Psychotherapy (Drs Hoerst, Bohus, and Schmahl), Central Institute of Mental Health, Mannheim, Germany.

BORDERLINE PERSONALITY disorder (BPD) is a severe, often debilitating mental disorder that affects approximately 2% of individuals in the community[1] and up to 20% of psychiatric inpatient samples.[2] In general, BPD typical behavior includes impulsivity, affective instability, and difficulty in controlling anger. These behaviors are manifestations of a core syndrome of BPD: pervasive malfunction of the affect regulation system.[2-4] Self-reported impulsivity seems to be a stable trait over time and highly predictive of BPD psychopathology over long-term follow-up.[5]

Regarding the neural underpinnings of affective dysregulation in BPD, dysfunction in the limbic and prefrontal regions has been reported in BPD.[6,7] This frontolimbic network primarily consists of the anterior cingulate cortex (ACC), orbitofrontal and dorsolateral prefrontal cortex, hippocampus, and amygdala. The ACC is involved in both cognitive and affective functions,[8] which can be associated with BPD-related symptoms, including impulsivity, cognitive distortions, and affective instability.

Many neuroimaging studies of BPD have focused on abnormalities in the ACC. Magnetic resonance imaging volumetric

studies have been inconsistent in their findings. Significant volume reductions have been reported in the right ACC,[9] but this was not confirmed in a larger sample using voxel-based morphometry.[10] Other volumetric studies have shown bilateral gray matter (GM) reductions in the ACC in patients with BPD[11] and male patients with BPD.[12] Minzenberg et al[13] have reported left lateralized reduction in the ACC in patients with BPD compared with healthy control subjects. Volumetric alterations that were correlated with impulsivity have also been reported for the left ACC in patients with BPD.[14] Fluorine 18–labeled deoxyglucose positron emission tomography studies revealed altered baseline metabolism in prefrontal regions, including the ACC.[15,16] In an ^{18}fluorodeoxyglucose positron emission tomography study using a fenfluramine challenge, impulsive-aggressive patients with BPD showed significantly less activity in the cingulate cortex.[17] Abnormal function of the ACC was reported in impulsive patients with BPD and a negative correlation with impulsivity scores was found.[18] Last, functional magnetic resonance imaging studies also showed significant activation in the ACC during recall of unresolved negative life events[19] and decreasing hemodynamics in response to negative stimuli in the right-sided ACC.[20]

Proton magnetic resonance spectroscopy (MRS) is increasingly used for brain research because it is the only method that allows a noninvasive in vivo observation of different neurometabolites such as glutamate, glutamine, phosphocreatine and creatine (total creatine [tCr]), *N*-acetylaspartate and *N*-acetyaspartylglutamate (total NAA [tNAA]), and choline-containing compounds.

The research in the field of spectroscopy in patients with BPD is young. Only a few studies have assessed neurometabolite concentrations in BPD. The first study using MRS in patients with BPD found a significant reduction of the absolute tNAA concentration in the dorsolateral prefrontal cortex.[21] Another MRS study by Tebartz van Elst et al[22] investigating the amygdala region in patients with BPD found a significant increase of tCr concentrations in the amygdala, which was positively correlated with trait anxiety. We recently found significantly reduced tNAA and tCr concentrations in the left amygdala of patients with BPD. Patients with BPD with comorbid posttraumatic stress disorder (PTSD) showed lower levels of tCr compared with patients with BPD without PTSD and healthy controls.[23] To our knowledge, there is currently only 1 published study investigating ACC metabolism in BPD using proton MRS. Rüsch et al[24] acquired spectra in the ACC region and found significantly higher tNAA and glutamate concentrations and a trend for lower glutamine levels in patients with BPD and co-occurring attention-deficit/hyperactivity disorder (ADHD), leaving open the syndromal specificity of these findings.

In summary, there is rising evidence that patients with BPD exhibit deficits in the structure and function of the ACC. Stress-associated impulsivity is a key feature of BPD and can be regarded as a form of executive dysfunction. The anterior part of the cingulate cortex has been characterized as "executive" in function, whereas the posterior region is characterized as "evaluative."[25] Therefore, the ACC was chosen as the region of interest to investigate whether its metabolism may modulate impulsivity. This study was designed to answer the following questions: Is it possible to replicate findings of higher tNAA and glutamate concentrations in the ACC of a larger sample of patients with BPD? Are glutamate concentrations in the ACC correlated with self-reported impulsivity scores or severity of borderline symptoms?

METHODS

SUBJECTS

Approval for this study was obtained from the local ethics committee. Thirty unmedicated female subjects meeting *DSM-IV* criteria for BPD and 31 healthy female control participants were recruited at the Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, Mannheim, Germany. Thirty patients (mean [SD] age, 29.33 [7.6] years) and 30 healthy controls (mean [SD] age, 28.60 [8.0] years) were included in the final analysis (see "Results" section).

Patients and healthy controls were recruited over a period of approximately 1 year. Diagnostic assessments were performed by clinically trained, experienced raters for both groups. Psychiatric diagnoses were assessed by 2 structured interviews: the German versions of the Structured Clinical Interview for *DSM-IV*[26] and the International Personality Disorder Examination.[27] The interrater reliability for the International Personality Disorder Examination was $\kappa = 0.77$. Written informed consent was obtained after thorough explanation of the study procedures. The healthy control group was assessed with the same instruments as the BPD group (German versions of the Structured Clinical Interview for *DSM-IV* and International Personality Disorder Examination). We only included right-handed participants with a currently sufficiently stable condition to undergo the magnetic resonance scanning process. Exclusion criteria were lifetime diagnosis of schizophrenia or bipolar I disorder, current drug or alcohol abuse, or current use of psychotropic medication for at least 3 months. The exclusion of current alcohol and drug abuse within 6 months prior to the study was done using the German version of the Structured Clinical Interview for *DSM-IV*.

Thirteen of the 30 patients with BPD had a lifetime diagnosis of PTSD, 11 of whom also fulfilled criteria for current PTSD. Other co-occurring axis I disorders included 18 patients with lifetime major depressive disorder; 3 with current major depression; 7 with past substance abuse; 4 with current anorexia nervosa; 4 with current bulimia nervosa; 1 with current specific phobia; 7 with current social phobia; 5 with current panic disorder; 5 with current generalized anxiety disorder; 1 with current agoraphobia; and 3 with current obsessive-compulsive disorder. Self-reported impulsivity was assessed in all participants with the Barratt Impulsiveness Scale (German version[28]), which comprises the subscales motor impulsiveness (acting without thinking), cognitive impulsiveness (cognitive speed, speed in making decisions), and nonplanning impulsiveness (lack of future-oriented problem-solving strategies). Participants also underwent the following psychometric assessments: State-Trait Anxiety Inventory,[29] Beck Depression Inventory,[30] Borderline Symptom List[31] (only in patients), and the German adaptation of the Dissociative Experience Scale[32] (*Fragebogen zu Dissoziativen Symptomen*[33]). We were able to assess the ADHD Checklist scores[34] in 20 of 30 patients. Demographic and psychometric information is summarized in **Table 1**.

Table 1. Demographic and Psychometric Characteristics of Healthy Controls and Patients With BPD

	Mean (SD) [Range]		
	Healthy Controls (n=30)	Patients With BPD (n=30)	*P* Value
Age, y	28.60 (8.0) [20-45]	29.33 (7.6) [20-45]	.72
Alcohol, g/wk	21.58 (20.9)	15.74 (30.6)	.39
Cigarette consumption, cigarettes/d	1.2 (3.2)	11.8 (13.8)	<.001[a]
BMI	22.78 (3.8)	26.99 (8.2)	.01[a]
Sex	All female	All female	
Handedness	All right	All right	
		(n=20)	
ADHD Checklist score		18.80 (5.9) [8-31]	
BDI score	2.10 (2.9)	25.17 (8.7)	<.001[a]
BIS total score	73.87 (10.1)	92.86 (8.8)	<.001[a]
BIS cognitive impulsivity subscore	25.47 (3.6)	32.11 (3.5)	<.001[a]
BIS motor impulsivity subscore	22.23 (4.6)	29.69 (5.3)	<.001[a]
BIS nonplanning impulsivity subscore	26.17 (4.6)	31.31 (3.3)	<.001[a]
BSL score		171.93 (55.5)	
FDS score	2.91 (3.4)	23.69 (12.3)	<.001[a]
STAI state score	32.80 (9.9)	58.76 (8.1)	<.001[a]
STAI trait score	30.62 (7.6)	47.90 (10.5)	<.001[a]

Abbreviations: BDI, Beck Depression Inventory; BIS, Barratt Impulsiveness Scale; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BPD, borderline personality disorder; BSL, Borderline Symptom List; FDS, German version of the Questionnaire for the Assessment for Dissociative Symptoms; STAI, State-Trait Anxiety Inventory.

[a]Statistically significant at $P<.05$.

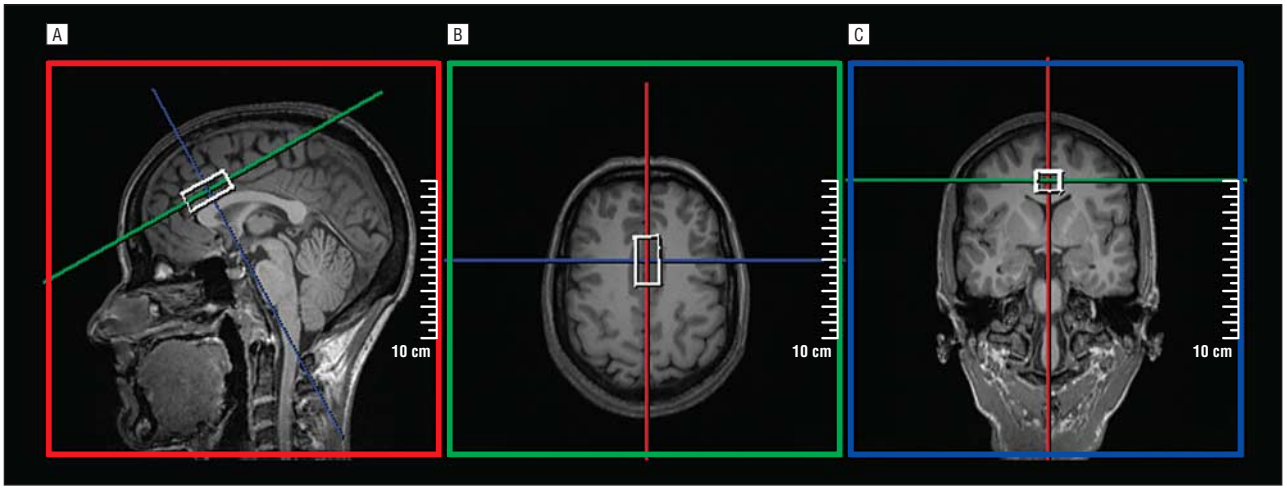

Figure 1. Position of the anterior cingulate cortex voxel in T1-weighted images. A, Sagittal. B, Transverse. C, Coronal.

MAGNETIC RESONANCE IMAGE ACQUISITION/MRS

In vivo single-voxel proton MRS was performed with a 3-T whole-body magnetic resonance scanner with a 12-channel receive-only head coil (Magnetom TIM Trio; Siemens Medical Solutions, Erlangen, Germany). We acquired a 3-dimensional magnetization prepared rapid acquisition gradient-echo imaging data set and reconstructed orthogonal coronal and transverse planes parallel and perpendicular to the long side above the corpus callosum. The placement of the ACC voxel was very well defined. Guided by the reconstructed images, we placed the single voxel ($15\times20\times12\,mm^3$) on the anterior edge of the corpus callosum and directly above it centered on the interhemispheric fissure (**Figure 1**).

Spectra were acquired with a point-resolved spectroscopy sequence using the following parameters: echo time (TE)=80 milliseconds and repetition time=3000 milliseconds. At a TE of 80 milliseconds, we obtained a good separation of glutamate from other metabolites. The spectral pattern for glutamate and glutamine at a TE of 80 milliseconds has been depicted by Schubert et al.[35] In addition, we also acquired 6 fully relaxed, unsuppressed water spectra with a repetition time of 10 seconds, 2 acquisitions, and 6 different TEs (30, 80, 200, 500, 800, and 1100 milliseconds) for eddy current correction and for extrapolating the absolute water signal at a TE of 0 millisecond. The transmitter frequency for the acquisition of water-suppressed spectra was set to the chemical shift value of the gamma methylenecyclopropene protons of the glutamate signal (–2.3 ppm relative to the water resonance) whereas spectra without water suppression were obtained with a nonshifted transmitter frequency. This ensured equally located excitation volumes for glutamate and water signals. The metabolite values were scaled with the extrapolated water signal at a TE of 0 millisecond. The water spectrum with a TE of 80 milliseconds was used for eddy current correction.

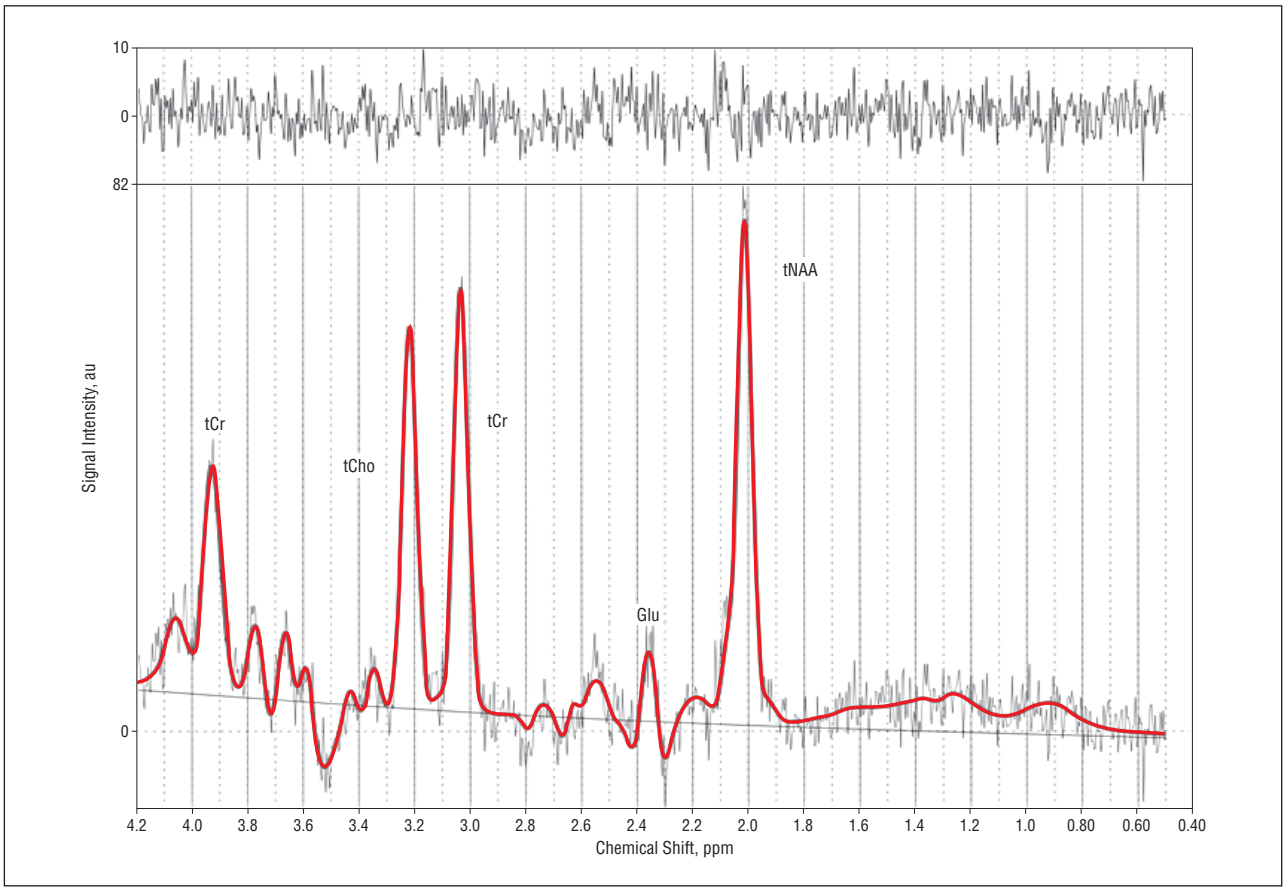

Figure 2. Representative spectra with LCModel fit of the anterior cingulate cortex voxel. Glu indicates glutamate; tCho, choline-containing compounds; tCr, phosphocreatine and creatine; tNAA, *N*-acetylaspartate and *N*-acetyaspartylglutamate.

MRS DATA PROCESSING AND ANALYSIS

The MRS data were analyzed with LCModel[36] using a GAMMA-simulated[37] basis set for a TE of 80 milliseconds. Spectral fits were accepted when the Cramér-Rao lower bounds of the fit were less than 20%.

The spectroscopic results were referenced to the extrapolated water signal at a TE of 0 millisecond and repetition time of 10 seconds. We also accounted for the different amounts of GM, white matter, and cerebrospinal fluid (CSF) in the measured voxel and their different water concentrations (GM, 45 mM; white matter, 39.4 mM)[38] by segmenting the high-resolution T1-weighted 3-dimensional images and extracting the data for the point-resolved spectroscopy sequence voxel location, which was corrected for the chemical shift displacement of each metabolite.[39] In a final step, we used literature values for each metabolite's T1[40] and T2[41] correction.

STATISTICAL ANALYSIS

Group effects on metabolite changes in the ACC were tested using a multivariate analysis of covariance with body mass index (BMI), number of cigarettes per day, and GM to brain matter (BM) ratio (GM:BM = GM/[white matter + GM]) as covariates because these variables all significantly differed between the 2 groups in a *t* test and thus may influence the results. The CSF-independent GM:BM ratio accounts for possible differences of metabolite concentrations in GM and white matter.

Partial correlation between psychometric scores and metabolite concentrations was calculated while controlling for group (healthy controls vs patients with BPD), BMI, number of cigarettes per day, and GM:BM ratio. Additionally, after splitting the groups, we repeated the partial correlation controlling for BMI, number of cigarettes, and GM:BM ratio. The significance criterion was set to $P < .05$. All data were analyzed using SPSS 15 for Windows (SPSS Inc, Chicago, Illinois).

RESULTS

Patients with BPD differed significantly from controls in all psychometric assessments (Table 1). Patients scored significantly higher in measures of anxiety (State-Trait Anxiety Inventory), depression (Beck Depression Inventory), impulsivity (Barratt Impulsiveness Scale), and dissociative symptoms (the German adaptation of the Dissociative Experience Scale).

We obtained ACC spectra of sufficient quality in 30 of 30 patients and 30 of 31 healthy controls. In these spectra, all metabolites of interest (glutamate, choline-containing compounds, tCr, and tNAA) passed the step of quality control. We used the Cramér-Rao lower bounds less than 20% as the quality criterion because this has been suggested as a rough criterion for estimates of acceptable reliability by Provencher[36] and is a standard applied by most LCModel users. As an additional criterion for good spectral quality, the mean (SD) signal to noise ratio was 16.1 (3.8) and the mean (SD) full width half maximum was 4.9 (1.2) Hz for our metabolite signals. One representative example spectrum with LCModel fit from the ACC is depicted in **Figure 2**.

Only 1 spectroscopic measurement could not be conducted because of anxiety in the scanner for 1 healthy control.

The segmentation of the ACC voxel resulted in a mean volume of 70.4% GM and 21.8% CSF in healthy controls and 73.2% GM and 18.5% CSF in patients with BPD. We found a significant group difference for the GM and CSF content of the MRS voxel between the 2 groups. The healthy control group showed significantly lower GM and higher CSF content (**Table 2**). Therefore, in addition to the CSF correction of the metabolite concentrations, the GM:BM ratio was used as a covariate in the multivariate analysis of covariance.

Table 2. Neurochemical Concentrations Using a MANCOVA and Composition of the ACC Voxel Using a *t* Test

	Mean (SD)		
	Healthy Controls (n=30)	Patients With BPD (n=30)	*P* Value
tNAA, mmol/L	9.39 (1.6)	9.69 (0.6)	.45
tCr, mmol/L	7.95 (1.3)	8.29 (0.8)	.53
tCho, mmol/L	1.88 (0.3)	1.97 (0.2)	.15
Glu, mmol/L	7.46 (0.7)	7.70 (0.7)	.03[a]
CSF, %	21.84 (3.5)	18.49 (4.9)	.003[a]
GM, %	70.37 (3.1)	73.23 (3.8)	.002[a]
WM, %	7.66 (1.9)	8.16 (2.7)	.41

Abbreviations: ACC, anterior cingulate cortex; BPD, borderline personality disorder; CSF, cerebrospinal fluid; Glu, glutamate; GM, gray matter; MANCOVA, multivariate analysis of covariance; tCho, choline-containing compounds; tCr, total creatine; tNAA, total *N*-acetylaspartate; WM, white matter.
[a] Statistically significant at $P<.05$.

The statistical analysis revealed significantly higher levels of glutamate ($P=.03$) in the ACC in patients with BPD as compared with healthy controls (Table 2). Subgrouping for current PTSD (n=11), lifetime PTSD (n=13), and lifetime depression (n=18) did not yield significant differences between these subgroups. Additionally, partial correlation analyses controlling for group, BMI, number of cigarettes per day, and GM:BM ratio demonstrated a positive correlation between glutamate concentration and the Barratt Impulsiveness Scale total score ($r=0.330$; $P=.02$) (**Table 3** and **Figure 3**) as well as between glutamate concentration and the cognitive impulsiveness subscore ($r=0.353$; $P=.009$) (Table 3 and **Figure 4**) but neither for motor impulsiveness nor for nonplanning impulsiveness.

After splitting the group, we still found significant correlations between glutamate concentration and the Barratt Impulsiveness Scale total score for both groups ($r=0.425$; $P=.03$ for the healthy controls group and $r=0.508$; $P=.009$ for the BPD group) as well as between glutamate concentration and the cognitive impulsivity subscore for both groups ($r=0.393$; $P=.04$ in the healthy controls group and a clear trend $r=0.358$; $P=.08$ in the BPD group). Additionally, we found a correlation between glutamate and motor impulsiveness ($r=0.412$; $P=.04$) in the BPD group. Other subscales of the Barratt Impulsiveness Scale (motor impulsiveness and nonplanning impulsiveness) (Table 3) did not correlate significantly.

Partial correlation analyses controlling for BMI, number of cigarettes per day, and GM:BM ratio showed no correlation between the ADHD Checklist score and the

Table 3. Partial Correlation Between Glutamate Concentration and Impulsivity Controlling for Group, BMI, Cigarettes, and GM:BM Ratio

	ACC Glu[a] Healthy Controls and BPD		ACC Glu[b] Healthy Controls		ACC Glu[b] BPD	
	r	*P* Value	*r*	*P* Value	*r*	*P* Value
ADHD Checklist score					0.316	.22
BDI score	−0.140	.31	−0.276	.16	−0.068	.75
BIS total score	0.330	.02[c]	0.425	.03[c]	0.508	.009[c]
BIS cognitive impulsivity subscore	0.353	.009[c]	0.393	.04[c]	0.358	.08
BIS motor impulsivity subscore	0.212	.12	0.235	.24	0.412	.04[c]
BIS nonplanning impulsivity subscore	0.218	.11	0.372	.06	0.355	.08
BSL total score					0.363	.06
BSL self-perception score					0.428	.03[c]
BSL affect regulation score					0.394	.04[c]
BSL autoaggression score					0.056	.78
BSL dysthymia score					0.126	.53
BSL isolation score					0.388	.046[c]
BSL intrusions score					0.479	.01[c]
BSL hostility score					0.285	.15
FDS score	0.123	.38	−0.235	.24	0.430	.03[c]
STAI state score	0.174	.21	0.150	.46	0.300	.15
STAI trait score	−0.122	.38	0.317	.11	−0.375	.07

Abbreviations: ACC, anterior cingulate cortex; BDI, Beck Depression Inventory; BIS, Barratt Impulsiveness Scale; BM, brain matter; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BPD, patients with borderline personality disorder; BSL, Borderline Symptom List; FDS, German version of the Questionnaire for the Assessment for Dissociative Symptoms; GM, gray matter; Glu, glutamate concentration; STAI, State-Trait Anxiety Inventory.
[a] Controlling for group, BMI, number of cigarettes per day, and GM:BM ratio.
[b] Controlling for BMI, number of cigarettes per day, and GM:BM ratio.
[c] Statistically significant at $P<.05$.

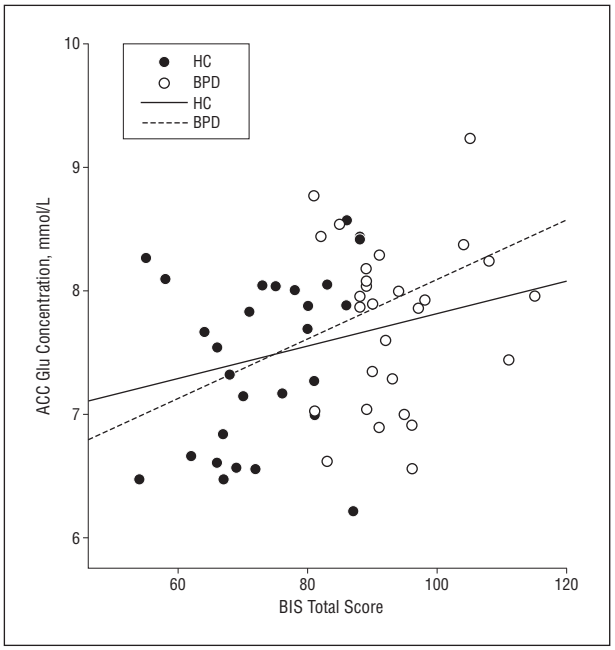

Figure 3. Scatterplot of glutamate (Glu) levels and total Barratt Impulsiveness Scale (BIS) score. ACC indicates anterior cingulate cortex; BPD, patients with borderline personality disorder; HC, healthy controls.

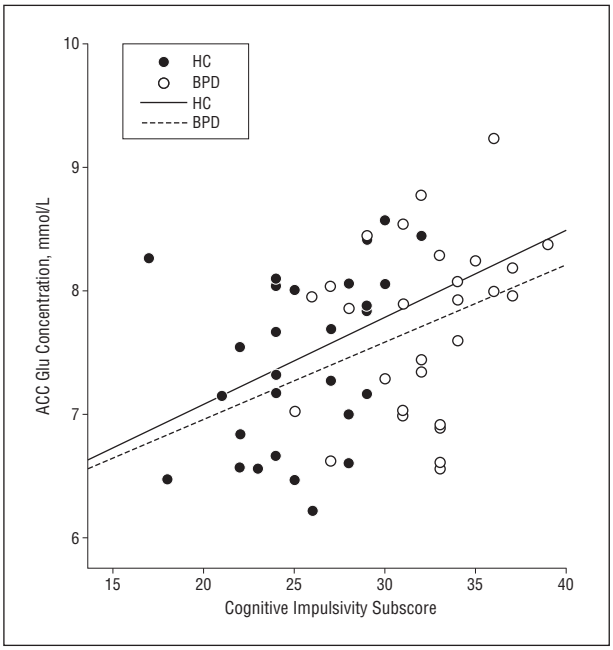

Figure 4. Scatterplot of glutamate (Glu) levels and the Barratt Impulsiveness Scale cognitive impulsivity subscore. ACC indicates anterior cingulate cortex; BPD, patients with borderline personality disorder; HC, healthy controls.

glutamate concentration (n=20; r=0.316; P=.22). We found positive correlations between glutamate concentration and subscores of the Borderline Symptom List in the patient group (self-perception, r=0.428; P=.03; affect regulation, r=0.394; P=.04; isolation, r=0.388; P=.046; intrusions, r=0.479; P=.01; and a trend for the Borderline Symptom List total score, r=0.363; P=.06) (Table 3). We also found a correlation between glutamate concentration and dissociative symptoms (r=0.430; P=.03) (Table 3 and **Figure 5**) in the BPD group. Additionally, we found a trend for a negative correlation between number of cigarettes per day and glutamate concentration (P=.09).

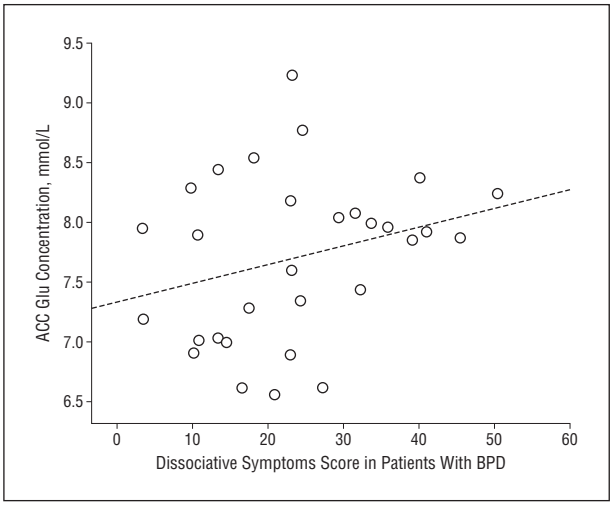

Figure 5. Scatterplot of glutamate (Glu) levels and dissociative symptoms score in patients with borderline personality disorder (BPD). ACC indicates anterior cingulate cortex.

COMMENT

This study has 2 major findings: BPD is associated with higher levels of glutamate in the ACC, and there are positive correlations between glutamate levels and self-reported measures of impulsivity and subscores of the Borderline Symptom List.

Previous studies have reported altered tNAA, tCr, and glutamate levels in BPD. In this study, we focused on glutamate and tNAA concentrations because the only previous study, to our knowledge, on the ACC found altered glutamate and tNAA concentrations,[24] and in a recent study, we found lower tNAA concentrations in the amygdala.[23] Recent studies have shown that tNAA concentration reduction can be reversible, thereby suggesting that tNAA concentration does not necessarily reflect a loss of neurons but is rather sensitive to pathological processes affecting the functioning of neurons.[42] Glutamate is the major excitatory neurotransmitter in the human brain. After release of glutamate in the synaptic cleft, it is taken up by astrocytes, where it is converted to glutamine. Glutamine then diffuses back to the presynaptic neuron and is reconverted to glutamate.[43] The ACC as our region of interest plays an important role in glutamatergic neurotransmission, shown by animal studies.[44] Bozkurt et al[44] found a high glutamate receptor density in the ACC of macaque monkeys. Abnormal levels of frontal glutamate seem to play a role in several psychiatric diseases comprising dysfunctions in motivation and drive, such as major depression,[45-48] schizophrenia,[49,50] and ADHD.[51] There is also some preliminary evidence that antiglutamatergic agents may reduce self-injurious behavior in BPD.[52] Quantification and separation of glutamate and glutamine using proton MRS is challenging. The amino acids glutamate, glutamine, and γ-aminobutyric acid do

not appear as single resonance peaks in the spectrum but as overlapping multiplets because of their similar chemical structures. Whereas Rüsch et al[24] chose a TE of 30 milliseconds, we decided to sacrifice signal to noise for a better separation of glutamate from glutamine and chose a TE of 80 milliseconds.[35]

To our knowledge, there is only 1 study investigating the ACC region in patients with BPD using MRS. Rüsch et al[24] acquired spectra in the ACC region in 14 patients with BPD with co-occurring ADHD and 18 healthy control subjects[24] and found higher levels of tNAA and glutamate in the patient group. We could replicate the finding of higher glutamate concentration in the patient group but not higher tNAA concentration. The higher tNAA concentration in the group of Rüsch et al may be due to co-occurring ADHD. In our study, only 2 of 20 patients fulfilled criteria for ADHD (ADHD Checklist score ≥25).[53] Rüsch et al argue that higher glutamate concentration is associated with ADHD. However, we could not find a correlation between glutamate concentration and ADHD scores, but a correlation between glutamate concentrations and the severity of BPD symptoms. Therefore, we assume higher glutamate concentration to be independent of ADHD but a marker for BPD. In contrast to Rüsch et al, who investigated the ventral part of the ACC, we examined a voxel comprising parts of the ventral as well the dorsal ACC.

The second main finding of our study is the positive correlation between glutamate concentration and self-reported impulsivity, particularly cognitive impulsivity. Impulsivity is a personality trait that is present in healthy people and is often increased in several psychiatric disorders. The impulsivity construct, as represented in the Barratt Impulsiveness Scale,[28] is of qualitative character. The transition in impulsivity scores between healthy subjects and patients is fluent with a broad overlap. Increased impulsivity is observed in several psychiatric disorders like impulse control disorders (pathological gambling, kleptomania), personality disorders with impulsive features (borderline, antisocial, histrionic, narcissistic), manic episodes of bipolar disorder, ADHD, neurological disorders with behavioral disinhibition, and substance abuse.[54] Impulsivity is a core characteristic of BPD and is associated with increased risks such as substance abuse or suicide attempts.[4] Patients with impulsive behavior showed abnormal ACC function and volume.[9,17,18] However, 2 recent studies on neuropsychological and behavioral disinhibition in BPD showed that unmedicated patients with BPD barely differ from healthy controls in attentional capacity and impulse control.[55,56] Both studies also revealed mildly enhanced self-reported impulsivity in patients with BPD. The discrepancy between self-reported and behavioral impulsivity measures in patients with BPD may indicate that the current emotional state moderates behavioral impulsivity in BPD.[57] Domes et al[58] state that though individuals with BPD may have higher trait impulsivity than comparison groups (as assessed with the Barratt Impulsiveness Scale), actual impulsive behavior would primarily occur only when they are experiencing significant negative affect.

Sensation seeking and impulsivity are related psychopathological constructs; however, they cannot be considered to be congruent. Current knowledge posits sensation seeking as 1 of several aspects of impulsivity[59] or even as independent constructs.[60] Therefore, the difference between our findings and those of Gallinat et al[61] may be related to differences between these 2 aspects of psychopathology.

Supporting our results, recent findings implicate a role of glutamate neurotransmission in impulsivity and impulse inhibition.[62] After injection of *N*-methyl-D-aspartate receptor antagonists, such as CPP (3-[(R)-2-carboxypiperazin-4-yl]-propyl-1-phosphonic acid), dizocilpine (MK801), and ketamine, an increase of impulsive action has been reported.[63,64] These results indicate a specific role for glutamate receptor units in impulsive action. In addition, metabotropic glutamate receptors (in particular mGluR1 and to a lesser extent mGluR5) have been shown to reduce impulsive choice.[65] By infusions of CPP into the medial prefrontal and infralimbic regions, altered glutamate neurotransmission associated with impulsive action was observed.[64,66,67]

The association of the glutamate signal and dissociation is of particular interest, since the ACC plays an important role in the mediation of dissociative symptoms.[68,69] Concordantly, *N*-methyl-D-aspartate neurotransmission has been also linked to dissociation.[70] The finding that other measures of BPD (Borderline Symptom List subscores and dissociation symptoms) also are correlated with glutamate concentration supports the assumption that glutamate metabolism in the ACC of patients with BPD is not only related to impulsivity, but also to other aspects of BPD psychopathology.

The finding of higher CSF and lower GM concentrations in the control group MRS voxel was unexpected. These measures do not correlate with any other measure assessed, especially not with the amount of alcohol consumed and BMI. These findings need to be interpreted with great caution, since our squared MRS voxel is not a volumetric measure of the ACC as a whole and the whole-brain volume was not taken into account. Most volumetric studies that found reduced volumes in patients with BPD investigated more rostral portions of the ACC.[9,12,13]

There were several limitations of this study. We could only assess ADHD score in 20 of 30 patients. We excluded patients with current drug and alcohol abuse within 6 months prior to the study using the Structured Clinical Interview for *DSM-IV*, but we did not use urine toxicology screens. We did not have a control MRS region, eg, the posterior cingulate cortex, so we cannot claim that our findings are specific to the ACC. The lack of a psychiatric control group is another limitation of the study. Furthermore, our sample was entirely female. We chose an entirely female sample because we wanted to investigate a more homogeneous subgroup of patients with BPD. Currently, to our knowledge, all other relevant MRS studies of BPD also only included females.[21,22,24] Another limitation is that this study included a large number of statistical tests that have to be corrected for multiple comparison if there is no clear a priori hypothesis. For our main hypotheses (altered tNAA, tCr, and glutamate concentrations as well as a correlation of glutamate concentration with impulsivity), it was felt that a correction for multiple comparison was not appropriate.

In conclusion, we found increased glutamate metabolism in the ACC of patients with BPD as compared with

healthy controls. An interesting new finding was the association of impulsivity with glutamate metabolism in the ACC. The impulsivity finding was independent of the presence of BPD; however, other measures of BPD (affect regulation, isolation, and intrusions) were also correlated with glutamate concentration. The hypothesis of increased glutamate levels as a marker of impulsivity should be tested in further studies in healthy persons as well as other psychiatric populations.

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Correspondence: Mareen Hoerst, Dr.sc.hum, J5, Department of Neuroimaging, Central Institute of Mental Health, 68159 Mannheim, Germany (mareen.hoerst@zi-mannheim.de) and Gabriele Ende, Dr.rer.nat, Department of Neuroimaging, Central Institute of Mental Health, 68159 Mannheim, Germany (gabi.ende@zi-mannheim.de).
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