Glutamate levels in the anterior cingulate cortex correlate with self-reported impulsivity in patients with borderline personality disorder and healthy controls

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Introduction:
Stress associated impulsivity belongs to the key features of borderline personality disorder (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" [1]. Therefore, the anterior cingulate cortex (ACC) was chosen as the region of interest for single voxel proton magnetic resonance spectroscopy (^{1}H MRS) to investigate whether its metabolism may modulate impulsivity.

Methods:
In vivo single voxel ^{1}H MRS was performed at a 3T whole body MR scanner (Siemens, Erlangen, Germany) in 30 female BPD patients and 30 group-matched healthy controls (HC). We acquired a sagittal 3D mprage data set and reconstructed the 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 (15x20x12 mm^3) on the anterior edge of the corpus callosum and directly above it centered on the interhemispheric fissure (figure 1).

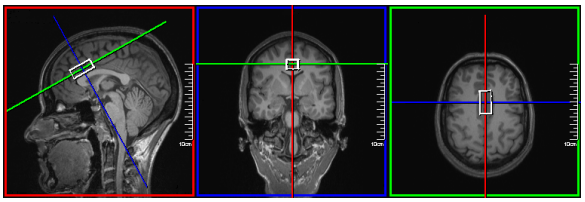

Fig. 1: Sagittal (left) und reconstructed coronal (middle) und transverse (right) images for voxel placement at the ACC

Spectra were acquired with a PRESS sequence using the following parameters: TE = 80 ms, TR = 3000 ms, BW 2400 Hz, 2048 data points and 100 averages. An echo time of 80 ms was chosen to obtain a good separation of glutamate (Glu) from other metabolites [2]. In addition, we also acquired six fully relaxed unsuppressed water spectra with TR = 10 s, two acquisitions, and six different TEs (30, 80, 200, 500, 800, 1100 ms) for eddy current correction and for extrapolating the absolute water signal at TE = 0.
To quantify the psychopathological dimensions of anxiety, depression, impulsivity, borderline symptoms, dissociation and hyperactivity all participants filled in the state-trait-anxiety-inventory (STAI), beck-depression-inventory (BDI), barratt impulsiveness scale (BIS), borderline symptom list (BSL), the questionnaire for the assessment for dissociative symptoms (FDS) and ADHD-Checklist. All participants were free of psychotropic medication. The MRS data were evaluated with LCModel [3] using a simulated basis data set for TE = 80 ms for all quantified metabolites. Spectral fits were accepted when the Cramér-Rao lower bounds (CRB) of the fit was 20 % or less. Last but not least a fully automated segmentation of the high resolution T1 weighted 3D images into grey matter (GM), white matter (WM) and cerebrospinalfluid (CSF) using SPM 2 algorithms and MATLAB 6.5 [4] was performed for each individuum to determine the composition of the spectroscopic voxel.

Results:
Spectroscopic data from the ACC region are available for 30 patients (age 29.33 ± 7.6 years) and 30 group-matched healthy controls (age 28.60 ± 8.0 years). Group effects on metabolite changes in the ACC were tested using a multivariate analysis of co-variance (MANCOVA) with BMI, number of cigarettes per day and GM to brain matter ratio as covariate because these variables all significantly differed between the two groups in a t-test and thus may influence the results. Partial correlation between psychometric scores and metabolite concentrations were calculated while controlling for group (HC vs. BPD patients), BMI, number of cigarettes per day and GM/BM ratio as covariate.
All metabolites such as total N-acetylaspartate (tNAA), total creatine (tCr), total choline (tCho), glutamate (Glu) and myo-inositol (mI) passed the quality control (CRB ≤ 20%). The main finding of this study is a significant increase of Glu in the ACC of female patients with BPD compared to healthy controls (p = 0.028). Additionally, a positive correlation between Glu concentration and the BIS total score (figure 2, left) as well as between Glu concentration and the cognitive impulsiveness sub score (figure 2, right) was observed. Additionally, we could not find a correlation between the ADHD-Checklist score and the Glu concentration (n =20 ; r = 0.316; p = 0.216). However we found positive correlations between Glu and sub cores of the BSL in the patient group (self-perception r = 0.428; p = 0.026, affectregulation r = 0.394; p = 0.042, isolation r = 0.388; p = 0.046, intrusions r = 0.479; p = 0.011 and a trend for the BSL total score r = 0.363; p = 0.062).

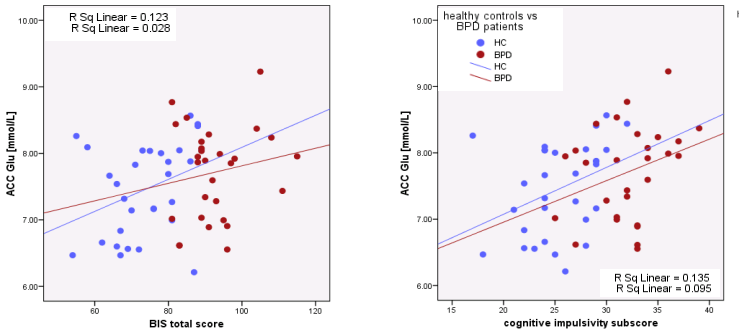

Fig.2: Scatter plot of glutamate levels with the total BIS score (left) and glutamate with cognitive impulsivity sub score (right)

Discussion:
This study has two major findings: BPD is associated with higher levels of Glu in the ACC, and there are positive correlations between glutamate levels and self-reported measures of impulsivity and sub scores of the Borderline Symptom List. There is only one study investigating the ACC region in BPD patients using MRS. Rüsch et al. acquired spectra in the ACC region in 14 BPD patients with co-occuring ADHD and 18 healthy control subjects and found higher levels of tNAA and Glu in the patients group [5]. We could replicate the finding of higher Glu in the patient group but not higher tNAA. Rüsch et al. argue that higher Glu is associated with ADHD. However we could not find a correlation between Glu and ADHD scores, but a correlation between Glu concentrations and the severity of borderline symptoms. In conclusion, our results support the hypothesis that higher glutamate in the anterior cingulate cortex is associated with borderline personality disorder scores and self-reported impulsivity, the latter independent of borderline personality disorder. Therefore, it can be speculated that increased glutamate levels in the ACC are a marker of increased impulsivity and borderline personality disorder. Studies in other psychiatric patient populations should confirm this finding.

References:
[1] Vogt BA et al. Cereb Cortex, 1992, 2, 435-443. [2] Schubert et al. Neuroimage, 2004, 21, 1762-1771 [3] Provencher SW et al. MRM, 1993, 30, 672-679 [4] Weber-Fahr W et al. Neuroimage, 2002, 16, 49-60. [5] Rüsch et al. World J Biol Psychiatry, 2008, 1-10.