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Magnetic resonance spectroscopy of the anterior cingulate cortex in eating disorders

Andreas A.B. Joos [a,*,1], Evgeniy Perlov [b,1], Martin Büchert [c], Armin Hartmann [a], Barbara Saum [a], Volkmar Glauche [e], Tobias Freyer [b], Wolfgang Weber-Fahr [d], Almut Zeeck [a,2], Ludger Tebartz van Elst [b,2]

[a] University of Freiburg, Department of Psychosomatic Medicine and Psychotherapy, Freiburg, Germany
[b] University of Freiburg, Department of Psychiatry and Psychotherapy, Freiburg, Germany
[c] University of Freiburg, Department of Diagnostic Radiology, Medical Physics, Freiburg, Germany
[d] University of Mannheim, Department of Medical Physics, Mannheim, Germany
[e] University of Freiburg, Department of Neurology, Freiburg, Germany

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ABSTRACT

The anterior cingulate cortex plays a key role in eating disorders (ED), but it remains an open question whether there are deviations of the neurochemistry of this region in patients with ED. Seventeen adult female patients with ED (10 with bulimia nervosa, 7 with anorexia nervosa) were compared to 14 matched female healthy controls using single voxel magnetic resonance spectroscopy of the anterior cingulate cortex. Group comparisons did not reveal any differences between patients and controls, but a positive correlation between glutamate and myo-inositol signals with "drive for thinness" in patients with bulimia nervosa was found in exploratory correlation analyses.

1. Introduction

In women, the lifetime prevalence of anorexia nervosa (AN) is 0.9%, and of bulimia nervosa (BN) 1.5% (Hudson et al., 2007), the core psychopathology consisting of drive for thinness (DT) and characteristic disturbances of eating behaviour. Structural imaging studies have shown cerebral atrophy in AN, including the anterior cingulate cortex (ACC) (Castro-Fornieles et al., 2009; Krieg et al., 1989; Joos et al., 2010; McCormick et al., 2008; Mühlau et al., 2007). Potential pseudoatrophic changes in BN (Krieg et al., 1989) could not be verified by a recent voxel-based morphometry investigation (Joos et al., 2010). Functional magnetic resonance imaging demonstrated increased perfusion of the ACC in both, AN and BN, when confronted with disease specific stimuli, i.e. food (Schienle et al., 2009; Uher et al., 2004). The ACC is a critical converging zone for cognitive and affective processing (Bush et al., 2000). Furthermore, the ACC is involved in processes of physiological eating behaviour (Schienle et al., 2009; Führer et al., 2008). Decreased resting perfusion of the ACC and medial prefrontal cortex was reported in AN (Takano et al., 2001). Other brain regions implicated in the pathogenesis of eating disorders (ED) concern the parietal cortex in particular (Frank et al., 2004; Uher et al., 2004; Uher et al., 2005; Castro-Fornieles et al., 2009)—the inferior part of which being essential for sensory integration of egocentric coordinates (Joos et al., 2010; Medina et al., 2009). In AN, the right amygdala has received attention (Vocks et al., 2010; Miyake et al., 2010; Seeger et al., 2002).

One tool for the non-invasive assessment of cerebral neurochemistry is magnetic resonance spectroscopy (MRS). ^{1}H-MRS studies organic molecules of a region of interest depending on the energy absorbed by hydrogen atoms by the compound and its environment (Licata and Renshaw, 2010). Very few MRS studies have been carried out in ED patients, and they exclusively concentrated on those with AN. Investigated brain areas varied greatly. Ohrmann et al. (2004) described a reduction of the combined glutamate (Glu) + glutamine (Gln) signal (i.e. Glx) in the ACC, which was attributed to depressive symptoms, however. They reported reduced levels of myo-inositol (mI) and creatine (Cr) in the dorsolateral prefrontal cortex, in addition. Castro-Fornieles et al. (2007) reported a reduction of *N*-acetyl-aspartate (NAA), Glu and mI in the medial frontal cortex in 12 adolescent AN patients.

An earlier study by Roser et al. (1999) found a decrease of lipids in frontal white matter (WM) and occipital grey matter (GM) as well as a reduction of mI in the former, while another study reported increased choline (Cho) levels in the occipital WM (Mockel et al., 1999).

In summary, MRS studies have not yet yielded a clear neurochemical pattern as a hallmark of ED. Regions of interest varied, and some studies assessed metabolite ratios and not absolute signals, which make the interpretation of putative signals difficult.

* Corresponding author. University of Freiburg, Department of Psychosomatic Medicine and Psychotherapy, Hauptstraße 8, D - 79104 Freiburg, Germany. Tel.: +49 761 270 6928; fax: +49 761 270 6885.
E-mail address: andreas.joos@uniklinik-freiburg.de (A.A.B. Joos).
[1] These authors contributed equally to this work.
[2] These senior authors contributed equally.

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Given this background, this study investigated the neurochemistry of the ACC, which is a critical region in ED. In addition to investigating restrictive AN (AN-R) patients, this is the first report to include a well defined sample of BN patients. The study aimed to examine commonalities of neurochemical deviations in ED patients, as these patients share core psychopathological features such as DT, and it also focused on subgroup differences, which are to be expected as AN is characterized by malnourishment, whereas BN by definition is not.

Based on previous results we hypothesized Glx, mI and NAA concentrations to be reduced in the ACC, in particular in AN-R.

As a second aim, we carried out an exploratory analysis to test for associations between neurochemical substrates of the ACC and core eating disorder psychopathology, i.e. DT and bulimia (Pike and Mizushima, 2005; Hartmann et al., 2009; Penas-Lledo et al., 2009). This latter part of the study was not hypothesis-driven, as it is the first of its kind.

2. Methods

2.1. Participants

MRS data of 17 female patients with ED (10 with BN, 7 with AN-R), recruited at the Department of Psychosomatic Medicine and Psychotherapy, University of Freiburg, were studied. Inclusion criteria were a diagnosis of AN-R or BN according to DSM IV, on the basis of a clinical interview by a senior board-certified psychiatrist, duration of illness of at least 1 year, and an age of 18 or more. Exclusion criteria were metallic implants, psychosis, severe medical illness, claustrophobia, neurological disease and neuroleptic exposure, i.e. antipsychotic medication. Fourteen MRS datasets of age-matched healthy female subjects, who had been screened for abnormal eating habits and neuropsychiatric disease, were used as controls.

Two additional MRS datasets of ED patients and two sets of healthy controls had to be omitted due to strong metabolite deviations, as explained in Section 2.3. All behavioural and spectroscopic data reported here refer to the remaining complete datasets of 17 ED patients and 14 controls.

Current body mass indices (BMIs) were calculated and the following questionnaires used in order to assess psychopathology: The Eating Disorder Inventory (EDI-2), a widely used self-report questionnaire, scale 1 covering DT and scale 2 covering bulimic symptoms and cognitions (Garner, 1991), and the Beck Depression Inventory (BDI) (Beck et al., 1995). In order to estimate crystalline verbal intelligence, the multiple choice verbal comprehension test (MWT-B), a 37-item list, each item containing five words (four nonsense, one correct), was used (Merz et al., 1975); a raw value of 21–30 corresponds to an intelligence quotient of 91–109 (Lehrl, 1995). After complete description of the study to the subjects, a written informed consent was obtained. The study was approved by the University of Freiburg Ethical Committee.

2.2. MRI data acquisition

The MRI and proton MRS data were obtained at the Department of Radiology at the University of Freiburg on a 3 T whole-body system (TRIO, Siemens Erlangen, Germany) using an eight-channel head coil. For image-guided voxel positioning, first a T1-weighted 3D MPRAGE (Magnetization Prepared Rapid Acquisition Gradient-Echo Imaging) data set was acquired with the following parameters: TR = 2200 ms, TE = 4.91 ms, TI = 1000 ms, flip angle = 12°, matrix 512 × 512 pixels, 160 slices at 1 mm, and FOV = 256 × 256 cm^2.

A cubic voxel (dimension 20 × 20 × 20 mm^3) was placed angulated parallel to the transverse images midline and anterior to the corpus callosum to cover the left and right ACC (Fig. 1).

We used a standard PRESS (point-resolved spectroscopy) sequence with the following parameters: TE = 30 ms, TR = 3000 ms. Ninety-six averages were acquired within 4.8 min. Non-water-suppressed scans with identical parameters except TR = 10,000 ms and number of averages = 16 were subsequently acquired. This reference spectrum was used for eddy current correction and absolute quantification using the fully relaxed water signal as internal reference.

2.3. Spectroscopic analysis

Segmentation of the high resolution anatomical 3D dataset was done with SPM5 using the well-validated 'unified segmentation' of brain tissue in GM, WM and cerebrospinal fluid (CSF) (Ashburner and Friston, 2005). Coordinates of the location of each voxel were transferred from each spectroscopic dataset to the corresponding individual anatomical image. Then, inside each spectroscopic voxel,

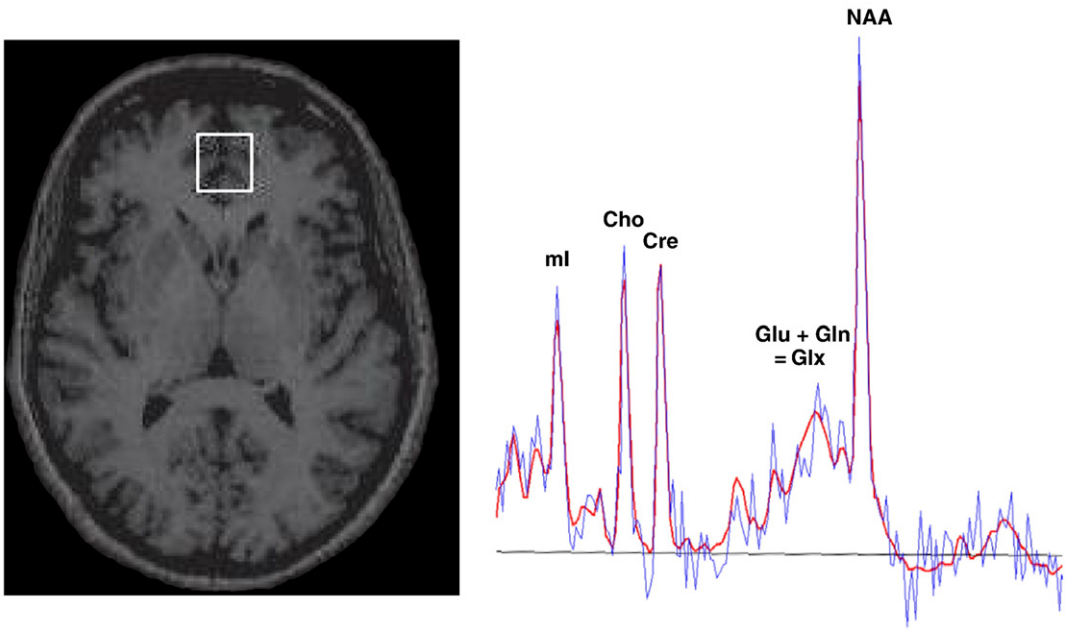

Fig. 1. Voxel localization in the anterior cingulate cortex and typical spectra obtained. NAA, *N*-acetyl-aspartate; mI, myo-inositol; Cre, creatine; Glu, glutamate; Gln, glutamine; Glx, glutamate and glutamine; Cho, choline compounds.