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^{1}H-MR spectroscopy in ultra-high risk and first episode stages of schizophrenia

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ABSTRACT

Using proton magnetic resonance spectroscopy biochemical characteristics in early stages of schizophrenia were examined. N-acetylaspartate, choline and creatine were measured in hippocampus, anterior cingulate gyrus (ACC) and medial prefrontal cortex (mPFC) of 24 first episode and 30 ultra-high risk patients. Careful LCModel analyses revealed no differences between the patient groups and 31 healthy controls, casting doubt upon the idea of metabolic changes in early stages of psychosis.

1. Introduction

Schizophrenia is a debilitating psychiatric disease with a prevalence of about 1%; thus, better comprehension of its pathophysiology is necessary. The neurodevelopmental hypothesis of schizophrenia supports the idea that the evolution of schizophrenia might partly be due to disturbances in early individual development (Falkai et al., 2001). These defects might result in symptoms of schizophrenia after maturation of the brain (Weinberger, 1987). Longer duration of untreated psychosis or prodromal stages is suggested as a predictor of poor outcome in schizophrenia (Bottlender et al., 2003). In order to use the full potential of treatment it is necessary to develop sufficient methods for early detection and diagnosis of prodromal or ultra-high risk (UHR) states and full-blown schizophrenia. Neuroimaging of UHR subjects is still at the beginning. First studies explored structural as well as functional deficits in UHR stages of schizophrenia. Pantelis et al. (2003) found smaller gray matter volumes in the frontal and temporal lobes in those UHR patients, who converted to schizophrenia compared to non-converters. In a structural MRI study, Phillips et al. (2002) found no difference of left hippocampal volume in high-risk subjects who developed psychosis compared to a healthy control group. In another fMRI study, smaller differential activation between task-relevant and task-irrelevant stimuli in various brain regions in high-risk individuals compared to healthy controls was found (Morey et al., 2005). Related to the neurodevelopmental model of schizophrenia the meaning of these initial findings in UHR subjects is still unclear. Further information about abnormalities in UHR stages of schizophrenia may derive from proton magnetic resonance spectroscopy (^{1}H-MRS) which is an established method to examine brain neurochemistry in vivo. The metabolite most frequently detected with ^{1}H-MRS is the amino acid N-acetylaspartate (NAA). NAA has been described as a marker of neuronal density and viability, although its exact function is still unclear (Tsai and Coyle, 1995). Another essential metabolite is choline which arises from cell membrane phospholipids, marks cellular density and membrane turnover (Han and Gross, 1991). NAA and choline (Cho) can be measured using ^{1}H-MRS (Ross and Bluml, 2001). If this procedure is employed, the quite constant neuronal constituent creatine (Cr), representing the energy metabolism of the cell, serves as a standard for comparison. Brain metabolites have already been examined in several studies. In a review by Steen et al. (2005) it was summarized that most studies provided evidence for reduced NAA in the hippocampus and the frontal lobe of schizophrenic patients.

However, ^{1}H-MRS studies in UHR subjects have been limited due to inconsistent findings. Wood et al. (2003) found elevated

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NAA/Cr and Cho/Cr ratios in the dorsolateral prefrontal cortex of UHR individuals, while Jessen et al. (2006) observed reduced NAA/Cr and NAA/Cho ratios in the left frontal lobe and reduced NAA/Cr in the anterior cingulate cortex in at-risk subjects and schizophrenic patients. Wood et al. (2003) concluded that a decrease of Cr causes the increase of NAA/Cr and reflects hypometabolism in the frontal lobe prior to the onset of psychosis. Jessen et al. (2006) speculated that the reduction of NAA/Cr in the left frontal lobe and the anterior cingulate gyrus represent a vulnerability indicator for schizophrenia in at-risk individuals while elevated choline in the anterior cingulate gyrus may be a predictor for conversion to schizophrenia. An interpretation of these findings still requires exploration of brain metabolites in early stages of schizophrenia.

In this study, we investigated the metabolic ratios of NAA/Cr and Cho/Cr in the anterior cingulate cortex (ACC), the left hippocampus (Hip), and the medial prefrontal cortex (mPFC) in subjects with an ultra-high risk of developing schizophrenia and in first episode schizophrenics compared to healthy controls. These brain regions were chosen because of the reported structural and functional alterations in high-risk and schizophrenic patients in these areas (Yucel et al., 2003; Pantelis et al., 2003). It was hypothesized that changes of neuronal metabolism can not only be found in first episode patients with schizophrenia, but in UHR subjects, as well.

2. Methods

2.1. Subjects

The investigation was performed according to the Declaration of Helsinki. After the study had been approved by the ethics committee of Charité, University Medicine Berlin, a total of 85 people were included: 30 (19 male) were UHR subjects, and 24 (17 male) were suffering from their first episode of schizophrenia. 31 (16 male) healthy participants served as controls. UHR patients were regarded as such if self-limiting psychotic symptoms were present for less than one week (brief limited intermittent psychotic symptoms, BLIPS), if attenuated psychotic symptoms (APS) occurred as assessed with the Structured Interview for Prodromal States and the Scale of Prodromal Symptoms (SIPS/SOPS) (Miller et al., 1999), or if there were cognitive basic symptoms with a relevant rating in the Bonn Scale for the Assessment of Basic Symptoms (BSABS-P) (Klosterkotter et al., 2001), or if there was evidence for genetic risk combined with worsening of social functioning (Witthaus et al., 2009). UHR patients suffering from any severe neurological or psychiatric comorbidity or substance abuse except nicotine were excluded from participation. Within 9 months after MRI scan, two of the 30 UHR patients made transition to schizophrenic psychosis. The others were relatively stable due to the committed work in the Early Recognition Center.

First episode patients met DSM-IV criteria for schizophrenia and had not experienced an episode with psychotic symptoms longer than one week before the current episode which itself did not last longer than one year by the time of examination. Both, the UHR subjects and the first episode schizophrenic patients were classified using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Interviews were performed by experienced clinical psychiatrists, diagnostic decisions were based on clinical symptomatology and the Structured Clinical Interview for DSM-IV disorders (SCID I + II; First et al., 1996). Exclusion criteria comprised history of substance abuse, except nicotine, history of clinically significant neurological or co-morbid psychiatric illnesses or abnormalities in MRI examination. Control subjects were recruited via advertisements on local notice-boards and from hospital staff. A standardized demographical interview as well as Mini-SCID was performed in order to rule out exclusion criteria. Healthy volunteers with a personal or family history of psychiatric illness were excluded. All participants gave written informed consent. Demographic and clinical data of the participants are provided in Table 1.

2.2. Magnetic resonance spectroscopy

Magnetic Resonance Spectroscopy was carried out on a 1.5 T Scanner (Siemens, Erlangen, Germany) using a standard head coil. Volumes of interest (8 ml each) were defined in the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (PFC), and left hippocampus (LHIPP) (see Fig. 1). Axial, sagittal and coronal T2 weighted localizing sequences were acquired. Single voxel ^{1}H-MRS (PRESS, TR = 1500 ms, TE = 140 ms, flip angle 90°, vector size 1024, frequency 1000 Hz, averages 200) was performed in these areas after positioning in a standardized procedure: ACC voxel - midsagittal superior to the anterior border of the corpus callosum, PFC voxel - midsagittal voxel anterior to the corpus callosum, hippocampal voxel comprising the left hippocampal head with the voxel being tilted along the hippocampal axis.

Spectra were analyzed using LCModel with the respective metabolite basis set for PRESS and TE at 140 ms (Provencher, 1993). Further statistical analysis was done on the LCModel estimate of the Cho/Cr and the NAA/Cr ratios. For the NAA/Cr ratio, we used the sum of NAA and NAAG (N-Acetylaspartate-Glutamate), as the NAAG signal is localized in the shoulder of the NAA peak and often cannot be separated from the NAA peak. We still refer to the NAA + NAAG/Cr as the NAA/Cr ratio in the following text.

Only spectra fulfilling the following quality criteria were used for further analysis: Full width at half maximum (FWHM) < 0.1 ppm, Signal-to-Noise Ratio (SNR) > 5, Cramer-Rao-Lower-Bounds (CLRB) < 5.

2.3. Statistical analysis

Demographic data were compared using χ^2-test, ANOVA, and *t*-tests. Differences in metabolic ratios between the 3 groups were analyzed with a one-way ANOVA. The level of significance was set at $p < 0.05$, a statistical trend at $p < 0.10$.

3. Results

Details of demographic data and PANSS Score are presented in Table 1. Table 2 shows a quality parameter summary for the

Table 1
Demographic data (mean ± std).

	Controls	Ultra-high risk	First episode SZ
N	31	30	24
Age in years (range)	25.5 ± 5.2 (18–33)	25.6 ± 4.5 (18–35)	26 ± 6.3 (18–38)
Gender (m/f)	16/15	19/11	17/7
Primary/secondary education (years)	12.4 ± 1.5	11.7 ± 1.7	11.0 ± 1.6
Ethnicity	All Caucasian	All Caucasian	21 Caucasian, 2 Asian, 1 African
PANSS pos score	–	11.9 ± 3.4	19.5 ± 5.1
PANSS neg score	–	13.6 ± 5.2	17.5 ± 5.0
Medication		Risperidone (*N* = 2) Olanzapine (*N* = 1) Promethazine (*N* = 1) Paroxetine (*N* = 1)	Risperidone (*N* = 3) Amisulpride (*N* = 1)
Duration of psychosis (1st episode SZ) or first symptoms (UHR)		35.2 ± 25.2 months	16.2 ± 19.0 months