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Proton magnetic resonance spectroscopy in subjects at risk for schizophrenia

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Abstract

We used proton magnetic resonance spectroscopy (^{1}H MRS) to examine biochemical characteristics of the brain tissue in subjects at risk for schizophrenia. Nineteen participants fulfilling research criteria for an early ($n=10$) or a late ($n=9$) at-risk syndrome, 21 patients with full disease according to DSM IV and 31 healthy control subjects were included in the study. Single-voxel ^{1}H MRS was performed in the left frontal lobe, the anterior cingulate gyrus and the left superior temporal lobe. Subjects were followed longitudinally to detect conversion to schizophrenia. We observed a significant reduction of the metabolic ratios NAA/Cr and NAA/Cho in the left frontal lobe and of NAA/Cr in the anterior cingulate gyrus in both at-risk groups and in the schizophrenic patients compared with healthy controls. Those at-risk subjects, who converted to schizophrenia within the observation period, had a higher Cho/Cr and a lower NAA/Cho ratio in the anterior cingulate gyrus compared with non-converters. NAA/Cr did not differ between converters and non-converters. Six at-risk subjects were taking antidepressants, two were taking antipsychotics. There was no difference in any metabolic ratio in any region between at-risk subjects with and without medication. We conclude that the reduction of the neuronal marker NAA in the left prefrontal lobe and the anterior cingulate gyrus may represent a vulnerability indicator for schizophrenia in at-risk subjects, while elevated Cho in the anterior cingulate gyrus may be a predictor for conversion from the prodromal state to the full disease.

Keywords: Schizophrenia; Prodrome; Frontal lobe; Anterior cingulate gyrus; Superior temporal gyrus; *N*-acetylaspartate; Choline

1. Introduction

The definition of vulnerability indicators for schizophrenia is essential for understanding the course of the disease and for creating prevention programs. Clinical at-risk syndromes include positive and negative symptoms (Klosterkotter et al., 2001), as

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well as impairment of various cognitive domains (Brewer et al., 2005; Hawkins et al., 2004; Wood et al., 2003a). However, the biological underpinnings of at-risk syndromes are only poorly understood. With structural MRI, Phillips et al. (2002) found no difference of hippocampal volume in at-risk subjects compared to healthy controls. Yucel et al. (2003) observed that significantly fewer subjects in a high-risk group had a well developed paracingulate sulcus and significantly more had an interrupted left cingulate sulcus compared with controls. This finding did not differ in frequency between subjects, who converted to schizophrenia compared to non-converters. Pantelis et al. (2003) reported smaller gray matter volumes in the right medial and lateral temporal lobe, inferior frontal lobe and in the bilateral cingulate gyrus in at-risk subjects, who converted, compared with non-converters. Wood et al. (2005) found smaller left hippocampal volumes in high-risk subjects without a family history of schizophrenia as compared with high-risk subjects with a positive family history. In a recent comprehensive review of structural MRI findings in at-risk subjects and first episode patients, Pantelis et al. (2005) concluded that early (pre- and perinatal) and late (postpubertal) neurodevelopmental lesions together interact with external factors around the onset of psychosis in a very active process of brain change, particularly in frontal and medial temporal regions.

Recently, functional brain imaging studies were performed in at-risk subjects. In an fMRI study, Morey et al. (2005) reported smaller differential activation between task relevant and task-irrelevant stimuli in the anterior cingulate gyrus, the inferior frontal gyrus and the middle frontal gyrus in high-risk subjects compared with a control group in a continuous visual oddball task. Using ^{18}F-altanserin as a positron emission tomography (PET) ligand, Hurlemann et al. (2005) found a reduction of the 5-HT2A receptor in the prefrontal cortex in high-risk subjects compared with controls.

Proton magnetic resonance spectroscopy (^{1}H MRS) is a widely established MR-technique for the quantification of various biochemical tissue compounds in vivo, and contributes unique information, independent of other neuroimaging modalities. The most prominent molecule detected with ^{1}H MRS is the amino acid *N*-acetylaspartate (NAA). Even though the exact function of NAA in brain metabolism is unclear, it is a generally accepted marker for neuronal density and function. In a recent review of 64 studies, Steen et al. (2005) concluded that a reduction of NAA in the frontal lobe, but also in other brain areas is a consistent finding in schizophrenia. The second molecule group, which can be measured with ^{1}H MRS, is the choline containing compounds (Cho). Since the Cho signal is primarily composed of cell membrane phospholipids, an increased Cho is interpreted as evidence for increased membrane turnover. An increase of Cho has been observed in schizophrenia repeatedly (e.g. Bustillo et al., 2002a; O'Neill et al., 2004). The third resonance, which can be detected with long echo times, is the creatine and phosphocreatine signal (Cr). Cr represents components of the cell's energy metabolism.

In one published ^{1}H MRS study, which compared at-risk subjects with healthy controls, no change of NAA, but an increase of the metabolic ratios NAA/Cr and Cho/Cr was observed and interpreted as evidence for a decrease of Cr suggesting hypometabolism. There was no difference between converters and non-converters (Wood et al., 2003b).

In our study, we used ^{1}H MRS to examine the left frontal lobe, the anterior cingulate gyrus and the left superior temporal lobe in at-risk subjects, patients with schizophrenia and healthy controls. The rationale to choose these regions was the reported structural and functional changes in schizophrenic patients and at-risk subjects in the frontal lobe and the anterior cingulate gyrus. The superior temporal gyrus was included, because post-mortem and MRI studies have found evidence for schizophrenia related structural alterations in this region (Falkai et al., 1995; Park et al., 2004).

The present work was conducted as part of the early recognition program of the German Research Network on Schizophrenia (GRNS) (Hafner et al., 2004). In this project an early and a late at-risk syndrome are defined, of which the definitions are given below. Subjects of both groups were included in the study.

2. Methods

2.1. Subjects

The exact recruitment procedure of subjects with either an early or a late at-risk state in the GNRS is described in detail elsewhere (Hafner et al., 2004). In brief, subjects with suggestive complaints were screened by general practitioners, counseling services or others with a 17-item checklist (ERIraos Checklist, Early Recognition Inventory/Interview for the Retrospective Assessment of the Onset of Schizophrenia) (Hafner et al., 2004), which was created for this