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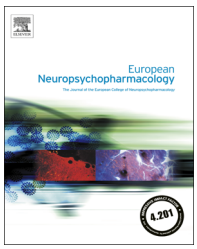

Associations of hippocampal metabolism and regional brain grey matter in neuroleptic-naïve ultra-high-risk subjects and first-episode schizophrenia

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Abstract
Hippocampal pathology has been shown to be central to the pathophysiology of schizophrenia and a putative risk marker for developing psychosis. We applied both ^{1}H MRS (proton magnetic resonance spectroscopy) at 3 Tesla and voxel-based morphometry (VBM) of high-resolution brain structural images in order to study the association of the metabolites glutamate (Glu) and N-acetyl-aspartate (NAA) in the hippocampus with whole-brain morphometry in 31 persons at ultra-high-risk for psychosis (UHR), 18 first-episode schizophrenia patients (Sz), and 42 healthy controls (all subjects being neuroleptic-naïve). Significantly diverging associations emerged for UHR subjects hippocampal glutamate showed positive correlation with the left superior frontal cortex, not seen in Sz or controls, while in first-episode schizophrenia patients a negative correlation was significant between glutamate and a left prefrontal area. For NAA, we observed different associations for left prefrontal and caudate clusters bilaterally for both high-risk and first-episode schizophrenia subjects, diverging from the pattern seen in healthy subjects. Our

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results suggest that associations of hippocampal metabolites in key areas of schizophrenia might vary due to liability to or onset of the disorder.

1. Introduction

The high-risk state for psychosis has become a major paradigm in schizophrenia research that is relevant for both early clinical intervention as well as the study of the biological basis of schizophrenia (Fusar-Poli et al., 2013). Subjects at ultra-high risk (UHR) of developing psychosis show a number of cognitive as well as brain structural and functional changes similar to those seen in schizophrenia (Cooper et al., 2014; Fusar-Poli, 2012; Palaniyappan et al., 2012). These alterations reflect, to differing extent, the contribution of genetic risk or liability, changes seen in the prodrome, and changes at the onset of schizophrenia (Jung et al., 2012).

The hippocampus has been of particular interest for UHR studies, since it is central to the pathophysiology of schizophrenia, especially in the context of glutamatergic dysfunction (Tamminga et al., 2012). Structural changes of the hippocampus have been demonstrated with magnetic resonance imaging (MRI) in both first-episode and chronic populations (Adriano et al., 2012), and multi-modal imaging has revealed multiple abnormal hippocampal markers in UHR subjects (Wood et al., 2010).

Magnetic resonance spectroscopy (MRS) has increasingly been used to assess metabolic changes in UHR subjects and during transition to psychosis, as it provides additional information about specific metabolites, such as glutamate (Glu), or markers of neuronal integrity, such as N-Acetyl-aspartate (NAA). There is some evidence that NAA is decreased in the hippocampus in schizophrenia (Steen et al., 2005), although there have been conflicting results (He et al., 2012), and the influence of several aspects, like chronicity of disease or medication, needs further evaluation. However, the pathophysiological process accompanying changes of Glu and/or NAA in the hippocampus in emerging psychosis might not only include changes in the level of these metabolites, but more importantly also changes in their effects on functional parameters and connectivity with other key regions of schizophrenia pathophysiology, and/or on remote neural network. This has been suggested by a number of recent studies that combined MRS with other structural and/or functional imaging techniques. Kraguljac and colleagues reported that the association between NAA and Glu concentrations in the hippocampus (as seen in healthy controls) was lost in a large sample of schizophrenia patients, indicating a decoupling of these physiologically interrelated metabolites (Kraguljac et al., 2012). In a subsequent study, the same group also identified a correlation between NAA and combined glutamate and glutamine markers with hippocampal volume in unmedicated Sz patients (Kraguljac et al., 2013). Abnormal levels of hippocampal metabolites, however, also appear to influence remote areas, as seen in diverging correlation patterns between hippocampal NAA and prefrontal activation measured with functional MRI (Hutcheson et al., 2012).

In UHR subjects with at-risk mental state (ARMS), a series of recent studies has suggested that hippocampal glutamate changes might lead to a number of structural and functional changes in interconnected networks (Egerton et al., 2012). Hippocampal glutamate was correlated with striatal [18F]-DOPA uptake, an indicator of striatal dopamine turnover, and a putative indicator of transition to psychosis (Stone et al., 2010). Also, the physiological association between hippocampal glutamate and medial temporal brain activation seen in healthy subjects was lost in UHR subjects with ARMS status (Valli et al., 2011). Currently, it is unclear whether the loss of such associations (studied as correlations between two structural/functional markers) is related to liability or to transitional processes towards the onset of psychosis.

Against the background of these findings, we investigated the relation between the metabolic markers glutamate and NAA in the hippocampus with brain structure (i.e. morphometry) for three different groups: UHR subjects identified in an early psychosis programme, patients with first-episode schizophrenia, and healthy controls. We tested the hypothesis that correlations between hippocampal Glu and/or NAA with other key brain regions implicated in previous studies, i.e. the lateral prefrontal cortex, anterior cingulate cortex, thalamus, and the hippocampus itself, would show a group effect indicating that associations are different depending on risk vs. actual onset of schizophrenia. In order to avoid confounding effects of medication, which have been shown in previous MRS studies on Glu (Poels et al., 2014), we only included subjects who were neuroleptic-naïve, i.e. had never been treated with antipsychotics.

2. Experimental procedures

2.1. Subjects

We included in this study a total of 91 subjects: 31 persons at ultra-high-risk (UHR) of developing psychosis, 18 patients with first-onset schizophrenia (Sz), and 42 healthy control subjects. Demographic details are given in Table 1. Groups did not differ in age (ANOVA: $F=0.211$; $p=0.81$) or gender composition (Chi-square-test: $p=0.525$). All study participants provided written informed consent to a study protocol, which had been approved by the Ethics Committee of Jena University Medical School and was in accordance with the Declaration of Helsinki. This is a sub-sample of a cohort used in a previous study of brain structure in UHR and first-episode schizophrenia patients, which focused on different UHR subgroups (Nenadic et al., 2015).

Clinical assessment of UHR subjects included a Comprehensive Assessment of At-Risk Mental Status exam (CAARMS), administered by a trained rater of the department's early psychosis intervention unit. Sz patients met DSM-IV-TR criteria for schizophrenia. Clinical