Interaction of hippocampal volume and N-acetylaspartate concentration deficits in schizophrenia: A combined MRI and 1H-MRS study at 3 T

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Introduction

In the hippocampus of schizophrenic patients, volume deficits [1] assessed with magnetic resonance imaging (MRI) and neurochemical dysfunctions [2] diagnosed using proton MR spectroscopic measurement of N-acetylaspartate (NAA) are robust and reliable observations. NAA is an important cerebral amino acid derivative involved in the synthesis pathways of glutamate [3], which in turn has been implicated as a pathobiological substrate of schizophrenic symptomatology and associated with histological alterations and brain volume deficits in schizophrenia [4]. However, the possible interaction between regional NAA reduction and local volume deficits has been scarcely targeted in previous investigations. We used single voxel ^{1}H-MRS at 3 Tesla to measure absolute NAA concentrations and, as a gold standard of CNS volumetry, a validated delineation protocol for the hippocampus [5] to study this interaction.

Subjects and Methods

In 29 schizophrenic patients and 44 control subjects, a multimodal imaging study with ^{1}H-MRS and MRI volumetry of the left hippocampus was performed. All subjects gave written informed consent. MR examinations were performed on a 3T-scanner (MEDSPEC 30/100, Bruker Medical) using a birdcage coil. Following T_1-weighted imaging of the whole brain at a resolution of 1 x 1 x 1.5 mm^3, proton spectra were acquired using PRESS (T_E = 80 ms, T_R = 3 s, n = 128) from a voxel of 2 x 3 x 2 cm^3 including the left hippocampus (HC). For metabolite quantitation a time domain-frequency domain method [6] was employed involving automatic retrospective frequency and phase drift correction, non-parametric background estimation, and uncertainty assessment using a Bayesian approach that accounts for background fit uncertainty [7]. A measured metabolite basis set and prior knowledge for frequency, linewidth and phase were used in the fitting. For quantitation an external water phantom was used; fitted amplitudes were corrected for effects of T_2 of NAA (determined in HC of 3 volunteers as 267 ms), coil loading differences, and cerebrospinal fluid content of the voxels (obtained from segmentation using SPM2).

Results and Discussion

The mean uncertainty for the determination of NAA amounted to 2.7 %. The mean total brain volume was the same in patients and controls (in cm^3: 1505 ± 119 vs. 1508 ± 135). Compared to the control group, the hippocampus of the patients exhibited a significantly smaller volume (in mm^3: 2752 ± 405 vs. 2986 ± 319, left; 2877 ± 408 vs. 3163 ± 331, right; p = 0.005 by MANOVA) and significantly lower NAA concentration (in mmol/l: 11.04 ± 0.81 vs. 11.60 ± 1.05, p = 0.003; left). For the left hippocampus of schizophrenic patients, but not of healthy controls, a significant negative correlation between hippocampal NAA concentration and volume (r = –0.454, p = 0.013, controlled for age) was observed (Figure). None of the MR parameters was associated with psychopathology, duration of illness, or years of antipsychotic treatment.

The results argue for a coexistent neurochemical and structural deficit in the hippocampus of schizophrenic patients. The inverse relationship between the two parameters was observed in patients only and may reflect an interaction of neurochemistry and brain morphology as a pathobiological mechanism in schizophrenia. This observation is compatible with the important role of NAA in the synthesis of excitatory neurotransmitters and the hypothesized role of glutamate for brain morphology.

References

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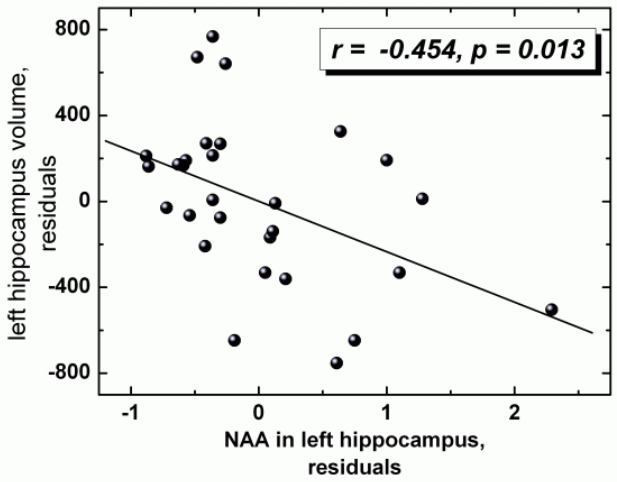

Fig.: Residuals of the left hippocampal volume and residuals of the NAA concentration in the left hippocampus voxel of schizophrenic patients (n = 29).