# Proton MRS at 3 tesla in brain of schizophrenic patients: elevated glutamate and reduced NAA in hippocampus

F. Schubert[1], F. Seifert[1], K. Leopold[2], M. Krebs[2], M. Schaefer[2], J. Gallinat[2]
[1]Physikalisch-Technische Bundesanstalt, Berlin, Germany, [2]Psychiatry and Psychotherapy, Charite Universitaetsmedizin, Berlin, Germany

## Introduction

Recent findings have revitalized the glutamate hypothesis of schizophrenia [1]. On the other hand, improved methods for the selective determination of glutamate in brain using proton MRS have emerged [2,3], permitting a more profound examination of the role of this neurotransmitter in the schizophrenic brain in vivo. Following the glutamate hypothesis one might expect elevation of glutamate levels in distinct gray matter regions. This has been well substantiated in a recent MRS study at 2T [4] where indeed increased glutamate concentrations were found in the hippocampus of schizophrenic patients. Regarding other metabolite levels in the brains of schizophrenic patients the findings are rather heterogeneous, but often N-acetylaspartate (NAA) is reduced [5] indicating neuronal dysfunction. We performed proton MRS in hippocampus and different cingulate regions of schizophrenic patients and healthy controls, focusing on quantitation of both glutamate and NAA in order to test the hypothesis of disturbed neurotransmission/energy metabolism and a possible parallel axonal loss.

## Subjects and Methods

Eighteen patients (age 18 to 40 years) having schizophrenia according to DSM-IV criteria were examined and compared with 30 healthy age matched volunteers. All subjects gave written informed consent. They were free of neurological, cardiovascular, hepatic, renal and metabolic diseases. 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$^3$, 1H-MR spectra were acquired using PRESS optimized for glutamate detection [3] ($T_E$ = 80 ms, $T_R$ = 3 s, $n$ = 128) from 3 voxels: 2 x 3 x 2 cm$^3$ including the left hippocampus (HC), 2.5 x 4 x 2 cm$^3$ including the anterior cingulate gyrus (AC), and 2 x 2 x 2 cm$^3$ including the posterior cingulate gyrus (PC). FASTMAP was used for shimming. For metabolite quantitation a time domain-frequency domain program package [3] was employed that included automatic retrospective frequency drift correction, non-parametric background estimation, and uncertainty assessment using a Bayesian approach that accounts for background fit uncertainty [6]. NAA, glutamate (Glu), choline-containing compounds (tCho), creatine plus phosphocreatine (tCr), and glutamine resonances were quantified, including phantom spectra and prior knowledge for frequency, linewidth and phase. For quantitation an external water phantom was used; fitted amplitudes were corrected for relaxation times, coil loading differences, and cerebrospinal fluid content of the voxels. For the latter the $T_1$-weighted images were segmented using SPM2.

## Results and Discussion

Uncertainties for the determination of NAA, Glu, tCho and tCr amounted to 2.5 – 14 %. In contrast, uncertainties for glutamine were too large (> 50 %) for consideration in the statistical analysis. No differences in the concentrations of tCho and tCr between schizophrenic patients and control subjects were detected in any of the voxels analyzed. Figure 1 shows the mean levels of Glu and NAA (± standard deviation) in the three voxels. Apart from regional level differences, the Glu concentration in the HC voxel was significantly higher (11.8 mmol/l *vs* 10.4 mmol/l, $p$ = 0.001) and the NAA concentration significantly lower (10.5 mmol/l *vs* 11.2 mmol/l, $p$ = 0.016) in patients than in controls whereas there were no significant differences for the AC and PC voxels. The same conclusions hold for the concentration data obtained without CSF correction, indicating that the differences were not due to different CSF contents of the voxels.

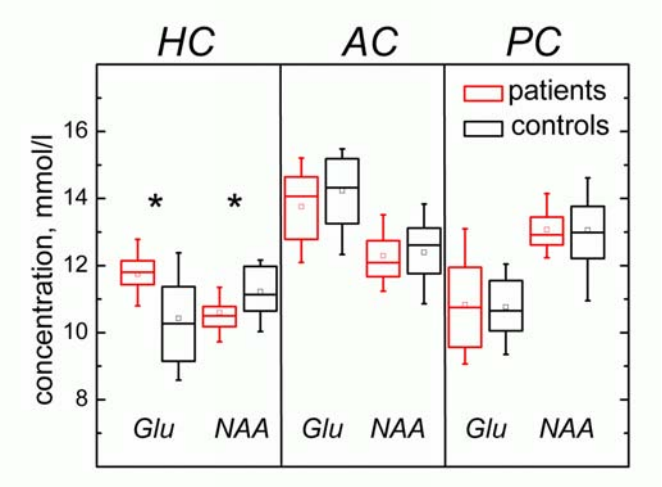


Fig. 1. Comparison of glutamate and NAA levels measured in the 3 voxels in schizophrenics and healthy controls.
*: $p$(Glu) = 0.001; $p$(NAA) = 0.016.

These results do not confirm a diminished NAA level in the cingulate of schizophrenic patients, as found by others [eg 7,8]. However, the recently reported Glu increase in hippocampus in schizophrenia [4] was clearly reproduced. Being accompanied by a reduced NAA level in this brain voxel, our finding suggests dysfunctional glutamatergic neurotransmission with concomitant disturbed neuronal integrity in a region playing a key role in the pathophysiology of schizophrenia.

## References

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