

In vivo assessments of glutamate, GABA, and NAAG in schizophrenia

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Introduction

The major excitatory and inhibitory neurotransmitter systems, glutamate and gamma-aminobutyric acid (GABA) respectively, are implicated in the pathophysiology of schizophrenia. N-acetylaspartylglutamate (NAAG), a modulator of the glutamatergic system that acts as an mGluR3 agonist and weak NMDAR antagonist, may also be altered in schizophrenia. This study used proton magnetic resonance spectroscopy (¹H-MRS) to measure these chemicals in medial prefrontal (MF) and centrum semiovale (CS) brain regions in subjects with and without schizophrenia.

Methods

Eighteen subjects with chronic schizophrenia and 19 healthy subjects participated in this study. Patient subjects were treated with second-generation antipsychotic medications except clozapine, and were not taking benzodiazepine or anticonvulsant medications. General cognitive function was assessed with the Repeatable Battery Neuropsychological Status (RBANS), and psychiatric symptom severity for patients was assessed with the Brief Psychiatric Rating Scale (BPRS). MR scanning was conducted at 3T (Philips Achieva) using an 8-channel receive head coil. For detection of glutamate (Glu) and glutamate+glutamine (Glx), spectra were acquired with a PRESS sequence (TR=2000 ms, TE=35 ms, 2048 points, 2000 HZ, 64 averages). For detection of GABA, spectra were acquired with a MEGA-PRESS sequence (TR=2000 ms; TE=68 ms; 14 ms editing pulses applied at 1.9 and 7.5 ppm; 256 averages). For detection of NAAG, spectra were acquired with a MEGA-PRESS sequence (TR=2000 ms; TE=140 ms; 40 ms editing pulses applied at 4.6 and 4.2 ppm; 256 averages). PRESS spectra were analyzed using fully automated, standard curve fitting software (LCModel), as well as software developed in-house or the analysis of MEGA-PRESS (csx3). Spectroscopic voxel sizes were 3.5 X 3.5 X 3.5 cm for MF and 5.0 X 3.0 X 3.0 cm for CS. Figure 1 illustrates voxel placements and spectra.

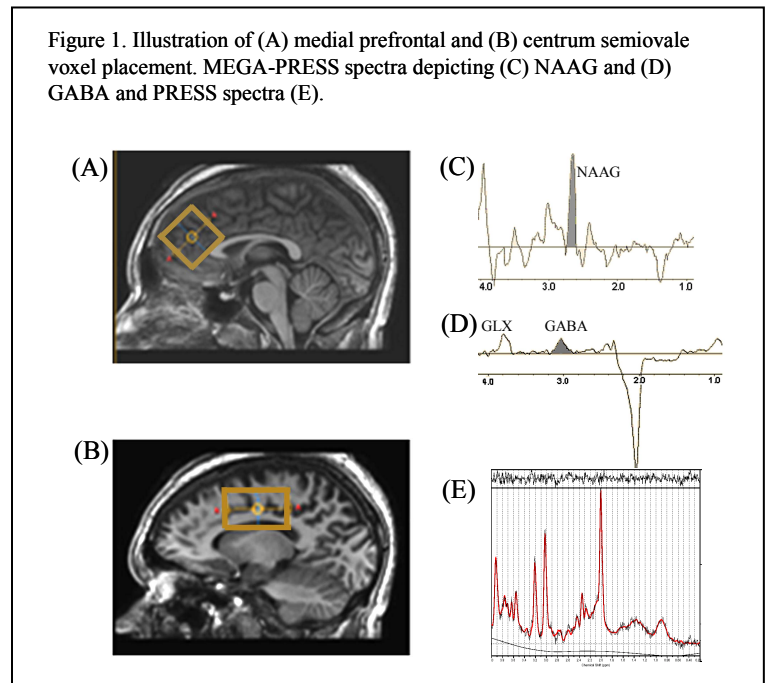


Figure 1. Illustration of (A) medial prefrontal and (B) centrum semiovale voxel placement. MEGA-PRESS spectra depicting (C) NAAG and (D) GABA and PRESS spectra (E).

Results

Medial frontal glutamate+glutamine was reduced in schizophrenia compared to controls ($t = 2.02$, $p = 0.05$). Greater MF glutamate was related to better attention performance in schizophrenia ($r = +0.45$, $p = 0.07$) but poorer attention performance in controls ($r = -0.44$, $p = 0.07$). There were no statistically significant differences in NAAG and GABA/Cr between groups, but there was a trend for higher MF glutamate+glutamine/GABA ratio in schizophrenia compared to controls ($t=1.95$, $p = 0.06$). Medial frontal glutamate/GABA ratios were positively correlated with attention performance in schizophrenia ($r = +0.44$, $p = 0.09$) but not controls ($r = +0.08$, $p = 0.75$). Higher levels of CS NAAG were associated with greater negative symptom severity ($r = +0.55$, $p < 0.05$) in schizophrenia.

Discussion

Reduced MF glutamate+glutamine in chronic schizophrenia supports previous studies (1). The association between higher NAAG and greater negative symptoms is consistent with NMDAR hypofunction in schizophrenia. Altered MF glutamate/GABA may reflect aberrant excitatory/inhibitory tone in schizophrenia. These alterations may contribute to attention processing impairments commonly observed in schizophrenia. In conclusion, these results provide further support of altered glutamatergic and GABAergic mechanisms in schizophrenia and illustrate the feasibility of in vivo measurements of GABA, glutamate, and NAAG in a single MR scan session.

Reference: (1) Theberge et al. (2003); Am J Psychiatry 160: 2231-3

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