GABA and glutamate in schizophrenia: a 7T 1H-MRS study

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Target audience

Scientists and clinicians interested in the neurobiology of schizophrenia and/or measurement of neurometabolite levels *in vivo* using ^{1}H-MRS at a magnetic field strength of 7T.

Purpose

The purpose of this study was to examine alterations in GABA (gamma-aminobutyric acid) and glutamate (Glu) levels in patients with schizophrenia as compared to healthy control subjects. Schizophrenia is characterized by a loss of brain tissue, which may represent an ongoing pathophysiological process. Mechanisms that may be involved are the glutamatergic and GABAergic systems [1]. Performing ^{1}H-MRS at an ultra-high magnetic field strength of 7T results in increased sensitivity and spectral resolution, which are particularly important when measuring Glu and GABA.

Methods

Participants: 18 schizophrenia patients (age 27.6±6.1, M/F=13/4) and 23 matched healthy control subjects (age 27.7±5.3, M/F 16/7) participated in this study. All participants underwent a general cognitive assessment using the full Wechsler Adult Intelligence Scale (WAIS)-III [2].

MR acquisition: All investigations were performed on a 7T whole body MR scanner (Philips, Cleveland, OH, US). A birdcage transmit head coil was used in dual transmit driven by 2x4 kW amplifiers, in combination with a 32-channel receive coil (both Nova Medical Inc., Burlington, MA, US). For the assessment of Glu an sLASER sequence (TE=28ms, TR=5s, 32 averages) [3] was used (fig.1A). Non-water-suppressed spectra were obtained for quantification (acquisition time=10s, carrier frequency was set to the chemical shift of H_2O). GABA-edited experiments were conducted using a MEGA-sLASER sequence (TE=74ms, TR=4s, 64 averages) [4] (fig.1B). Voxels were located in the medial prefrontal and medial occipital lobe (fig.2). Prior to the MRS exams, second order B_0 shimming was applied using the FASTERMAP algorithm at the voxel of interest [5,6]. In order to minimize chemical shift displacement artifacts, the highest possible B_1 field was generated by optimizing the phase of both transmit channels to locally assure constructive B_1 interferences [3,7].

Spectral fitting and quantification: Fitting of the sLASER spectra was performed with LCModel-based software implemented in Matlab [8], which uses a priori knowledge of spectral components to fit metabolite resonances [9]. To correct for the contribution of gray matter, white matter and cerebrospinal fluid in each voxel, segmentation was performed using the SPM8 software package. Fitting of the MEGA-sLASER spectra was performed by frequency-domain fitting of the GABA and Cr resonances to a Lorentzian line-shape function in Matlab. GABA levels were expressed as the ratios of their peak areas relative to the peak areas of the Cr resonance. Spectra with a CRLB of 20% or more were excluded from the study.

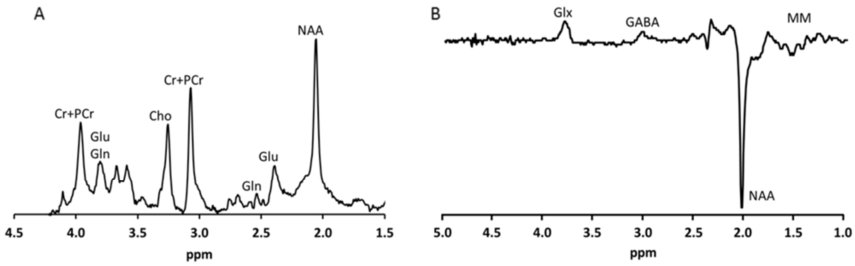

Figure 1. A: Typical sLASER spectrum. B: Typical MEGA-sLASER spectrum.

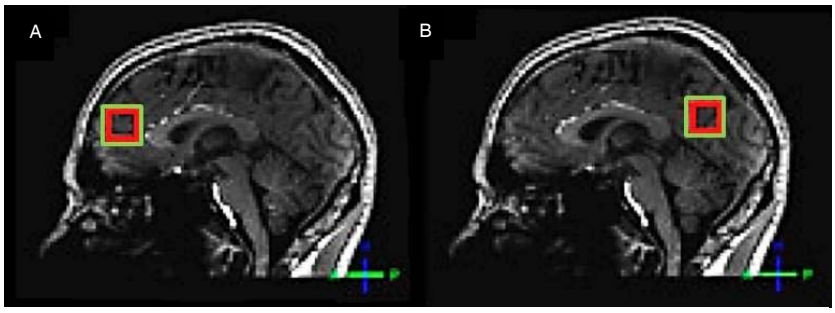

Figure 2. Voxel placement in (A) the medial prefrontal lobe and (B) the medial occipital lobe. sLASER voxels (2x2x2cm^3) are shown in red and MEGA-sLASER voxels (2.5x2.5x2.5cm^3) are shown in green.

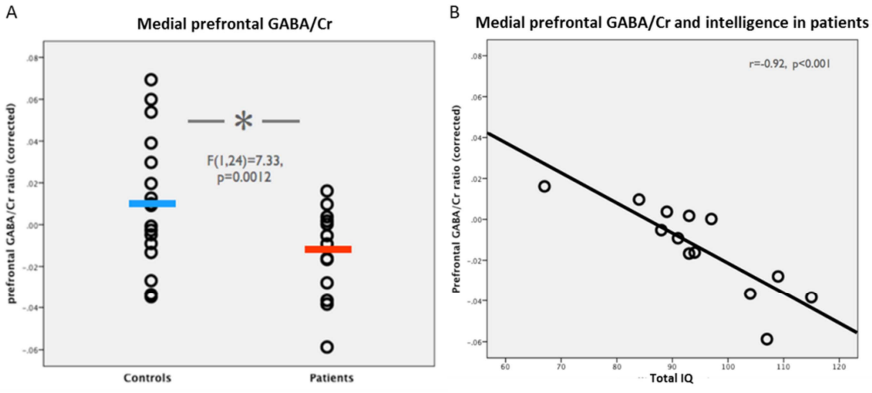

Figure 3. A: Patients show lower prefrontal GABA/Cr ratios as compared to healthy controls, when correcting for age, sex and gray and white matter fractions in the voxel (p=0.0012). The blue (controls) and red (patients) bars indicate group averages. B: Prefrontal GABA/Cr ratios in patients decrease with increasing total IQ (p<0.001).

Results/Conclusion

The main finding of this study is that prefrontal GABA/Cr ratios in patients were significantly lower as compared to healthy controls (p=0.0012) (fig.2). Moreover, the lower prefrontal GABA/Cr ratios in patients were strongly correlated with their level of general cognitive functioning (p<0.001), with high functioning patients showing lower GABA/Cr ratios (fig.3). This could be because of a cognitive functioning associated risk factor for schizophrenia [10] or it could reflect a compensatory mechanism to continue functioning at an above average level [11]. No significant differences were found for Glu between patients and healthy controls. Glu levels in patients resemble Glu levels in controls around age 25 [1], which could explain there was no effect for Glu found in this relatively young population.

References

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