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

Anouk Marsman¹, Rene C.W. Mandl¹, Dennis W.J. Klomp³, Marc M. Bohlken¹, Vincent O. Boer², Anna Andreychenko⁰, Wiepke Cahn¹, Rene S. Kahn¹, Peter R. Luijten², and Hilleke E. Hulshoff Pol³
¹Psychiatry, University Medical Center Utrecht, Utrecht, Netherlands; ²Radiology, University Medical Center Utrecht, Utrecht, Netherlands; ³Radiotherapy, University Medical Center Utrecht, Utrecht, Netherlands

Target audience
Scientists and clinicians interested in the neurobiology of schizophrenia and/or measurement of neurometabolite levels in vivo using ¹H-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 ¹H-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.

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 or it could reflect a compensatory mechanism to continue functioning at an above average level [11]. No significant differences were found for Glu levels in patients decrease with increasing total IQ (p<0.001). 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).

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 H2O). 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 B0 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 B1 field was generated by optimizing the phase of both transmit channels to locally assure constructive B1 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.

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