Catch me if you can: GABA spectroscopy with shifted editing pulse frequencies

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Introduction: γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the human cerebral cortex. Loss or dysfunction of GABAergic neurotransmission is associated with many neurological and psychiatric conditions such as epilepsy, schizophrenia and mood disorders [1-4]. However, detecting GABA is a challenging task as its resonance at 3 ppm overlaps with the much stronger creatine (Cr) signal. The solution to this problem is provided by a spectral editing technique which also allows better quantification of glutamate (Glu), glutamine (Gln) and glutathione (GSH). The thus edited GABA signal still overlaps with co-edited macromolecule resonances. We investigated two methods of GABA editing using two different reflection frequencies and obtained spectra from the ACC (anterior cingulate cortex) in 49 healthy subjects.

Methods In vivo single voxel 1H MRS was performed at a 3.0 T whole body MR scanner with a thirty-two channel head coil (Siemens Magnetom TIM Trio) in 49 healthy subjects. The ACC voxel (40x30x20mm³) was placed based on an isotropic 1 mm³ mprage data set with reconstructed coronal and transverse planes aligned with the shape of the corpus callosum (see Fig. 1). We also placed 6 orthogonal fat saturation bands to avoid signal interference. No participant had a lifetime history of schizophrenia or affective disorder. Approval for this study had been obtained from the local ethics committee. 41 spectra were included in the final analysis of GABA (19 males, 22 females, mean age 34.7 yrs, exclusions due to insufficient spectral quality), 48 spectra for the other metabolites (23 males, 25 females, mean age 35.7 yrs, one exclusion due to positive drug screen for THC). Measurements of GABA were obtained using a MEGA-PRESS editing sequence which uses the J-coupling between the GABA-H4 resonance at 3.01 ppm and GABA-H3 resonance at 1.89 ppm to reveal the GABA resonance, with TE = 68ms, TR = 3000ms, 96 averages, 2048 acquisition points. (see Fig. 1). Two subsequent editing acquisitions were made. First with the frequency of the editing pulse switching between 1.9 ppm and 7.5 ppm (center frequency 4.7 ppm) and second switching between 1.9 and 1.5 ppm (center frequency 1.7 ppm). As shown in figure 3 the latter diminishes contamination by nearby macromolecule resonances [5, 6]. For quantification of GABA the acquired spectra were analyzed using the jMRUI-Software [7]. For the other metabolites, LCModel was used [8]. A fully automated segmentation of the high resolution T1-weighted mprage data into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using SPM 5 algorithms and MATLAB 7.9 was performed to determine the composition of each spectroscopic voxel [9]. All metabolites were corrected for CSF content and scaled with the water signal at TE = 30ms.

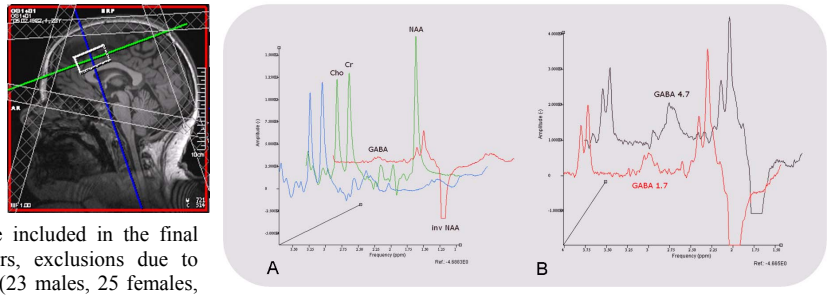


Figure 1: Sagittal images with voxel and fat saturation placement; exemplary spectra.

Results: The mean GABA to H_2O ratio obtained with the transmitter frequency set to -1.7 ppm was only 44.8% of the ratio obtained with the transmitter frequency set to -4.7 ppm with standard deviations of 15.9 % and 10.9%, respectively. We did not find any significant correlation between GABA and age (Fig.2), sex or gray-matter-to-brain-matter-ratio (GM/BM) (age: r=0.011 p=0.946; sex: t=0.604 p=0.550; GM/BM: r=-0.099 p=0.538). The latter might be explained by the low variance of GM/BM in our voxels (min 0.52, max 0.69).

Figure 2

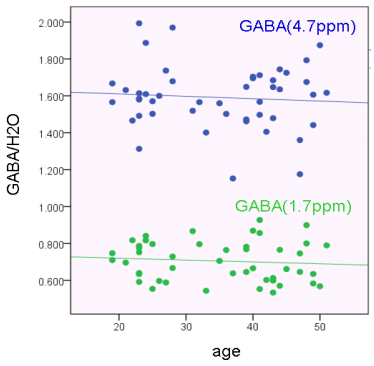
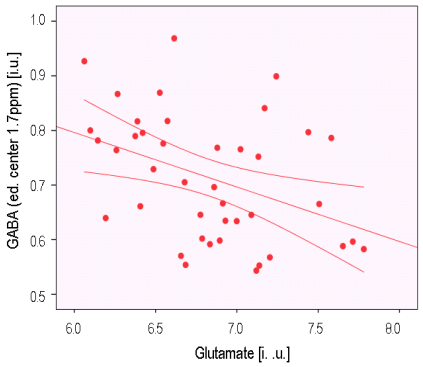


Figure 3



Quantification of all other metabolites was excellent. A mean glutamate of 6.93 mmol/l, SD 0.56 with mean Cramér-Rao lower bounds of 3.98% (see Fig. 4) could be determined due to the editing technique as well as the excellent SNR obtained from the relatively large voxel (mean SNR for Glu 8.7). Glutamine and glutathione could be quantified with concentrations of 1.48 mmol/L, age-corrected SD 0.11, and 1.34 mmol/L, age corrected SD 0.10, respectively. Both metabolites showed significant positive correlations for age (Gln: r=0.388 p=0.006; GSH: r=0.287 p=0.048). Interestingly we found a significant inverse correlation between GABA (-1.7ppm) and glutamate concentrations in the ACC (r=-0.398, p=0.010 see Fig. 3). There was no significant correlation between GABA and any other metabolite.

Discussion: These are preliminary results suggest a macromolecule contribution of >50% to the GABA resonance at 3.0 ppm in healthy subjects.
Glutamatergic excitation and gabaergic inhibition are understood as opposing processes in the human cerebral cortex. Glutamate is also the biochemical precursor of GABA. Since glutamate is used when the GABA concentration increases an inverse correlation of their concentrations in the ACC in healthy subjects could reflect this balance. As the ACC is a key region to emotional control and is strongly connected to the limbic system, further analysis in regard of personality trait questionnaires is on the way [10].

References

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