Impact of spectra quality on GABA quantitation with ^{1}H-MEGA-PRESS sequence

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Target audience: Researchers and members of the Psychiatric MR Spectroscopy Study Group and of the Magnetic Resonance Spectroscopy Community.

Purpose: Proton magnetic resonance spectroscopy (^{1}H-MRS) offers the opportunity to quantify non-invasively neurotransmitters in the human brain and to obtain information about neurotransmitter turnover in physiological and pathological conditions [1]. However, since the spectroscopic quantitation of GABA is typically complicated by signal overlapping of other brain metabolites and its low concentration (c_{GABA} = 1-2 mM [2]), the exploration of inhibitory neurochemical mechanisms requires sophisticated techniques, such as ^{1}H-MEGA-PRESS method. This spectral editing technique acquires a non-edited and an edited spectrum within one examination. The subtraction spectrum provides the elimination of disturbing resonances and thus facilitates the quantitation of GABA. In the present study the accuracy and reproducibility of GABA detection with ^{1}H-MEGA-PRESS was evaluated by *in vitro* and *in vivo* measurements. Simulations were performed with respect to SNR_{GABA} and linewidth, while taking into account the limited acquisition time (TA) of *in vivo* studies.

Methods: All ^{1}H-MEGA-PRESS measurements were performed using a 3 T whole-body MR scanner (Magnetom Trio TIM, Siemens, Germany) and a twelve channel phased array receive-only head matrix coil. *In vitro* spectra (V = 25 x 25 x 25 mm³, TE/TR = 68/10000 ms, NAS = 64, repetition = 29) were acquired using a phantom containing GABA, Glu, Gln, Cr, NAA and mI in aqueous solution (c_{GABA} = 10 mM), mimicking the relative concentration ratios in the brain. The single spectra were adapted to *in vivo* conditions by successive line broadening (FWHM = 0.02-0.08 ppm) and adding extra noise (SNR_{GABA} = 1-17). The *in vivo* measurement was performed in the insular cortex of a healthy volunteer (V = 30 x 15 x 15 mm³, TR = 4000 ms, NAS = 256). The *in vivo* data were used to generate nine spectra groups (by using a bootstrapping approach with 64 spectra) with varying SNR_{GABA}, which was adjusted by different numbers of averaged single spectra (NAS = 64, 80, 96, 112, 128, 144, 160, 176, 192). The GABA multiplet at 3 ppm was quantified as a linear combination of three constrained singlets by using AMARES (jMRUI package [3]). Absolute GABA concentrations were estimated by normalising the intensity of the GABA multiplet with the internal reference of the non-suppressed water signal [4]. The accuracy and reproducibility of GABA quantitation were evaluated with respect to the impact of SNR_{GABA} and linewidth on the mean concentrations and variation coefficients (CV).

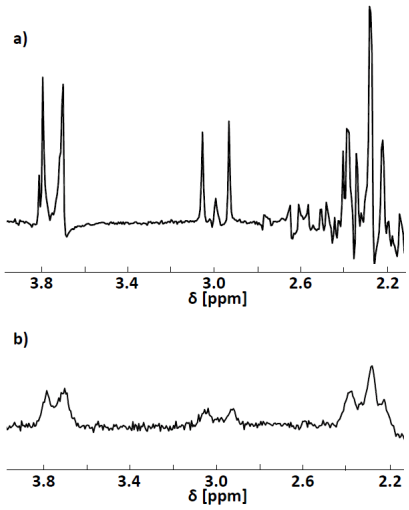

Fig. 1 Difference spectra of the ^{1}H-MEGA-PRESS sequence for a) *in vitro* conditions b) simulated *in vivo* conditions (FWHM = 0.03 ppm, SNR_{GABA} = 4).

Results: An original *in vitro* and a simulated line broadened ^{1}H-MEGA-PRESS difference spectrum with additional noise are shown in Figure 1, which demonstrates the hampered quantitation of GABA (3 ppm) *in vivo*. Within the simulation range neither the SNR_{GABA} nor the linewidth contribute substantially to the accuracy of GABA detection *in vitro*, since the calculated mean GABA concentrations reproduce very well the nominally adjusted concentration in the phantom (10 ± 0.5 mM). Contrary to the mean values, the CV of the calculated concentrations reveals substantial variations with respect to the SNR_{GABA} and linewidth (see Fig. 2). However, for a SNR_{GABA} > 2 the FWHM yields only a small impact on CV and for SNR_{GABA} > 6 CV remaines nearly unaffected by FWHM. As expected, for high SNR_{GABA} and narrow linewidths a high precision can be obtained (CV up to 2%). The calculated variations *in vivo* indicate a similar dependence on SNR_{GABA} as discussed for the *in vitro* results, illustrated by the distribution of c_{GABA} values in the boxplots of Figure 3.

Discussion: In the *in vitro* study the calculated GABA concentrations correspond very well to the nominally adjusted concentration in the phantom. For sufficiently small CVs (< 7 %) a SNR_{GABA} of at least 2 is required, whereas for SNR_{GABA} > 6 the calculated CVs remain nearly independent of FWHM. Moreover, the results of the *in vitro* simulations conform to the *in vivo* measurements concerning the impact of SNR_{GABA} on reproducibility. For brain investigations of pathological or physiological changes in GABA concentrations a high precision in metabolite quantitation is required. Thus, for *in vivo* measurements particularly SNR_{GABA} has to be improved. While this is feasible by increasing NAS, the extension of TA of the measurement is limited. Another opportunity for SNR_{GABA} optimization is the investigation of enlarged volumes, lacking in loss of localization, or the usage of apodization functions, accepting a tolerable line broadening.

References: [1] Maddock et al., Curr. Top. Behav. Neurosci., 2012, 11:199-251; [2] Govendraju et al., NMR Biomed. 2000, 13:129-153; [3] Stefan et al., Meas. Sci. Technol. 2009, 20; [4] Terpstra et al., Magn. Reson. Med. 2002, 47:1009–1012.

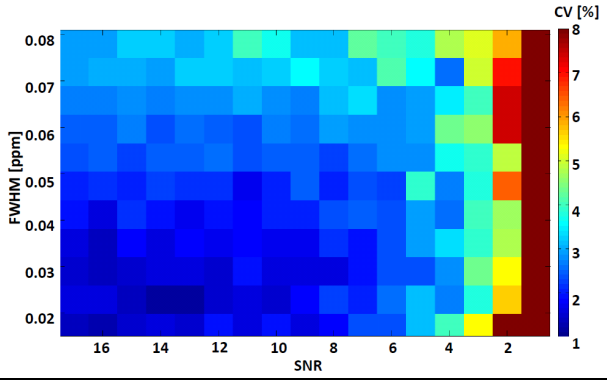

Fig. 2 Changes in variation coefficient with respect to FWHM and SNR_{GABA} *in vitro*.

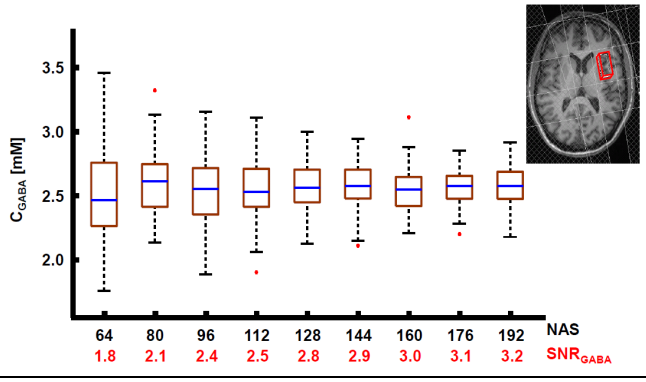

Fig. 3 Distributions of *in vivo* c_{GABA} values determined with varying SNR_{GABA} in the insular cortex.