MM-suppressed GABA measurements correlate more strongly with behavior than MM-contaminated GABA+ measurements

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Target audience: Scientists and clinicians with an interest in GABA, GABA-MRS, and sensory processing as well as regional and individual differences.

Purpose: Altered sensory processing is a key feature of a number of neurological and neurodevelopmental disorders where disrupted GABAergic processing is thought to play a role. Recently, we have shown that GABA levels, as measured by edited MRS (with the ‘MEGA-PRESS’ technique) in the sensorimotor cortex correlates with tactile frequency discrimination performance. One limitation of measuring GABA concentration at 3T with the MEGA-PRESS technique is that the editing pulse at 1.9 ppm also affects a macromolecule (MM) resonance at 1.7 ppm such that a significant part of the measured ‘GABA’ peak at 3 ppm (figure 1a) consists of MM. This peak is therefore often referred to as GABA+ to signify that it originates both from GABA and MM. We recently proposed a method of MM-suppression to measure ‘pure GABA’ by increasing TE to 80 ms and symmetrically applying more specific editing pulses at 1.9 and 1.5 ppm (figure 1a). In this study, we revisit earlier GABA-behavioral studies to investigate whether both GABA+ and GABA-pure in the sensorimotor region correlate with tactile performance.

Methods: 14 male, right-handed subjects were studied. Written informed consent was obtained under local IRB approval. Neuroimaging: All measurements were made using the MEGA-PRESS J-difference editing method on a 3T Philips ‘Achieva’ scanner (Philips Medical Solutions, Best, the Netherlands) equipped with a 32-channel head coil. Spectra were acquired from (3cm)3 volume in the right sensorimotor region (SM1) and centred on the right “hand knob” as identified in axial T1-weighted images and aligned with the cortical surface. Two scans were acquired: one standard MEGA-PRESS sequence (TE = 68 ms; editing pulse 14 ms placed at 1.9 (ON) and 7.6 (OFF) ppm) and one MM-suppressed MEGA-PRESS sequence (TE = 80 ms; editing pulse 20 ms placed at 1.9 (ON) and 1.5 (OFF) ppm). Both acquisitions used a TR 2000ms and 320 transients. Data were analysed using ‘Gannet’, which uses a Gaussian lineshape and baseline model to fit the edited GABA signal and a Lorentz-Gaussian lineshape to fit the unsuppressed water signal. Behavioral: All participants performed a battery of vibrotactile tasks designed to probe inhibitory function, including: (1) Reaction Time (RT); (2) static and a dynamic detection threshold task (DT); (3) Amplitude discrimination (AD) tasks with and without adaptation; (4) Frequency Discrimination (FD); (5) Temporal Order Judgement (TOJ).

Results: In SM1, the pure GABA signal was ~ 51 ± 15% smaller than GABA+. The pattern of vibrotactile data replicates prior results. GABA+ concentration over SM1 correlates weakly with amplitude discrimination (r = -0.21, n.s.) while GABA-pure correlates more strongly (r = -0.58, p < 0.02; Figure 2a). SM1 GABA-pure correlates significantly with the % difference in AD threshold between without and after adaptation (r = 0.55, p < 0.02, figure 2b). Both GABA+ and GABA-pure correlate weakly, but not significantly, with frequency discrimination. SM1 GABA+ correlates weakly but not significantly (r = -0.22) with the effect of a carrier on TOJ while GABA-pure does so significantly (r = -0.55, p < 0.02).

Discussion: While SM1 GABA+ only shows weak correlation with both AD and FD, GABA-pure shows stronger and significant correlations, particularly with AD and modulation of tactile responses in AD and TOJ-tasks, suggesting that GABA-pure is more sensitive to individual differences in inhibitory tone that have measureable behavioral outcomes. Earlier findings showed a correlation between frequency discrimination and GABA+ and the results presented here show much weaker and non-significant correlations, possibly due to a smaller range of thresholds among our current participants. GABA-pure also correlates with single-site adaptation and modulation of TOJ, suggesting that GABA predicts not only baseline thresholds, but the ability to modulate these thresholds as well, with more GABA predicting a larger effect of adaptation.

Conclusion. We have replicated earlier findings correlating vibrotactile behavior and SM1 GABA concentration, and have shown in this study that MM-suppressed GABA-pure measurements correlate more strongly than GABA+. MM-suppressed GABA-MRS may be sensitive to different GABAergic mechanisms in discrimination and adaptation. However, it is important to recognise that MM-suppressed MEGA-PRESS suffers from approximately a 50% decrease in signal, creating a noisier measure and therefore longer scan-times or more participants are recommended. 1. Puts et al. (2012) J. Neurosci 2. Edden et al. (2012) JMRI 3. Edden et al JMRI (in press) 4. Puts et al (2013) J Neurosc Meth. Sponsored by Autism Speaks, NIH: P41 EB015909; R21 MH098228; R01 EB016089