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

NICOLAAS A PUTS[1,2], Ashley D Harris[1,2], Peter B Barker[1,2], and Richard A Edden[1,2]

[1]Russell J. Morgan department of Radiology and Radiological Sciences, The Johns Hopkins University, Baltimore, Maryland, United States, [2]FM Kirby Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, Maryland, United States

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[1]. One limitation of measuring GABA concentration at 3T with the MEGA-PRESS technique is that the editing pulse at 1.9 ppm also effects 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[2] (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.

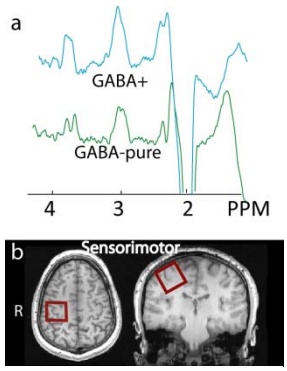

Figure 1. GABA+ (TE = 68 ms) and GABA-pure (TE = 80 ms). b. Voxel locations for SM1

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'[3], 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[4]: (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[4]. 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).

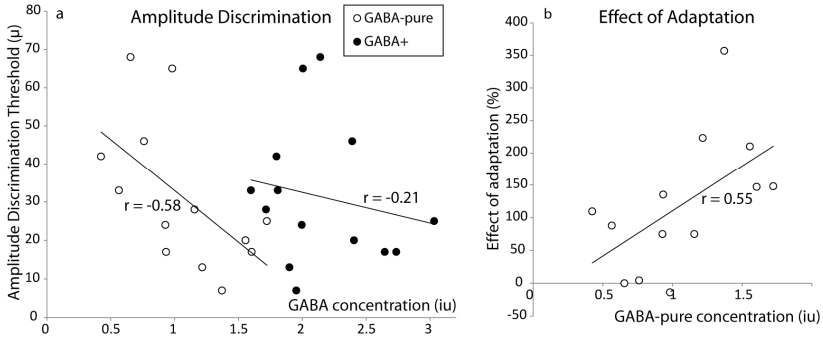

Figure 2. a. GABA-pure correlates more strongly with amplitude discrimination than GABA+. b. GABA-pure also predicts the effect of single-site adaptation.

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[1] 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 Neurosci Meth.*

Sponsored by Autism Speaks, NIH: P41 EB015909; R21 MH098228; R01 EB016089