

Baseline occipital perfusion inversely correlates with GABA after accounting for arterial arrival time discrepancies

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Target Audience: Researchers interested in neurovascular and neurochemical correlates of blood oxygenation level-dependent (BOLD) signal origins.

Purpose: Commonly-employed neuroimaging approaches in humans exploit hemodynamic or metabolic indicators of brain function. However, fundamental gaps remain in our ability to relate such hemo-metabolic reactivity to neurotransmission, with recent reports providing some paradoxical information regarding the relationship between basal perfusion, functional imaging contrast, and neurotransmission in awake humans^{1,2}. Here, sequential MR spectroscopy (MRS) measurements of the primary inhibitory neurotransmitter, γ -aminobutyric acid (GABA+macromolecules normalized by the complex N-acetyl aspartate - N-acetylaspartylglutamic acid: [GABA⁺]/[NAA-NAAG]), and MRI measurements of perfusion, fractional gray matter volume, and arterial arrival time (AAT) are recorded in human visual cortex from a controlled cohort of young adult male volunteers with neurocognitive battery-confirmed comparable cognitive capacity.

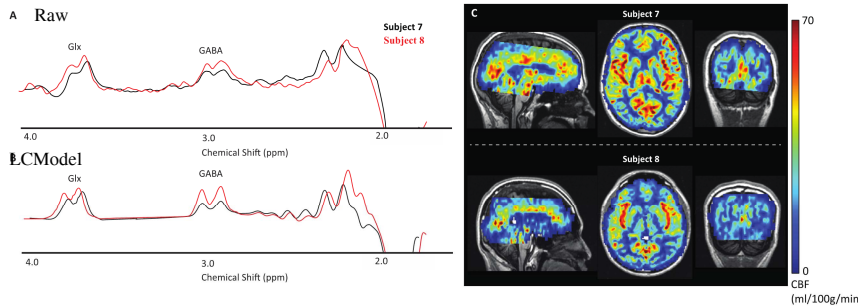


Fig. 1. GABA and ASL. Spectra (A) and LCModel fit (B) results from two representative subjects, showing the GABA doublet at approximately 3.0 ppm. (C) Orthogonal slice representations of the CBF maps for the same two subjects, which show lower CBF in the occipital cortex of the subject with higher GABA (Subject 8) and higher CBF in the occipital cortex of the subject with lower GABA (Subject 7).

with a temporal resolution of 300 ms over the range of expected AATs. For MRS, the 3 ppm GABA peak ([GABA⁺], which reflects GABA + macromolecules) was measured using J-difference MEGA-PRESS³⁻⁵ with TR/TE = 2000/73 ms, 320 spectra with 2048 samples each. The editing pulses were toggled between 1.91 and 7.4 ppm on alternate scans and the editing pulses had a bandwidth of 64 Hz. Care was taken to place the spectroscopy voxel (voxel dimensions: 25 x 30 x 22 mm) similarly in the occipital cortex between all volunteers. **Analysis.** The primary objective was to assess the correlation between the MRI measurements (i.e., baseline CBF and AAT) and the MRS measurement (i.e., [GABA⁺]/[NAA-NAAG]). To achieve this, the GABA voxel was superimposed onto the quantified CBF and AAT maps and CBF and AAT were recorded only for common cortical regions that overlapped between the CBF, AAT and MRS regions. A measure of error was calculated as the standard deviation (STD) of the CBF and AAT over the common region-of-interest or as the value of the Cramer-Rao Lower Bound (CRLB) of the [GABA⁺] measurement. Multiple regression was performed and normal probability plots, Pearson's R, and adjusted R values were calculated separately between the dependent variable (CBF) and the independent variables ([GABA⁺]/[NAA-NAAG] and AAT).

Results: Fig. 1 shows J-edited spectra from two subjects (A), along with the LCModel fit of these two spectra (B). In both cases, the GABA doublet at approximately 3.0 ppm is clearly visible; all volunteers were required to have CRLBs $\leq 15\%$ and therefore the quality of spectra from other subjects is similar to the quality of these presented cases. Subject 7 shows a reduced GABA peak relative to Subject 8, and this volunteer was found also to have higher occipital CBF (C). Fig. 2 shows scatter plots from all subjects and data for (A) CBF (multi-TI) vs. [GABA⁺]/[NAA-NAAG] ($R = -0.46$; $P = 0.037$), (B) CBF (single-TI) vs. [GABA⁺]/[NAA-NAAG] ($R = -0.12$; $P = 0.33$), and (C) AAT vs. [GABA⁺]/[NAA-NAAG] ($R = -0.13$; $P = 0.32$). It is observed that when accounting for blood transit time variations in the multi-TI pCASL fitting procedure, a significant albeit weak inverse relationship is found between CBF and [GABA⁺]/[NAA-NAAG]. This relationship disappears when the AAT is assumed to be constant in all volunteers, and finally the AAT itself does not appear to correlate significantly with [GABA⁺]/[NAA-NAAG]. Multiple regression analyses whereby multi-TI CBF (dependent variable) is investigated relative to [GABA⁺]/[NAA-NAAG], gray matter voxel fraction, and AAT for the multi-TI fitting procedure revealed an adjusted $R^2 = 0.61$ ($F = 6.2$), with most of the variability explained by [GABA⁺]/[NAA-NAAG] ($P = 0.096$) and AAT ($P = 0.005$), but not gray matter voxel fraction ($P = 0.361$).

Discussion: The primary finding of this work is that measurements of occipital GABA ([GABA⁺]/[NAA-NAAG]) using J-edited MEGA-PRESS spectroscopy inversely correlate with CBF in the same region. This finding provides some physiological basis for the recently reported inverse relationships between evoked BOLD responses and GABA^{1,6}. A secondary finding, which is important for explaining the prior inconsistencies between ASL-measured CBF and GABA, is that while blood arrival times do not appear to correlate strongly with [GABA⁺]/[NAA-NAAG], failure to account for arrival time in measurements of CBF can reduce or even eliminate the detectability of relationships between CBF and GABA.

Conclusion: This work reinforces the credibility of recently reported inverse correlations between BOLD functional imaging signals and inhibition^{1,2,6}, and additionally reconciles recent work whereby paradoxical correlations were observed between CBF-weighted ASL contrast and GABA.

References: 1. Donahue MJ, et al. *Neuroimage*. 2010;53:392-398. 2. Muthu SD, et al. *HBM*. 2012;33:455-465. 3. Keltner JR, et al. *MRM*. 1996;36:458-461. 4. Puts NA, Edden RA. *Prog Nucl Magn Reson Spectrosc*. 2012;60:29-41. 5. Waddell KW, et al. *Magn Reson Imaging*. 2007;25:1032-1038. 6. Muthu SD, et al. *PNAS*. 2009;106:8356-8361.

Methods: Healthy volunteers ($n = 16$; age = 23 ± 3 yrs; sex = M) provided informed, written consent. Each volunteer underwent a 3.0T MRI and MRS experiment. The MRI protocol consisted of (i) a 3D structural T₁-weighted MPRAGE (TR/TE = 5.4/2.5 ms; turbo gradient echo factor = 160; spatial resolution = $1 \times 1 \times 1$ mm³), and (ii) a gradient echo single-shot EPI (factor = 35) multi-inversion time (TI) pseudo-continuous arterial spin labeling (pCASL) sequence. The pCASL sequence (TR / TE = 4350 / 18 ms; spatial resolution = $3.43 \times 3.43 \times 6$ mm³; slices = 15) utilized a Hanning pulse train for blood water labeling with pulse duration = 0.5 ms and total labeling duration = 1200 ms; TI values = 200, 500, 800, 1100, 1400, 1700, 1900, 2300 ms (12 averages per TI), dual adiabatic background suppression for concomitant suppression of gray matter and white matter static tissue signal. The pCASL labeling duration was reduced slightly (duration = 1200 ms) to sensitize the approach to AAT, and the TI range was sampled

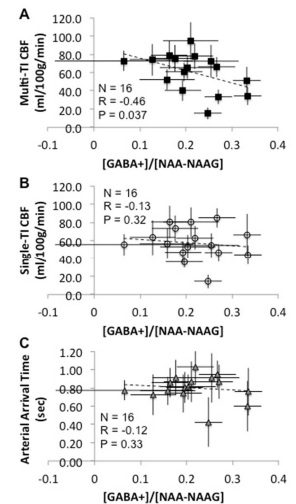


Fig. 2 (A) A significant ($P = 0.037$) inverse relationship is observed between the occipital [GABA⁺]/[NAA-NAAG] and CBF as calculated from the multi-inversion time (multi-TI) fitting procedure. (B) When a single-TI point is used (TI = 1700 ms) with an assumed, constant arterial arrival time (AAT) = 0.8s, this trend disappears. (C) No significant relationship is found between [GABA⁺]/[NAA-NAAG] and AAT.