Baseline GABA Concentration More Strongly Predicts Baseline BOLD Signal Synchrony than CBF in Visual Cortex

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TARGET AUDIENCE: Imaging scientists with an interest in understanding physiological origins of BOLD fMRI contrast

PURPOSE: *The purpose of this study is to understand the extent to which baseline cortical inhibition, assessed from edited MRS measurements of the primary inhibitory neurotransmitter γ-aminobutyric acid (GABA), and perfusion, assessed from arterial spin labeling (ASL) MRI measurements of cerebral blood flow (CBF), can be used to explain the synchrony of functional networks obtained from baseline blood oxygenation level-dependent (BOLD) contrast.* Recently, inverse relationships between *baseline* GABA concentration and *changes in* stimulus-induced (i) hemodynamic (BOLD; cerebral blood flow: CBF; and cerebral blood volume: CBV) activity[1] and (ii) MEG-measured gamma-frequency magnitude[2] have been reported. However, it remains unclear how *baseline* GABA concentration can be used to predict the strength of *baseline* BOLD networks. We hypothesize that owing to the unique energy budgets of glutamatergic (GLUergic) and GABAergic neurons[3], baseline GABA concentration can be used to predict the synchrony of functional networks determined from baseline BOLD in the same network. Here, we measure the relationship between baseline BOLD synchrony and baseline (i) CBF and (ii) GABA in human visual cortex and findings are interpreted in the context of physiological models of coordinated inhibition.

METHODS: Male volunteers (n=8; age=22±2 yrs) provided informed, written consent and were scanned at 3T (Philips). *Experiment:* BOLD MRI: Single-shot gradient echo EPI: slices=29, spatial resolution=3x3x4 mm^3, TR/TE=2500/35 ms, measurements=120. ASL MRI: Pseudo-continuous ASL (pCASL), slices=15, spatial resolution=3.5x3.5x7 mm^3, TR/TI/TE=4000/1700/13 ms. Structural MRI: Standard 3D T_1-weighted (1 mm isotropic) MPRAGE. MEGA-PRESS MRS: GABA spectra were obtained in the occipital cortex (30x30x40 mm^3) using J-difference editing (TR/TE=2000/78, averages=384). *Analysis:* BOLD MRI: Preprocessing was performed in FSL and included high frequency (f>0.1 Hz) noise removal, baseline drift correction, spatial smoothing (FWHM=3 mm), and affine motion correction. BOLD data were co-registered to standard space. Dual regression[4]: Multi-subject temporal concatenation ICA was performed using MELODIC to obtain a common visual network mask. An average time-course was computed from this ROI for each subject and used as the temporal model for evaluating the generalized linear model (GLM) parameter estimates. Z scores, a measure of baseline synchrony, were subsequently calculated from the parameter estimates. ASL MRI: Data were pair-wise subtracted and absolute CBF (ml/100gm/min) was calculated in the same ROI as above using kinetic models that account for pCASL labeling duration and off-resonance magnetization transfer effects. Finally, BOLD and ASL measures were co-registered to the structural MRI scans and normalized by the fraction of gray matter (GM) in the common ROI. MEGA-PRESS MRS: Data were frequency and phase corrected and GABA concentration, including macromolecule contamination and normalized by NAA-NAAG (GABA+/NAA-NAAG) and subsequently by voxel GM fraction was recorded using LCModel.

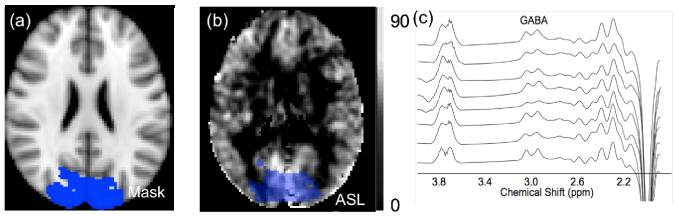

Figure 1*: Common (a) visual RSN mask and (b) mask overlaid on absolute CBF map. (c) GABA signal at 3.01 ppm can be seen in the visual cortex for all subjects (n=8).*

RESULTS: Fig. 1 shows one slice of the visual resting state network (RSN) map overlaid on the (a) standard atlas and (b) co-registered CBF map, along with (c) J-edited difference spectra for all subjects in the occipital cortex showing the GABA peaks at 3.01 ppm. Fig. 2 shows the correlative findings: an inverse correlation (a) between GABA+/NAA-NAAG and BOLD RSN synchrony, (r=-0.64, p=0.043) and (b) between GABA+/NAA-NAAG and baseline CBF (r=-0.62, p = 0.049). However, (c) the correlation of baseline BOLD connectivity with baseline CBF was much weaker (r = 0.2, p =0.32) than the relationship between baseline GABA and BOLD synchrony. Importantly, all trends were much weaker when measurements were not normalized by the percentage of GM in the voxel: connectivity vs. GABA (r = -0.04, p=0.44); and CBF vs. GABA (r =-0.22, p=0.30).

DISCUSSION: Our major finding is that resting state BOLD connectivity is more strongly correlated with GABA than with CBF. As GABA measurements are in principle a closer indicator of synaptic activity than CBF, this finding lends additional support for baseline BOLD networks representing better indicators of neuronal activity than vascular activity. It should also be noted that GABAergic interneurons are believed to be supported primarily by oxidative phosphorylation[3], and thus elicit little or no changes in CBF. Therefore, GABAergic activity may provide no BOLD contrast (which is derived primarily from a mismatch in CBF and CMR_{O2}), but rather the trends that are found here, as well as in the recent evoked BOLD and GABA literature, may be interpreted as showing inter-subject GABA variability which modifies the baseline inhibitory state, and thereby the activation threshold which GLUergic neurons must meet. Ongoing measurements in our laboratory, which incorporate electrical recording potential measurements, are being used to better understand this possibility.

CONCLUSION: This study investigated the relationship between baseline neuro-transmitter concentration, BOLD connectivity, and baseline CBF. Baseline CBF and RSN connectivity were not strongly correlated. However, we found strong associations between GABA concentration in the visual cortex and the baseline BOLD amplitude.

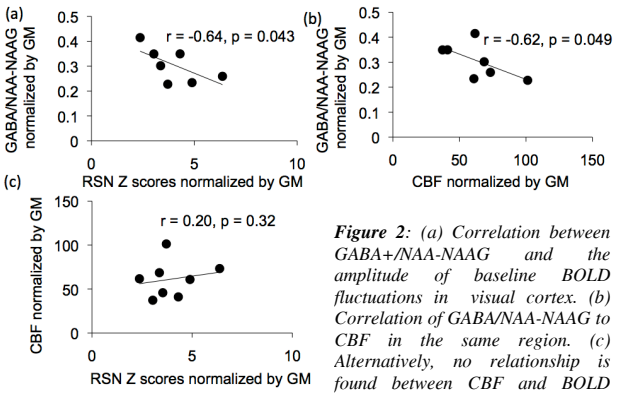

Figure 2*: (a) Correlation between GABA+/NAA-NAAG and the amplitude of baseline BOLD fluctuations in visual cortex. (b) Correlation of GABA/NAA-NAAG to CBF in the same region. (c) Alternatively, no relationship is found between CBF and BOLD amplitude in the same region*

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