Relationships between excitation-inhibition balance and whole-brain oxygen extraction fraction in human brain

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TARGET AUDIENCE: Researchers interested in relationships between neurochemistry, hemodynamics, and functional imaging signals.

INTRODUCTION: *The overall goal of this work is to incorporate neurochemical and metabolic MR measurements of brain function to better understand the relationship between excitation-inhibition balance and resting metabolism in human brain.* Neurotransmission is predominately governed by excitatory glutatmate (Glu)-mediated Gluergic and inhibitory γ-aminobutyric acid (GABA)-mediated GABAergic neurons, which metabolize glucose to meet their energy demands. GABAergic and Gluergic neurons also have distinct energy profiles. Recent developments in MRS and MRI, including J-edited MRS[1], CBF-weighted ASL[2], and blood oxygenation-weighted TRUST[3], have demonstrated that GABA and Glu values correlate with baseline as well as evoked hemo-metabolic brain imaging signals, and further that baseline metabolism correlates with evoked hemodynamic responses. These data support, but do not confirm, that relationships between baseline neurotransmission and metabolism are present or measurable with recently developed noninvasive neuroimaging tools. As such, the goal of this work was to experimentally assess the relation between baseline oxygen extraction fraction (OEF) and relative Glu and GABA concentrations from these the techniques. We hypothesize that the relative ratio of GABA/Glu will correlate with baseline OEF. Confirmation of this hypothesis would provide support for more comprehensive measurements of neuronal function to be inferred and modeled through sequential incorporation of these noninvasive approaches.

METHODS: *Experiment:* Male volunteers (n=12; age=22±2 yrs) who performed similarly on a neurocognitive battery as administered by a board-certified neuropsychologist provided informed, written consent and were scanned at 3T (Philips) Achieva scanner. Structural MRI: 3D T1-weighted (1 mm isotropic) MPRAGE. Neurochemistry: J-difference edited MRS[1] (occipital cortex; 30x30x40 mm^3; TR/TE=2000/78 ms, averages=384). Venous oxygenation: T2 Relaxation Under Spin Tagging (TRUST)[3] with four effective TEs (0, 40, 80, 160 ms), TR=1.98s per TE and transfer insensitive labeling technique (TILT) venous water labeling. *Analysis:* Spectra were frequency and phase corrected in MATLAB. The difference of the edited and unedited spectra were used to evaluate $GABA^+$/Cr ratios and Glx/Cr ratios using LCModel; $GABA^+$ includes macromolecular content in addition to GABA, Glx is the total concentration of Glu and its precursor, glutamine. Relative concentrations of GABA and Glu were evaluated as the ratio of ($GABA^+$/Cr)/(Glx/Cr). Y_v (venous oxygenation) was calculated in the sagittal sinus approximately 20 mm above the sinus congruence by converting the calculated R_2* to Y_v assuming Hct=0.41 and Y_a=0.98; OEF=1-Y_v/Y_a was also calculated. Spearman correlations of $GABA^+$/Glx, $GABA^+$/Cr, and Glx/Cr ratios with OEF were assessed.

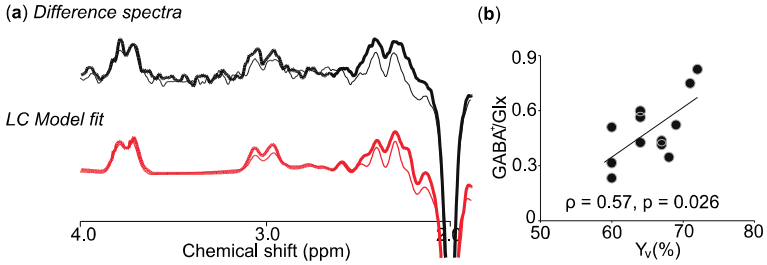

Figure 1: *(a) Representative J-edited spectra (black) and the corresponding LC Model fit (red) for 2 subjects with the lowest (thin line) and highest (thick line) baseline Y_v. The GABA peak is larger for the volunteer with Y_v = 71% than Y_v= 60% and a strong positive trend between $GABA^+$/Glx and Y_v is observed on average (p=0.026).*

RESULTS: Mean $GABA^+$/Cr=0.40±0.14 and Glx/Cr=0.81±0.07 while the ratio of ($GABA^+$/Cr)/(Glx/Cr) was 0.49±0.17 (Crame-Rao Lower Bound set to 10%). The mean gray matter volume in the spectroscopy voxel was 35.7±1.90%. Y_v in the sagittal sinus was 66.26±5.40%. Correlation and p-values between $GABA^+$/Cr and Y_v, Glx/Cr and Y_v, and $GABA^+$/Glx and Y_v were 0.53 (p=0.04), -0.08 (p=0.40), and 0.57 (p=0.03) respectively. Mean OEF assuming Y_a=0.98 was 0.33±0.04. Spearman correlation between $GABA^+$/Glx and OEF yielded ρ=-0.57 (p=0.03) **(Fig. 1)**.

DISCUSSION: The overall findings from this work are that TRUST-measured Y_v and J-edited measured GABA+/Glx appear to be positively correlated. No significant correlation was observed between Glx/Cr and Y_v, likely due to Glx having a more varied role beyond neurotransmission. These results reinforce the growing literature relating GABA to functional hemo-metabolic imaging signals[4-6]. Several issues must be considered in the context of this work. The spectroscopy voxel was located in the occipital cortex and Y_v measurements were performed in the sagittal sinus. Although region-wise $GABA^+$/Glx measures may vary within a subject, evidence has been provided for the relative ratio of $GABA^+$/Glx across subjects not varying by brain region in healthy tissue[7,8]. Macromolecular content was not corrected for in the GABA measurements; macromolecular contributions at TE=78 ms are not likely to be overwhelming, however, their possible contribution should be considered. Glx measurements refer to total Glu and glutamine concentration and comprise the neurotransmitter pool as well as Glu used for other cellular and metabolic processes.

CONCLUSION: The relative balance of GABA and Glu correlates positively with venous oxygenation and negatively with whole-brain oxygen extraction fraction.

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