GABA, glutamate, and perfusion changes during working memory

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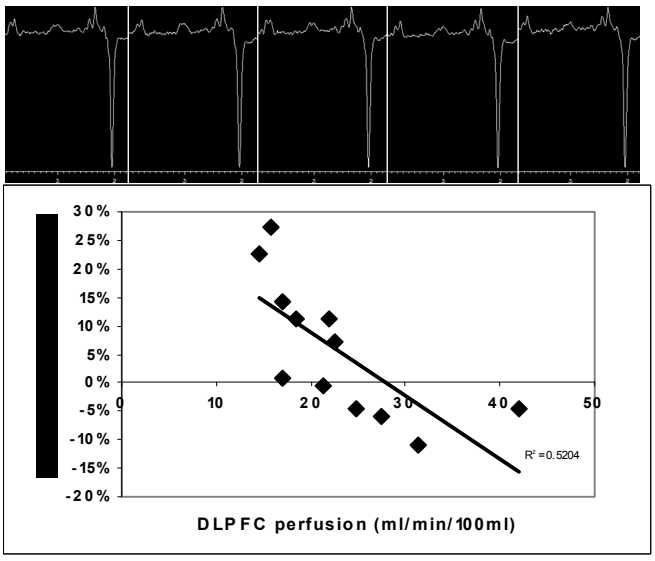
Introduction: Gamma-amino butyric acid (GABA), the primary inhibitory neurotransmitter in the human brain, has recently been linked to the resting perfusion and the peak gamma oscillation frequency, the blood oxygen level dependent (BOLD) fMRI signal, and changes in cerebral blood volume during visual stimulation.[1,2] GABA is also thought to be involved in working memory (WM) processing[3]. Arterial spin-labeling (ASL) perfusion MRI has also revealed increases in perfusion during the encoding condition of a memory-encoding task[4], but the relationship between GABA and perfusion changes during WM has not yet been established. This study investigates the relationship between haemodynamic and neurotransmitter activity by comparing the GABA and perfusion levels in the dorsolateral prefrontal cortex (DLPFC), one of the brain regions involved in WM processing,[5,6] during rest and WM.

Methods: The subject group consisted of 12 right-handed adults (5 female), ranging in age from 25 to 38 years, with no history of neurological or psychiatric illness. MR imaging and spectroscopy studies were performed with a 3T GE HD.xt TwinSpeed MRI scanner (GE Medical Systems, Milwaukee, WI, USA), using an 8-channel receive-only head coil. Five consecutive single-voxel MEGA-edited[7] ^{1}H MR spectra were acquired from a 2.5x3x4 cm^3 voxel of interest in the left DLPFC with TE/TR = 68/1800 ms and 320 averages (160 pairs), both during a rest condition and during continuous performance of a WM task. For the WM task, five or seven letters were presented for a stimulus period of 2 seconds and maintained in memory for a retention period of 5 seconds before a single letter appeared for a probe interval of 2 seconds .Subjects had to indicate by button press whether the letter was part of the stimulus set. ASL perfusion images were acquired during the same rest and task conditions using a QUIPSS II sequence[8] with TE/TR= 30/3000 ms, TI1/TI2= 600/1300 ms, sl th = 5 mm, gap= 1 mm, FOV= 24 cm, matrix = 64x64, and 60 control/label image pairs. Average perfusion values were calculated both in the DLPFC voxel of interest and across the whole brain for all subjects. MRS data were processed with LCModel[8]. Inter-correlations between GABA, Glu, the resting perfusion, and the change in perfusion during the task were evaluated using Spearman's rho.

Results: Resting GABA levels correlated positively with the resting DLPFC perfusion, as reported previously[2]. The resting GABA levels also correlated inversely with the change in DLPFC perfusion during the task ($p<0.05$). Despite a high inter-subject variability the average change in GABA concentration across the subject group showed an initial increase during the first working memory task relative to the resting level followed by a linear decrease across the four task runs ($R=0.99$, figure 1). Differences in GABA concentration between the baseline resting level and the first working memory spectrum from session 1 were significant at the $p=0.05$ level (paired t-test), and the decrease in GABA between the first and fourth working memory spectra also showed a strong trend towards significance ($p=0.08$). The change in glutamate+glutamine (Glx) from baseline to the first working memory task was also inversely correlated to the perfusion ($p<0.001$).



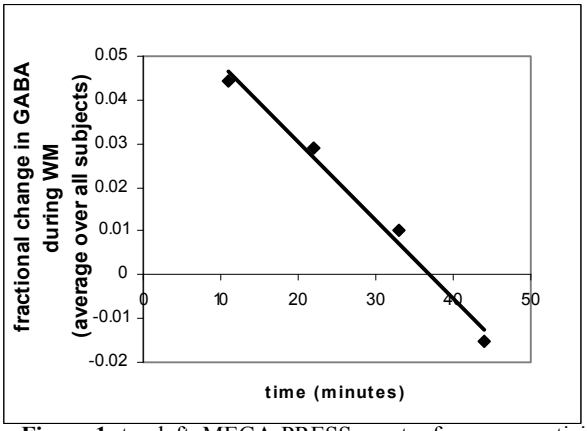


Figure 1: top left: MEGA-PRESS spectra from one participant during rest (panel 1) and WM (panels 2-5). Bottom left: inverse correlation between the resting perfusion and the change in Glx during WM. Right: average change in GABA during the WM task, (relative to baseline level 0 at time=0 minutes).

Discussion: The increase and subsequent reduction of GABA during WM suggests a rapid local modulation of GABAergic activity relative to resting GABA levels. The correlation with perfusion further suggests a coupling between neurotransmitter levels and local hemodynamic changes, lending further support to recent theories indicating that functional neuroimaging metrics like BOLD and ASL are dependent on the balance of excitation and inhibition required for cognitive processing.

References: [1]Muthukumaraswamy et al. PNAS, 106: 8357-61 (2009), [2]Donahue et al. Neuroimage 53:392-8 (2010), [3]Jensen et al. Learning & Memory 3:264-278 (1996), [4]Xu et al. Neurology 69(17):1645-6 (2007), [5]Smith and Jonides 283: 1657–61 (1999), [6]Michels L et al. (2010) PLoS One. 2010 5(4):e10298, [7]Edden and Barker MRM 58:1276-1282 (2007), [8]Wong et al. MRM 39:702-708(1998).