Cortical hemodynamics and GABAergic inhibition. Resting GABA levels in human visual cortex correlate with BOLD, ASL-measured CBF and VASO-measured CBV reactivity

M. J. Donahue[1,2], J. Near[1,2], and P. Jezzard[1,2]
[1]Clinical Neurology, Oxford University, Oxford, United Kingdom, [2]Physics Division, FMRIB Centre, Oxford, United Kingdom

Introduction. Neurovascular coupling between neuronal activity, energy metabolism and cerebral blood flow, prompted by synaptic excitation and inhibition, ensures an adequate delivery of oxygen and glucose to the brain [1]. Recently it was shown that synaptic inhibition with γ-aminobutyric acid (GABA) is inversely correlated with the blood-oxygenation-level-dependent (BOLD) signal change [2]. However, the BOLD contrast mechanism is complexly dependent on CBF, CBV, oxygen metabolism and the presence of draining veins, and therefore the relationship between GABA and functional neuroimaging modalities sensitive to constituent hemodynamic parameters is of interest. Here, we investigate the relationship between baseline GABA and hemodynamic reactivity in human visual cortex (VC) by performing GABA spectroscopy, BOLD fMRI, CBF-weighted (CBFw) arterial spin labelling (ASL) fMRI [3] and cerebral blood volume (CBV) weighted (CBVw) vascular-space-occupancy (VASO) fMRI [4]. In addition, we measure baseline CBF (ASL) and arterial CBV (aCBV) (using iVASO-DS) [5]. The hypotheses to be investigated are (1) due to the close link between hemodynamic reactivity and synaptic activity, there should be a negative relationship between BOLD, CBFw and CBVw reactivity with GABA and (2) baseline CBF and aCBV will negatively correlate with GABA. The results should help illuminate the relationship between neurochemical inhibition and MR-measured cerebral hemodynamics and can provide a platform for non-invasively investigating how cerebral hemodynamics are influenced by GABAergic tone.

Methods. *Experiment.* All volunteers (n=12; age=29.5±4.1 yrs; 6M/6F) provided informed consent and were scanned at 3.0T (Siemens). Spectroscopy. Prior to functional imaging, a baseline GABA measurement was obtained using MEGA-PRESS (TE/TR = 69/2000 ms; 192 averages; 3x3x3 cm^3) [7]. The voxel was placed in the VC and care was taken to avoid scalp and the sagittal sinus. Editing was achieved using a 14 ms dual banded Gaussian pulse with water suppression band centred at 4.7 ppm and GABA editing band alternating between 1.9 ppm and 7.5 ppm in even and odd acquisitions, respectively. Imaging. BOLD (GE EPI; TE/TR=40/2000 ms), VASO (GE EPI; TE/TR/TI=14/5000/1054 ms) and ASL (FAIR 3D GRASE; TE=39/TR/2500/1600 ms), with common spatial resolution=3.8x3.8x3.8 mm^3, were used for assessing fMRI reactivity. *Stimulus*. Alternating (8 Hz) blue/yellow flashing checkerboard (40/20s off/on x 3). A resting iVASO-DS (GE EPI; TE/TR/TI=14/1789/989 ms; 3.8x3.8x3.8 mm^3) scan was incorporated to measure baseline aCBV. *Analysis*. Spectroscopy. All spectra were apodized with a 5 Hz filter, and zero and 1st order phase corrections were applied. GABA levels relative to NAA were measured using AMARES [8] and NAA levels relative to Creatine were measured from odd subspectra using LCModel [9]; an institutional unit (i.u.) GABA:Creatine ratio was determined. Imaging. Images were corrected for motion and baseline drift. Signal changes were recorded for each scan; activation criteria: z>2.3 (BOLD; ASL), z<-2.3 (VASO). For resting analysis, aCBV from iVASO-DS and CBF from baseline periods of the ASL fMRI scan were recorded in VC.

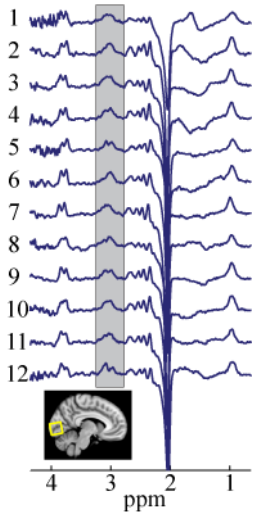

Fig. 1. GABA peaks (gray).

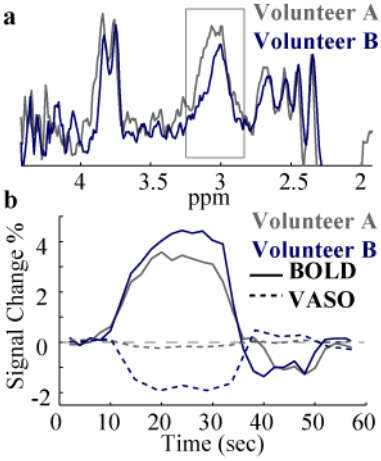

Fig. 2. MEGA-PRESS GABA (box) (a); BOLD and VASO reactivity (b).

Results and Discussion. Results. Fig. 1 shows MEGA-PRESS spectra (n=12) and GABA peaks (gray). Fig. 2 shows representative spectra (a) for volunteers with low (blue) and high (gray) GABA and the corresponding BOLD and CBVw-VASO block-averaged time courses (b). An inverse correlation between baseline GABA and magnitude BOLD and VASO signal changes is evident. Fig. 3 shows reactivity vs. baseline GABA for BOLD (a), CBFw-ASL (b) and CBVw-VASO (c). An inverse correlation is found between GABA and BOLD (R=0.68) and VASO (R=0.75), whereas, a weak positive correlation between ASL and GABA (R=0.38) is observed. The baseline ASL-CBF (d) and iVASO aCBV (ml blood/ml parenchyma) (e) plots are shown to the right. Discussion. These results reveal that baseline GABA negatively correlates with BOLD reactivity, VASO-measured CBVw reactivity and iVASO-measured baseline aCBV in the VC, thereby providing evidence that baseline inhibitory neurotransmitter levels account for some variability in hemodynamic fMRI measures. Unexpectedly, the ASL-measured CBF exhibits a positive trend with GABA. While investigating this anomaly we noted larger intravascular contributions to the ASL signal in volunteers with higher GABA levels, which is consistent with a lower blood velocity. Using midazolam, which increases the conductance of $GABA_A$ receptors, flow velocities have previously been observed to decrease, relative to baseline, in anaesthetized rats [9]. Therefore changes in blood velocity, which are related to GABA levels, may account for this finding. Conclusion. BOLD and CBVw-VASO reactivity is inversely correlated with baseline GABA in human VC, whereas CBFw-ASL measures show a more complex trend which may be explained by blood velocity discrepancies. Thus, intersubject CBF comparisons may require a transit time map in addition to an ASL image acquired at a single TI. A link between neurochemical and MR-measured hemodynamic responses is demonstrated, suggesting that future fMRI experiments that probe the mechanistic relationships between cortical activity and GABAergic inhibition should be possible.

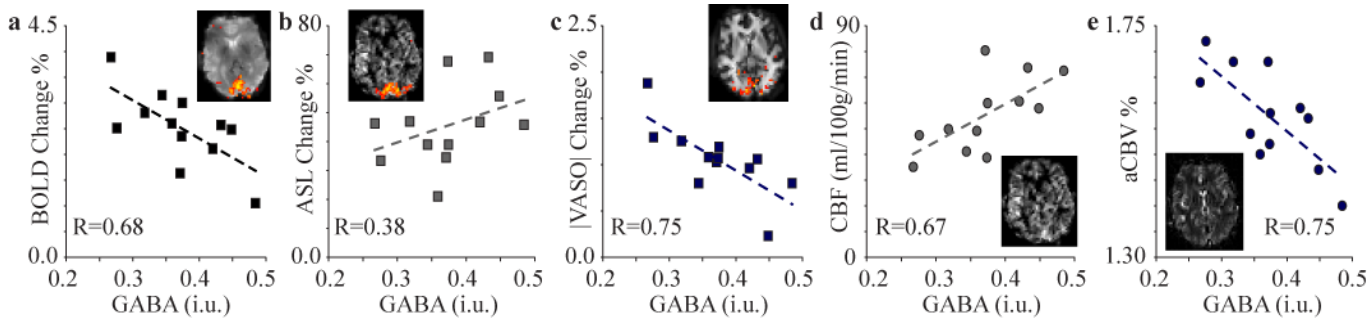

Fig.3. Effect (n=12) of baseline GABA on BOLD reactivity (a), ASL reactivity (b), |VASO| reactivity (c), baseline ASL-CBF (d) and baseline iVASO-DS-aCBV (e). Inlaid images are representative images from a single volunteer.

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