Endogenous GABA Concentration and Haemodynamic Responses to Graded Visual Contrast

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TARGET AUDIENCE: fMRI and MRS researchers interested in GABA's role in neurovascular coupling.

PURPOSE: The neurotransmitter γ-aminobutyric acid (GABA) plays an integral role in the excitation–inhibition balance in the brain and consequently is implicated in neurovascular coupling. Reports have shown that GABA concentration measured non-invasively with ^{1}H MRS predicts task-related BOLD and CBF responses[1–3]. In this study, we sought to investigate whether endogenous GABA levels are also associated with tuning properties of haemodynamic responses as assessed with a graded stimulus (a stimulus with varying levels of input). Here, tuning refers to characteristic haemodynamic activity in response to a particular feature or level of a stimulus, and can be represented as output (e.g., signal change) as a function of input (e.g., contrast). Using a graded visual contrast paradigm, we measured BOLD and CBF responses in the visual cortex. GABA concentration was measured with and without macromolecule (MM) suppression.

METHODS: Eighteen volunteers (11 F; $M_{age} \pm SD$ = 25.9 ± 3.6 years) underwent a 20-min visual simulation paradigm in a 3T GE Signa HDx scanner. Participants were presented with black and white, gamma-corrected, square-wave, annular gratings reversing at 6 Hz. Gratings were displayed for 30 s pseudorandomly at 0, 12.5, 50 and 100% contrast. Six 2.5-min blocks of gratings were shown, with each block always beginning with a rest condition. The experiment began and ended with 150 s of rest. BOLD and CBF responses were measured simultaneously using a dual-echo PICORE QUIPSS II pulsed ASL sequence with a spiral gradient echo readout ($TE_1/TE_2/TR$ = 2.9/30/2500 ms, TI_1/TI_2 = 700/1500 ms, voxel size = 3.5x3.5x5 mm^3, FOV = 22.4 cm, 12 slices). Single voxel ^{1}H MRS was used to quantify GABA concentration in the occipital lobe. Two 15-min MEGA-PRESS acquisitions were performed (TR = 1800 ms, 512 averages, 3x3x3 cm^3 voxel), one with standard placement of editing pulses (ON/OFF scans = 1.9/7.5 ppm; TE = 68 ms), and another employing symmetric editing to suppress MM contaminating the GABA peak (ON/OFF scans = 1.9/1.5 ppm; TE = 80 ms)[4]. A T_1-weighted FSPGR scan was acquired for image registration and tissue segmentation. MM-contaminated GABA concentration is denoted [GABA'+MM] and MM-suppressed GABA concentration is denoted [GABA']. A power law contrast response function, $S(c) = S_{max} \times c^{\gamma}$, was fit to participants' BOLD/CBF percent signal change response at each contrast level. $S(c)$ is BOLD/CBF response at contrast c. S_{max} is the modelled response at 100% contrast. The γ parameter represents the rate of response saturation, ranging from 0–1, with higher values corresponding to slower saturation.

RESULTS: Contrast tuning curves are displayed in Fig. 1. Fig. 2 shows representative spectra acquired using the two MRS techniques. Pearson correlations showed that for BOLD, γ was inversely related to [GABA'+MM] (r = –0.58, p = 0.01, 95% CI = –0.80, –0.19), such that participants with higher GABA levels had faster BOLD response saturation to contrast. There was a trend for CBF vs [GABA'+MM] (r = –0.45, p = 0.06, 95% CI = –0.74, –0.07) (Fig. 3). No relationship was seen for S_{max} vs [GABA'+MM] for BOLD or CBF. Additionally, [GABA'+MM] correlated with BOLD percent signal change, but only at 12.5 and 25% contrast (r = 0.53, p = 0.02 and r = 0.57, p = 0.01, respectively). [GABA'] did not correlate with γ, S_{max} or percent signal change for BOLD or CBF. We saw a positive relationship between γ_{BOLD} and γ_{CBF} (r = 0.61, p = 0.01, 95% CI = 0.23, 0.85), with CBF showing a faster rate of saturation than BOLD. No relationship was seen between BOLD S_{max} and CBF S_{max}. γ also strongly predicted percent signal change at 12.5% contrast (BOLD: r = –0.71, p < 0.01; CBF: r = –0.82, p < 0.01) and 25% contrast (BOLD: r = –0.64, p < 0.01; CBF: r = –0.55, p = 0.02).

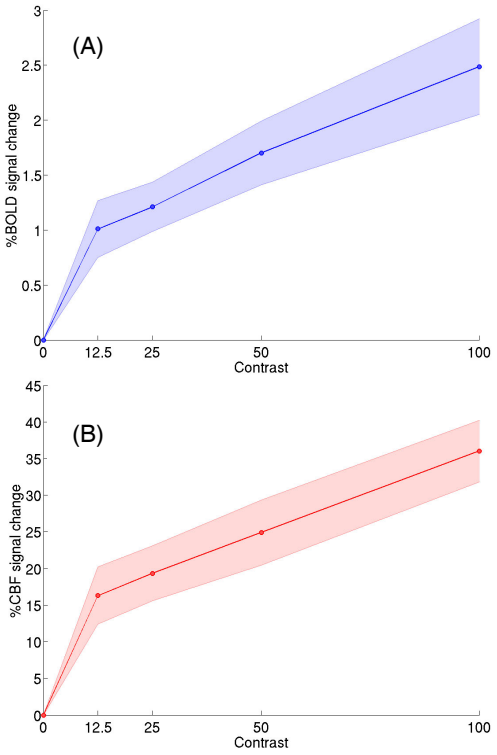

FIG. 1. *Contrast response functions for BOLD (A) and CBF (B) showing mean percent signal change at each contrast level across all participants. Coloured area is standard deviation.*

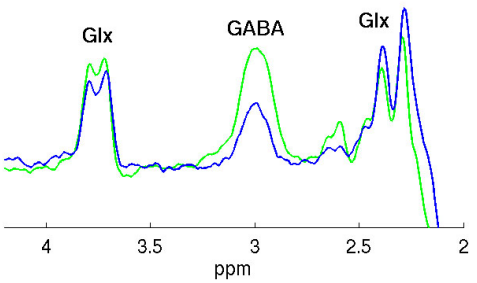

FIG. 2. *Representative MEGA-PRESS spectra. Green = MM-contaminated; blue = MM-suppressed.*

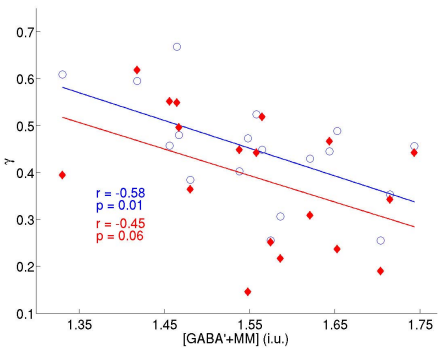

FIG. 3. *Rate of response saturation (γ) to graded visual contrast for BOLD (blue circles) and CBF (red diamonds) as a function of GABA'+MM concentration.*

DISCUSSION: Here we show for the first time that GABA concentration predicts saturation rate of BOLD and CBF responses to a graded stimulus. We suggest that GABA levels are not just related to haemodynamic measures in response to a stimulus at maximal input but may also be a marker of the dynamic range of these responses. This is supported by the fact that both GABA and saturation rate correlated with percent signal change at low contrasts, which follows previous findings of a dynamic range in contrast tuning at low contrast[5,6]. It is surprising that the MM-suppressed GABA measures did not also produce significant correlations with saturation rate. It is unclear how contaminating MM could contribute to haemodynamic contrast tuning properties; but it may be that because the GABA' peak is ~50% smaller than the GABA'+MM peak (see Fig. 2), the lower SNR necessitates a larger sample size.

CONCLUSION: Endogenous GABA concentration is associated with individual differences in haemodynamic contrast tuning, suggesting that it may be a mediator of the dynamic range of BOLD and CBF responses.

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