THE RELATIONSHIP BETWEEN NEUROTRANSMITTER LEVELS, BOLD CHANGES AND NEURAL OSCILLATIONS IN PRIMARY MOTOR CORTEX.

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Introduction: Studies investigating the origin of neural oscillations (rhythmic electrical activity in neural cell assemblies) have shown that the re-bound in power, seen in the β-frequency band (13-30Hz) following motor activity, can be predicted by the resting concentrations of γ-aminobutyric acid (GABA)[1]. These findings are in agreement with studies indicating that the post-movement β-rebound (PMBR) represents a period of GABAergic inhibition following movement. In addition, studies have shown that the peak frequency of stimulus-induced (SI) γ-oscillations (30-100Hz), in both visual and motor cortex, is also predicted by resting GABA concentration[1,2]. However, modelling of a cortical network containing inhibitory interneurons and excitatory pyramidal cells[3] indicates that the natural frequency depends on the balance of excitatory to inhibitory synaptic currents, suggesting that whilst GABA may predict the peak γ-frequency, it may be better to consider the ratio of excitatory to inhibitory neurotransmitter levels (i.e. Glutamate/GABA). In this study we utilize the increased spectral resolution afforded by 7T to quantify Glutamate (Glu), Glutamine (Gln) and GABA in order to determine whether the peak frequency in SI motor γ-oscillations is better predicted by the ratio of excitatory/inhibitory neurotransmitter levels than by GABA levels alone. In addition, a relationship has also been established between GABA, SI γ-frequency and the %change in blood oxygen dependent (BOLD) constrast, measured using functional magnetic resonance imaging (fMRI) in visual cortex[2,4]. We aim to assess whether this relationship holds in motor cortex.

Methods: 9 healthy right-handed subjects took part in the experiment which comprised resting measurements and a motor paradigm. In the paradigm, a screen displayed the words LEFT or RIGHT, indicating that the subject should continuously clench and unclench their respective hand, and the word REST. For MEG the task was performed for 8s, followed by a 12s rest period, while for fMRI the rest period was extended to 32s. All MR measurements were made using a Philips Achieva 7T system with a volume transmit coil and 32-channel SENSE recieve coil.

fMRI: Data were acquired using EPI (TE/TR = 25/2000ms, 2mm^3 isotropic voxels, FOV=112x112 voxels in-plane, 30 slices). For calculation of the %BOLD change, data were motion corrected, normalized and smoothed (3mm isotropic Gaussian kernel). Statistical parametric maps were generated in SPM8 ($p<0.001$ corrected, $k>=10$). %BOLD changes were calculated from the regions masked with the ROI output from SPM and further masked with the pre+post central gyrus mask from the Harvard-Oxford cortical atlas.

MRS: MR spectra were acquired with a STEAM sequence (TE/TM/TR=16/17/2000ms, bandwidth (BW)=4000Hz, No. points=4096, Volume of Interest (VOI)=20x20x20mm^3). 288 water-suppressed (ws) and 2 non-ws (nws) spectra were collected to allow absolute quantitation of metabolite concentrations. Metabolite concentrations were estimated, using LCModel. Baseline neurotransmitter levels (Glu, Gln and GABA) were estimated in both left and right primary motor areas (M1).

MEG: MEG data were acquired using a 275 channel CTF system (sample rate 600Hz). Data were initially band pass filtered (13 : 30Hz for β and 60-80Hz for γ) and projected into source space using a beamformer[5]. Pseudo-T statistical functional images were constructed for both the left and right hand tasks separately by comparison of oscillatory power in an active (0.5s-7.5s) and control (12.5s – 19.5s) time window . Resulting images were used to define locations of interest (LOI) in motor areas. To examine the time-frequency evolution of activity at those LOI, broadband (1-150Hz) MEG data were projected (again using a beamformer) to the LOI and filtered into overlapping 4Hz bands. The analytic signal was computed and its absolute value yielded timecourses showing variation in oscillatory amplitude for each frequency band. PMBR peak height and delay time were calculated by averaging across all bands between 15 and 28 Hz (mean corrected from 16.9-19.9s). Peak height was calculated from the maximum point (from 8-19.9s).

Results and Discussion: *Basal MRS:* Comparison of basal metabolite levels showed increased levels of Glu (+14±11%, p=0.01) and decreased GABA (-29±11%, p=0.02) in right motor cortex relative to left. No significant difference was found for Gln. This is interesting as it is well known that there are differences in fMRI and MEG responses to contralateral stimulation between dominant and non-dominant hands. *MEG:* Motor activity induced a decrease in oscillatory power in the ∝ and β bands, with both contralateral and ipsilateral peaks showing similar effects. No significant difference in PMBR was found between left and right motor cortex following contralateral motor stimulation. However, a significant increase in PMBR was seen in left M1 relative to right M1 for ipsilateral stimulation (+40±60%, p=0.05). Increases in γ activity were seen only in contralateral M1[1]. No significant difference was seen in γ peak frequency between left and right M1. *Relationship between %BOLD, neurotransmitter levels and M1 PMBR:* Grouping matched pairs of PMBR and %BOLD changes for both contralateral and ipsilateral motor stimulation (N=19 pairs) showed a significant positive correlation between PMBR and %BOLD (Fig 1a, p=0.04) indicating that changes in BOLD are related to underlying neural oscillations. In agreement with previous findings[5], PMBR was significantly correlated with resting GABA concentration (Fig 1b). Levels of Gln and Glu were not significantly correlated with PMBR in either ipsilateral or contralateral M1 indicating that the β-rebound is inhibitory in origin. *Relationship between %BOLD, neurotransmitter levels and M1 SI γ-frequency:* A significant positive correlation was found between the SI γ-frequency and resting concentration of GABA (p=0.01), in agreement with findings from Gaetz *et al*[1]. In addition, we found significant positive correlation between the SI γ-frequency and Glu (p=0.02). This correlation was stronger for Gln (p=0.01), which implies that this relationship is due to glutamatergic neurotransmission, since the Glu pool is partly metabolic in origin, and Gln pool size is likely to be more closely related to the Glu neurotransmitter pool. In contrast to previous findings in visual cortex[2], no relationship was found between %BOLD change and the SI γ-frequency in M1. Further, no correlation was found between GABA, Glu, or Gln and the %BOLD change.

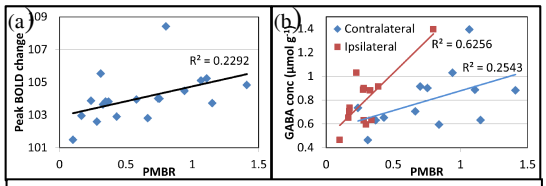

Fig 1: Plot showing relationship between (a)%BOLD and PMBR and (b) GABA concentration and PMBR

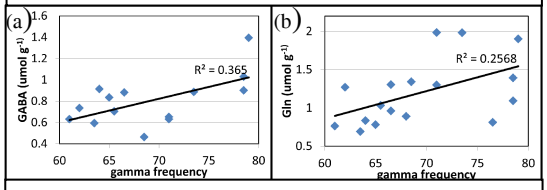

Fig 2: Plot showing relationships between (a) GABA and SI γ-frequency, and (b) Gln and SI γ-frequency

Conclusions: This study agrees with previous findings that the PMBR, measured using MEG in M1, is inhibitory in origin, and is not influenced by glutamatergic neurotransmission. The amplitude of the PMBR is found to be related to %BOLD change, suggesting a neural basis for fMRI BOLD responses in motor cortex. In addition, the SI γ-frequency can be related to levels of Glu as well as GABA, indicating that γ-oscillations are a product of both inhibitory and excitatory neurotransmission. In contrast to findings in visual cortex, BOLD changes in M1 did not appear to be related to SI γ-frequency in M1.

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References: 1. Gaetz, W. *et al. Neuroimage* **55** (2011). 2. Muthukumaraswamy et al, PNAS **106** (2009). 3. Brunel and Wang, *J Neurophysiol.* **90** (2003) 4. Donahue M and Near J. *et al,* Neuroimage **55** (2011). 5 Robinson and Vrba, *Recent advances in Biomagnetism,* (1998).