Investigating the neural basis of fcMRI

M. J. Brookes[1], J. Hale[1], C. Stevenson[1], J. Zumer[1], G. Barnes[2], J. Owen[3], S. Francis[1], S. Nagarajan[3], and P. Morris[1]

[1]Sir Peter Mansfield Magnetic Resonance Centre, University of Nottingham, Nottingham, United Kingdom, [2]Wellcome Trust Centre for Neuroimaging, University College London, London, United Kingdom, [3]Biomagnetic Imaging Laboratory, University of California San Francisco, San Francisco, California, United States

Introduction: In recent years, a great deal of fMRI literature has focussed on measuring functional connectivity (FC) between spatially separate but functionally related brain areas. FC is integral to human brain function and abnormal FC is thought to be responsible for pathological conditions (e.g. schizophrenia). Gaining a complete understanding of such phenomena therefore represents a key goal for neuroimaging. A number of data driven analysis techniques (e.g. ICA) have been employed to analyse resting state fMRI data and temporal correlation between BOLD timecourses has elucidated the structure of hitherto unknown brain networks. However, BOLD is an indirect measure of brain activity and the electrophysiological basis of haemodynamic FC cannot be assessed using fcMRI alone. MEG is a non-invasive technique that allows a more direct assessment of electrical brain function by measuring magnetic fields associated with synchronous current flow in pyramidal neurons. In an initial study[1], we used fcMRI and MEG to show that the envelopes of neural oscillations in the β frequency band (13Hz-30Hz), measured in MEG, were correlated between left and right motor areas, in a similar way to equivalent BOLD signals. In this study we extend this multimodal approach to explore in detail the nature of haemodynamic connectivity. We, (1) confirm that β oscillations are implicated in motor cortex FC, (2) employ three MEG FC metrics to investigate how β band oscillations mediate FC and (3) investigate the temporal dynamics of connectivity, showing that changes in FC occur on a timescale accessible to fMRI. Our study has implications to those developing fcMRI methodologies, and to those employing fcMRI to understand FC.

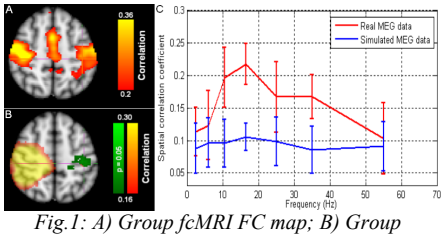

Fig.1: A) Group fcMRI FC map; B) Group fcMEG FC map computed using CAE; C) Spatial correlation between fcMRI and fcMEG.

Methods: Six healthy right-handed participants took part in two experiments. In the 1st 'resting state' experiment, subjects lay with their eyes open whilst 300s of resting state data were acquired. In the 2nd 'localiser' experiment, subjects performed a visually cued finger tap. BOLD data were acquired using a 7T Philips system. 24 contiguous EPI's (TR/TE 1500/25ms, 1.5x1.5x3mm^3 resolution, 198x72x192mm^3 FOV, SENSE 3) were acquired giving whole brain coverage. MEG data were acquired using a 275 channel CTF system (sample rate 600Hz). Co-registration of MEG to MRI was achieved using head digitisation and surface matching. Resting state and localiser recordings were repeated in both modalities.

fMRI data were motion corrected using spm5, corrected for respiratory and cardiac artifacts using RETROICOR, and spatially smoothed using a 3mm Gaussian kernel. The sensorimotor regions were localised by application of a GLM to localiser data. The peak in right motor cortex was selected as a seed region and the resting state signal from this region extracted. Correlation coefficients between this and BOLD signals from all other voxels were computed resulting in a correlation map showing resting state FC between the seed and all other brain areas. MEG data were filtered into frequency bands of interest. Localiser data were processed using SAM[2] to define a seed location in right motor cortex. Resting state MEG data were projected from sensor space to source space using a beamformer. For each voxel in source space, a Hilbert envelope was derived yielding a timecourse showing fluctuations in the envelope of oscillatory power for each band. To compute connectivity, projected MEG data were divided into *n* equal time segments of length Δ. Three metrics were then employed: i) ***CAE:*** For the seed and test locations, the average value of the Hilbert envelope was computed within each time window resulting in two new signals, each comprising *n* points. Correlation between these signals was then computed as a measure termed *Correlation of Average Envelopes*. ii) ***AEC:*** The correlation between seed and test envelopes was computed within each time segment (giving *n* correlation values). These were then averaged across segments yielding a metric termed *Averaged Envelope Correlation*. iii) ***ICoh:*** The imaginary part of coherence between the raw seed and test timecourses was computed within each segment and averaged across segments. The poor spatial resolution of MEG means that MEG voxels are not necessarily independent and cross talk between voxels could cause spurious connectivity. For this reason surrogate MEG data were constructed based on measured noise and simulated brain dipoles. All fcMEG metrics were also applied to surrogate data in order to obtain a null distribution and thus the statistical significance of results obtained from real data.

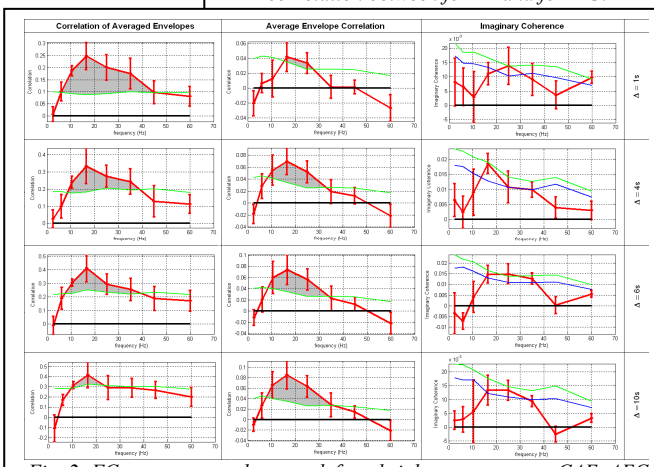

Fig. 2: FC measurement between left and right motor cortex: CAE, AEC and ICoh are plotted as a function of frequency for all 4 values of Δ.

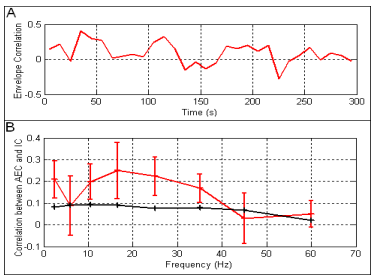

Fig. 3: A) Time course of resting state FC (AEC). Correlation between FC time courses measured using AEC and ICoh

Results: Fig. 1A and B show the group average fcMRI and fcMEG maps. The fcMEG map is computed using CAE and β band data. In both cases the seed is in right motor cortex and the highest correlation appears in left motor cortex (green overlay in Fig 1B indicates significance ($p<0.05$)). Fig. 1C shows numerically the spatial similarity between MEG and fcMRI based FC maps as a function of frequency. Using real MEG data (red line) spatial correlation between modalities is significantly ($p < 0.05$) higher than the same metrics applied to surrogate data (blue line). Fig. 2 shows FC measured between left and right motor cortices. (Locations based on localiser analyses.) The red lines show FC values whilst the green line shows the value required to achieve statistical significance ($p<0.05$). The 3 columns show the 3 fcMEG metrics whilst the rows show Δ = 1s, 4s, 6s and 10s. Note that the significance of AEC and ICoh increases with Δ whilst the significance of CAE decreases. Fig. 3A shows envelope correlation measured using β band data in 30 10s windows in a single subject. Note that significant changes in FC are apparent. Fig 3B shows correlation between FC timecourses (n=30, Δ=10s) generated using envelope correlation and imaginary coherence. Notice that the strongest agreement between FC techniques is for β band data.

Discussion and Conclusion: We have investigated electrodynamic effects that underlie haemodynamic FC measurement. Our results confirm that neural oscillations in the β band underlie haemodynamic motor cortex FC, with good spatial agreement between fcMRI and fcMEG. Fig. 2 shows that FC is observed using all three MEG metrics, however the timescale of the measurement, Δ, is important. CAE amounts to a low pass filter whilst AEC is effectively a high pass filter; it is interesting to note that AEC increases with Δ whilst CAE decreases. This implies an optimum timescale on which to measure electrophysiological FC, with maximal correlation within approximately a 10s window. (This is in agreement with recent work[3]). We have shown reasonable agreement between envelope correlation and Imaginary coherence, the implication being that electrophysiological envelope correlation is itself being driven by coherent bursts of oscillatory activity. Finite imaginary coherence implies a phase difference between oscillations in left and right motor cortices, and hence a finite time delay between hemispheres. Finally, we show marked changes in FC (Fig 3) across a 300s resting state experiment; the time scale of these changes is accessible to fcMRI. This outlines the importance of developing dynamic measurements of FC based on fcMRI data. (e.g. similar to measurements introduced by Chang and Glover[4]). Such metrics would shed light on the dynamic nature of not just motor cortex FC, but also activity and connectivity in other brain networks.

References: [1] Hale et al. Proc ISMRM 2010, Stockholm. [2] Robinson and Vrba, Biomag, 1998. [3] Liu et al, NeuroImage 51: 102-111, 2010. [4] Chang and Glover Neuroimage 50: 81-98, 2010. **Acknowledgements:** The Leverhulme Trust; Medical Research Council; Wellcome Trust; NIH; University of Nottingham