Assessing high frequency functional connectivity networks

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Introduction: Functional connectivity (fc), measured using fMRI, is typically assessed over long time periods (~5 minutes) (1). However, other modalities and recent fMRI work suggest that networks are non-stationary (2), that brain areas communicate on a dynamic basis (3), and that there are spontaneous neuronal events that may drive signal correlations (4). Here, we investigate the origin of correlations found between spatially distal brain regions in baseline (resting state) data and during task performance. Specifically we probe fc in the motor network (MN), dorsal attention network (DAN) and default mode network (DMN). By assessing signal correlations on varying timescales, and using paradigm free mapping (PFM) (4) (a model free method to detect discrete events in BOLD data with no prior knowledge) we test the hypothesis that fcMRI measures are driven by discrete periods of coordinated activity rather than low frequency oscillations.

Methods: Seven subjects took part in the study. The paradigm had 3 phases: ***Rest1:*** (0<t<300s) - subjects were instructed to rest with their eyes open; ***Task:*** (300<*t*<660s) - subjects performed a task (either a 'Motor' bilateral finger-tap or a '2-back' working memory task, responding with index-finger button press); ***Rest2:*** (660<t<1020s) - rest with their eyes open. All subjects performed the 'Motor' and '2-back' paradigms.

GE-EPI data were acquired using a Philips 7T Achieva system (2x2x2 mm^3, TE=25 ms, SENSE 3) with a TR=2 s and 30 slices. Cardiac and respiratory data were recorded. Data were realigned, corrected for slice timing (SPM5), RETROICOR corrected to remove physiological noise, and spatially smoothed (4mm Gaussian kernel). A GLM was used to identify voxels exhibiting significant BOLD change for the 'Motor' and '2-back' tasks; the voxel with the highest T-value and its 26 nearest neighbours were used as a seed region for the MN and DAN respectively. For the DMN, a seed region in posterior cingulate cortex was identified using MELODIC (FSL, Oxford). Standard seed-based correlation coefficient (cc) maps were made for all seeds for the Rest1 and Rest2 phases. Probe ROIs were defined for each subject as those regions exhibiting the highest cc score. For the MN seed, a probe ROI was found in the contralateral motor cortex; for the DAN, a seed in the lateral parietal area yielded a probe in the dorsolateral pre-frontal cortex; for the DMN: the probe was found in the inferior temporal gyrus/superior parietal regions.

To investigate temporal variations in functional connectivity, cc maps were then created between the seed and the probe ROIs for each of the 3 phases using a sliding window technique, with window lengths of 10-240 s. Fractional significant correlation (FSC) scores, defined as the fraction of sliding windows in which the probe significantly correlated with the seed, were computed for the seed and probe ROI in each network for each window length. Finally, data acquired during the 3 phases were analysed using PFM to identify spontaneous events, and the FSC analysis described above repeated on the PFM corrected data (i.e. raw data with discrete HRFs identified by PFM removed). For each seed/probe, the PFM output was temporally smoothed, and for each seed/probe a time point was classified as active if at least 35% of the voxels had a non zero PFM response.

Results: The correlation maps produced at different window lengths showed similar spatial patterns of activation in the MN, DAN and DMN, even for the 10 s window. Fig. 1 (blue line) shows that increasing the window length increases the FSC score, but this saturates at window lengths > 75s indicating that all windows show significant correlation. FSC scores were reduced for all subjects using PFM corrected data (Fig 1. red line) showing that discrete events contribute to the measured correlation. In the 'Motor' paradigm, Fig. 2A shows that considerably more events were detected by PFM in Rest2 phase compared to Rest1 phase for the MN; no trend was found for the DAN or DMN. Fig. 2B shows that during the '2-back' cognitive task, less spontaneous events occurred in the DMN during the task compared to both rest phases. Fig 2C shows that the number of motor events also decreased during the '2-back' cognitive task compared to rest.

Discussion: If a high FSC is found for a short window length, it is unlikely that the underlying correlations are mediated by low frequency oscillations since simulations (results not shown) indicate that under-sampling a low frequency signal reduces the correlation value. The FSC score for the PFM corrected data was reduced, suggesting that the correlations observed in the raw data, even at long time scales, were influenced by short events and not just low frequency oscillations. That said, underlying low frequency correlations are still apparent since the FSC score still increased with window length, even using PFM corrected data.

The trend for increased spontaneous events in the MN following the motor task is possibly due to discomfort caused by the 6 minute tapping task. There was no such trend for the number of events found in the DMN or DAN after the task. Spontaneous events were significantly reduced in the DMN during the '2-back' cognitive task, suggesting that short events are a significant factor in DMN signals, contradicting the hypothesis that low frequencies dominate correlations. The reduced number of events found in the MN during the '2-back' task may, at first, seem unexpected since the task involved a button press. However, it should be noted that the probe ROI is derived from the maximum T-score of the hand motor ROI, and thus did not fully coincide with the index finger motor regions used for the button press, and so there may be insufficient overlap or response amplitude to class the button press as an event which requires 35% of voxels to be active. The button press may however have suppressed larger hand movements during the task, and may also explain the increase in MN activity after the N-back task in some subjects.

Conclusion: Functional connectivity can be identified using short time windows indicating that it is not dominated by low frequency oscillations. Moreover functional connectivity is affected by short spontaneous events, and changes in the number of such events can be observed using PFM.

References: (1) Biswal B et al. (1995) MRM 34: 537-541, (2) Koene RA et al. (2010) J Neurophysiol 103: 297-321, (3) Varela F et al.(2001) Nature Reviews Neuroscience 2, 229-239, (4) Gaudes CC et al. (2010) HBM. *This work was funded by the MRC, Leverhulme trust and the University of Nottingham*

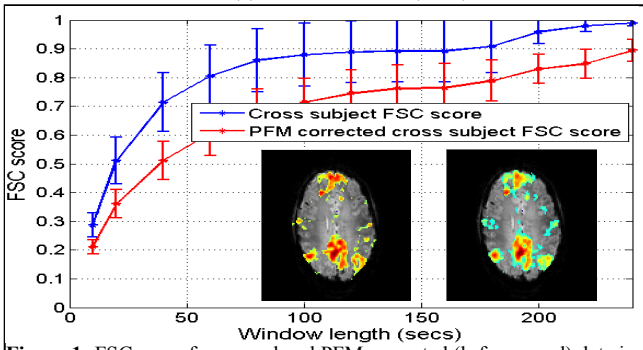

Figure 1: FSC score for normal and PFM corrected (hrf removed) data in the DMN Rest1 phase of the 'Motor' paradigm. Insert left, cc map with a window length of 40s and insert right, window length of 120s (rest1)

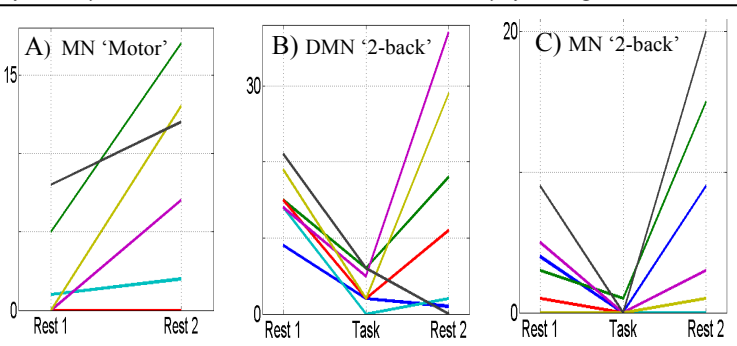

Figure 2: Each line represents a subject. A: number of events found rest1 and rest2 in the MN and motor data. B, C) change in the number of events found during over the 3 periods for the DMN in the 2-back data (B) and MN in the 2-back data (C)