Clustered Spontaneous Coordinated Network Events Contribute to Functional Connectivity

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Introduction: In functional MRI, functional connectivity can be measured via temporal correlation between BOLD measured at between spatially distinct brain regions[1]. Typical analysis assumes stationarity between the signals and generally considers frequencies <0.1 Hz. The origins of this low frequency signal are a matter of debate but spontaneous events may contribute. Even when the brain is apparently at 'rest' it will constantly perform tasks, whether attending to the outside word (e.g. listening, visual stimulation), movements or self generated thoughts. Even unilateral movements can evoke bilateral responses in the motor network and so this spontaneous activity must have an effect on functional connectivity.

Aim: To show that spontaneous BOLD events coordinated across a network, found by paradigm free mapping[2] (PFM), a model free method for detecting spontaneous BOLD events on a voxelwise basis without prior knowledge of their timings, and short window correlation analysis produce correlation maps displaying strong network structure and high connectivity between network nodes that is significantly higher than baseline level, contributing to long term measures of connectivity.

Methods: Twelve subjects were scanned on a 7T Philips Achieva system. Four minutes of resting state EPI data were recorded (TE/TR 25/2000ms, $2\times2\times2mm^3$ resolution) along with physiological data using a respiratory belt and VCG. SPM5 was used to realign and correct data for slice timing; physiological noise was removed using RETROICOR, images were smoothed (4mm FWHM Gaussian kernel) and corrected for drift (subtraction of a 3rd order polynomial). For each subject, spatial ICA[3] was used to mask of the nodes of the motor network (MN), fronto-parietal network (FPN) and default mode network (DMN) for each subject. Seeds were defined in the left motor cortex (MN), left dorsolateral prefrontal cortex (FPN) and the posterior cingulate cortex (DMN) by averaging all the voxel timecourses in the seed. Paradigm free mapping was applied to each data set to find BOLD events; the results of PFM include an activation timeseries (ATS) for each voxel that contains the timings and deconvolved amplitudes of the detected events. Nodal ATS were computed for each subject in each of the defined ICA nodes by summing all the voxelwise ATS of a single node. When a nodal ATS exceeded one standard deviation above its baseline, this was termed a Nodal Event; when all nodes of the same network exhibited a nodal event simultaneously, this was defined as a Coordinated Network Event (CNE). For each CNE, the number of contributing voxels were counted and normalised by the number of voxels in the network. For each network and subject, a single Coordinated Network Event time was chosen at random, using this time and the next 30s of data, a seed based correlation map was computed using the relevant seed. Additionally, for each subject a correlation map was computed for each network that was at a Null Period, not close in time to a Coordinated Network Event. These correlation maps were transformed into MNI space using FLIRT and averaged across subjects. Finally, the average correlation coefficient in the nodes of each network was computed both following the Coordinated Network Event and for the Null Period and averaged across subjects.

Results: Figure 1 compares average correlation maps calculated following CNEs (left) and during Null Periods (right). It shows and higher correlation between the nodes following a CNE than during the Null Periods. Notably the network structure is still apparent even when no strong coordinated activity is detected between the nodes. Figure 2 shows that there is a significant difference in correlation between the CNE and Null periods averaged across subjects (Wilcoxon sign rank test, $p < 0.05$). Table 1 shows the average percentage of a network that was active during a CNE. Coordinated Network Events were detected at a rate of ~ 3 per 4 minute in all networks and all subjects, consistent with low frequency oscillations reported in resting state fMRI data

Discussion: These results show that CNEs found by PFM cause significant network connectivity as assessed by correlation analysis. Correlation maps calculated using short window (30s) seed based correlation analysis, show remarkably similar network structure to those created using long windows and ICA[4], suggesting that functional connectivity is to a degree driven by discrete events. The network structure shown during a Null Period is attenuated compared to the period following a CNE, this suggests that other factors may be contributing to functional connectivity. It is notable that only 12 CNEs (one for each subject) produced the diffuse large area network depicted in figure 1, even though the individual events may have involved focal activation within each node. Nonetheless, a low percentage of each network (~34%) was active during each CNE, showing that the networks have functional substructures that do not involve the entire network to perform some given task.

Conclusion: Spontaneous events that are detected by PFM recruit multiple network nodes and contribute significantly to functional connectivity measures on a short timescale; this will contribute to long term connectivity measures. These events only involve a small fraction of the network nodes, highlighting the fact that a single network contains substructures that are involved in specific activities.

References: 1. Biswal et al Functional Connectivity in the Motor Cortex of Resting Human Brain using Echo-Planar MRI, MRM 1995; 9: 537-541, 2. Gaudes C et al Detection and characterization of single-trial fMRI BOLD responses: paradigm free mapping, HMB 2011; 9 (32): 1400-18 3. Beckmann CF, Smith SM (2004) Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE transactions on medical imaging* 23:137–52 4. Damoiseaux J et al. Consistent resting-state networks across healthy subjects, PNAS 2006; 37 (103): 13848-53
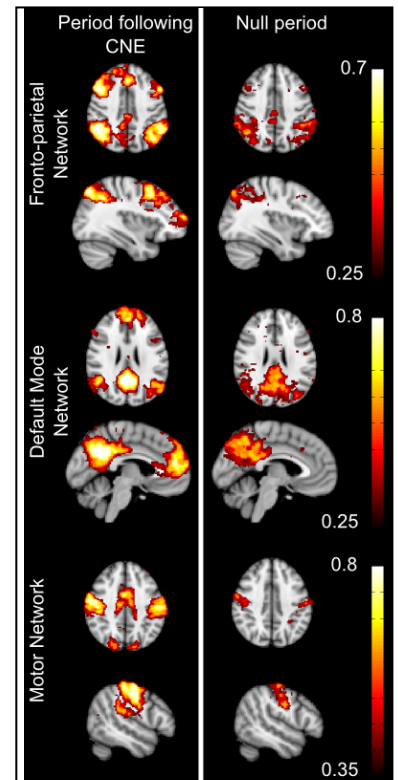
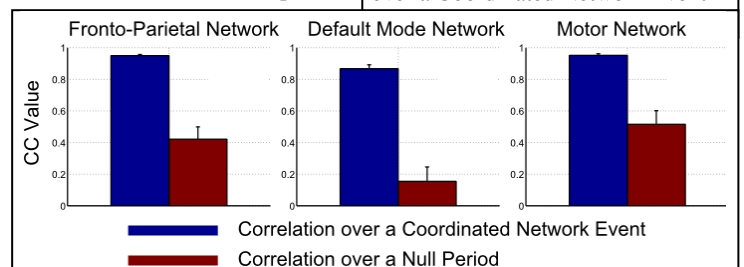Figure 1: Average correlation maps over a Coordinated Network Event

Figure 2 shows a significant decrease in correlation during the Null Period compared to the period following a Coordinated Network Event for all networks. (Wilcoxon sign rank test, $p < 0.05$).

Network	Percentage of active voxels during a CNE
MN	34 +/- 13%
FPN	32 +/- 8%
DMN	36 +/- 8%
All	34 +/- 7%

Table 1: % of network active following a CNE