Dynamic functional connectivity measures using fcMRI

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Introduction: Communication between brain areas and the formation of brain networks is key to understanding how the brain functions; furthermore perturbed functional connectivity (fc) within networks is thought to be responsible for some pathologies. Therefore it is important to better understand the processes underlying fc. In many fcMRI studies, fc is measured from the temporal correlation between BOLD timecourses from separate locations over long time windows (~5 min) [e.g. 1]. However, other modalities have shown that fc is non-stationary over time with significant modulation even in the resting state [2], and that this modulation occurs on a timescale accessible to fMRI. This suggests that measurement of fc on a shorter timescales using fcMRI could yield important new information. Indeed recent work suggests that the temporal variability in wavelet transform coherence can be used to asses non-stationarity [3]. Here three specific issues are addressed: 1) An empirical technique is proposed to derive the statistical significance of fc maps created for different time windows. 2) Dynamic changes in motor network (MN) and default mode network (DMN) connectivity over time on a 20 s timescale are demonstrated. 3) It is shown that fc information exists on both short (20s) and long (300s) timescales by filtering out fast fluctuations for long timescale analyses.

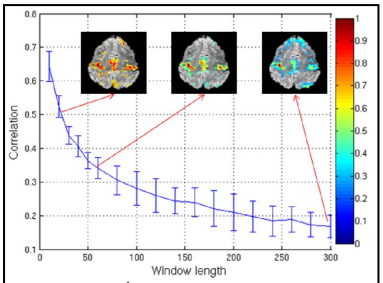

Fig. 1 95th percentile threshold for different window lengths. Top, fc map for window length of 20s, 60s and 300s

Methods: Six subjects took part in the study which was approved by the local ethics committee. A BOLD localiser experiment comprising a visually cued finger-tapping task (30s on; 30s off; 5 trials) was performed to plan subsequent slice placement and locate a motor seed region. This was followed by a 'Motor' experiment in which 720s of data were recorded: during the first 300s subjects were instructed to remain at rest with their eyes open, for 300<*t*<420s subjects were asked to tap their fingers and for the final 300s subjects again remained at rest. To give high sensitivity in fc data, EPI data were recorded using a 7T Philips Achieva system (1.5x1.5x3mm^3 voxel resolution, TE=25, SENSE 3). Localiser data were acquired with a TR of 1.5 s for 20 slices; the 'Motor' experiment was collected with a TR of 1s for 16 slices. Cardiac and respiratory data were acquired using a VCG and respiratory belt.

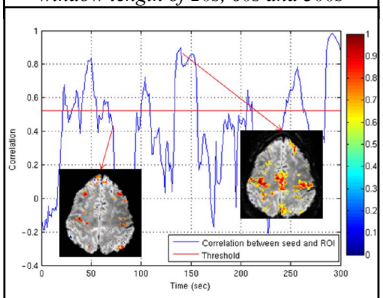

Fig. 2 Correlation timecourse for the motor network showing correlation maps at different time points for a 20s window

Analysis: For this study of the timescale of resting oscillations, all analyses were performed on the initial 300s of the 'Motor' experiment data. SPM5 was used for realignment and slice timing correction. RETROICOR was used to remove non-neuronal physiological noise and data were smoothed spatially using a 3mm Gaussian kernel. A GLM was generated for the localiser data and used to compute T-statistic maps; for each subject the voxel with the highest T-value in left motor cortex and its 26 nearest neighbours were used as a seed region for the motor network. An anatomically defined seed region (3x3x3 voxels) in the anterior cingulate cortex was also extracted for the DMN. Pearson correlation coefficients between MN and DMN seed regions and BOLD signals from all other voxels were computed resulting in correlation maps showing fc between the seed and all other areas. fc maps were generated for two time windows: Firstly, data were divided into 20s overlapping sliding windows, one for each point in the timecourse and fc maps computed within each window allowing dynamic assessment of fc. Secondly, a single fc map was generated using all 300s of the resting period. Finally, a 60s rolling average low-pass filter was applied to the data removing signals correlated on a short (<60s) time scale, allowing the discrete assessment of high and low frequency oscillations. fc maps were recomputed to assess the contribution of low frequency oscillations to resting state fc maps.

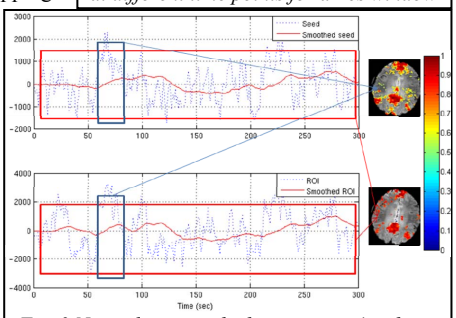

Fig. 3 Normal vs smoothed timecourse (seed top, ROI bottom) and corresponding correlation maps

The statistically significance threshold level for fc maps from differing time windows was computed empirically from surrogate fMRI data. To create surrogate data, signals from all brain voxels were Fourier transformed; the phase of each frequency element was randomised; signals were then inverse Fourier transformed. This yielded surrogate BOLD signals for all voxels with power spectra equivalent to those in the original data, but with any underlying correlation between voxels destroyed due phase randomisation. fc maps were constructed and the distribution of correlation coefficients in the surrogate data used as a null distribution. We computed the 95th percentile correlation value from the null distribution and used this to threshold the 'real' resting state data for each time window.

Results: Fig. 1 shows results of our empirical data derived thresholding technique. The plot, based on the surrogate fMRI data, shows the correlation coefficient required for 95% statistical significance, as a function of window length used to generate fc maps. As expected the null correlation coefficient distribution becomes broader as the window length is reduced. The fc maps shown in Figure 1 use this thresholding to display voxels significantly correlated with a seed in left motor cortex for 3 window lengths (20s, 60s, 300s, left to right). It can be seen that the characteristic spatial signature of the motor network is observed for all three timescales. Fig. 2 shows the variation in correlation coefficient measured between signals from the left MN seed and right motor cortices, for 20s sliding windows spanning the 300s rest period; the red line shows the threshold for statistical significance. Note that correlation varies significantly as a function of time with the appearance and disappearance of the characteristic motor network, as illustrated by the example fc maps generated using windows 70<t<89s and 136<t<155s. Fig. 3 shows the raw timecourses for regions of interest in the anterior (top) and posterior (bottom) cingulate cortex (blue) and these same timecourses smoothed with a 60s rolling average filter (red). The top correlation map shows DMN fc in a 20s window computed in the range 50<t<69 for the unsmoothed data, highlighting DMN fc on a short (<20s) time scale. The bottom map shows the DMN fc due to low frequency oscillations measured using the low pass filtered data and using a 300s window.

Discussion and Conclusion: We have used ultra-high field fcMRI to test the feasibility of measuring dynamic changes in brain fc between nodes of two well established resting state networks: MN and DMN. We have described a method to derive statistical thresholds for fc maps created using any temporal window (or any degree of temporal smoothing). Figure 2 shows that marked changes in fc occur during a typical resting state experiment on a timescale accessible to fcMRI, verifying findings from other neuroimaging modalities. Finally, by filtering data to remove fast signal changes we have shown that information used to construct fc maps occurs on both a short (<20s) and long (>60s) timescale. Future work in this area will look to exploit these analysis methods to assess how dynamic connectivity changes during a task positive state.

References: [1] Biswal B et al. (1995) MRM 34: 537-541; [2] De pasquale, PNAS; [3] Chang and Glover, [4] Hale et al, MAGMA, 2010 in press.

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