PRIOR COGNITIVE STATE CAN INFLUENCE FUNCTIONAL CONNECTIVITY NETWORKS AT THE INDIVIDUAL AND GROUP LEVEL.

Chris Tailby[1,2], David F Abbott[1,3], and Graeme D Jackson[1,3]

[1]Brain Research Institute, Florey Neuroscience Institutes, Melbourne, Victoria, Australia, [2]Psychological Sciences, University of Melbourne, Melbourne, Victoria, Australia, [3]Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia

Background

Resting state functional connectivity (FC) analysis, used to identify brain regions with shared variance in their temporal timecourses, is increasingly used in basic and clinical neuroscience. In basic science FC analysis has been used in attempts to map the "functional connectome" of the human brain, and in clinical science it has been used to identify abnormal network states in neurological and psychiatric disease (Biswal et al., 2010, *PNAS*, 107:4734). Large, multicentre data pooling resources now exist, such as the 1000 Functional Connectomes Project (www.nitrc.org/projects/fcon_1000/), enabling FC analyses using very large samples. Implicit in this approach is the assumption that "all resting states are created equal," permitting pooling of resting state data across subjects and centres irrespective of any other imaging protocols performed in temporal proximity to the collection of resting state data. Previous work has suggested that FC is dependent upon the cognitive task engaged in immediately prior to collection of resting state data (Waites et al, 2005, *HBM*, 24:59). We sought to explore this possibility further, as any bias introduced by prior cognitive state could propagate through to influence the results of FC analyses pooled across different subjects in whom resting state data has been obtained during different experimental protocols.

Methods

Twenty five healthy volunteers participated in the study. All protocols were approved by the relevant institutional Human Research Ethics Committee. The fMRI studies were carried out with a 3T GE Signa LX whole body scanner (General Electric, Milwaukee, WI), using a standard birdcage quadrature head coil. Functional images were acquired as a series of gradient-recalled echo planar imaging (GR-EPI) volumes (TR/TE = 3,600/40 ms, flip angle = 60 degrees, 25 oblique slices 4 mm thick + 1-mm gap, 24-cm field of view (FOV), 128 × 128 matrix). Subjects were scanned continuously for 27:00 minutes (450 volumes), alternating between periods of extended rest (90 volumes) and block design task (90 volumes, alternating rest and task every 10 volumes) according to the following sequence: rest1, task1, rest2, task2, rest3. The two tasks were a language task – Orthogoraphic Lexical Retrieval (OLR), and a motor task – finger tapping (Motor); task order was randomized across subjects. All preprocessing (time slice correction, realignment, normalization, smoothing [8mm FWHM]) and statistical analyses were performed using SPM8. Random effects analyses of the OLR and Motor activation tasks were preformed to identify language and motor seeds, identified as the voxels of maximal de/activation in each individual subject's OLR/Motor activation study within a 9.5 mm radius of the voxels of maximal de/activation in four distinct clusters in each of the OLR and Motor random effects SPMs, yielding eight seeds in total. FC analyses seeded from each of these seeds were conducted on each of the blocks of rest data (rest1, rest2, rest3). The seed timecourse was obtained as the average timecourse within a 5mm sphere centered on the seed voxel. The design matrix for FC analyses also included motion correction parameters, white matter, grey matter, and global within brain signals, along with discrete cosine functions used to exclude frequencies outside the range 0.01-0.8 Hz. We hypothesized that were prior cognitive state to influence FC, differences in FC maps would be greatest when comparing post-OLR rest blocks with post-Motor rest blocks. We therefore performed, separately at each seed location, repeated measures t-tests comparing, across subjects, FC maps from post-OLR blocks with FC maps from post-Motor blocks, yielding eight repeated measures t-tests in total. Resulting SPMs were initially thresholded at $p<0.001$ (uncorrected) to induce clusters, followed by topological FDRc at $p<0.00313$ ($p<0.025/8$) to control for the eight t-tests.

We also performed multisession analyses, comparing post-OLR and post-Motor FC from each of the eight seeds in each subject, to examine the prevalence of significant FC changes in individuals. These multisession analyses were used to construct penetrance maps.

Results

Robust FC maps were observed for each seed in each rest block in each subject (e.g. Figure 1). A significant difference was observed in one of the comparisons of post-OLR FC with post-Motor FC (FRCc $p<0.00313$): connectivity from a seed in precuneus to right precentral gyrus was increased after the Motor task relative to the OLR task; at a less conservative topological FDRc threshold of $p<0.05$ this increase in connectivity was observed bilaterally in precentral gyrus (Figure 2A,B). This suggests increased default mode connectivity to bilateral motor areas following performance of a motor task relative to following performance of a language task. Multisession analyses (e.g. Figure 3A,B), using a feature inducing threshold of $p<0.001$ (uncorrected) followed by topological FDRc at $p<0.05$ indicated that all subjects showed significant FC changes that depended upon prior cognitive state for at least two of the seed locations (median: 5 seed locations). Penetrance maps revealed, however, that the locus of these changes was highly variable across subjects (e.g. Figure 3A,B).

Conclusions

Using a sample of 25 healthy volunteers and controlling for multiple statistical tests, at the group level we observed a significant change in FC as a function of prior cognitive task in one of eight comparisons (based on a seed from the precuneus). At the individual level, changes in FC as a function of prior cognitive state were relatively common. Penetrance maps indicate that the locus of significant changes in FC in individual subjects were inconsistent across subjects, explaining the lack of significant findings at the group level. Collectively, these results indicate that while FC often exhibits moderate fluctuations in a given individual as a function of prior cognitive state, only for particular seeds do such fluctuations translate to effects at the group level, at least with groups of sample sizes such as ours. The potential import of such changes in large scale multicentre data sets is uncertain: if prior cognitive state varies from centre to centre, this could act as a source of additional variance; if the majority of sites collect data under similar circumstances this may actually serve as a variance reducing influence. Regardless, our data suggest that individual changes in FC contingent upon prior cognitive state are common, and can in certain circumstances produce effects that are expressed at the group level.

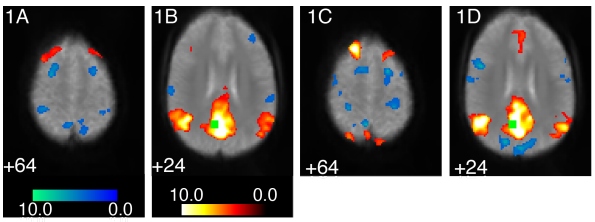

Fig 1: Example post-Motor (A,B) and post-OLR (C,D) FC maps obtained frpm one example participant using a seed in precuneus (green square). Hot colors: correlation; cool colors: anticorrelation.

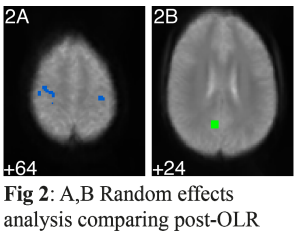

Fig 2: A,B Random effects analysis comparing post-OLR vs post-Motor FC maps seeded from precuneus (green square). Cool colors: post-Motor FC > post-OLR FC.

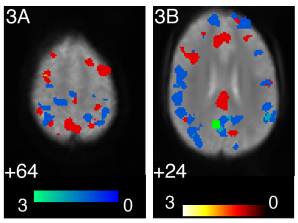

Fig 3: A,B penetrance map, summarising the multisession analyses of all 25 subjects, comparing post-OLR vs post-Motor FC maps seeded from precuneus (green square). Colors report n.