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A processing stream for timeseries and activation-based fMRI functional connectivity analysis

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Objective
While classical activation analysis is successful in identifying the brain regions implicated in the performance of specific tasks, more and more studies are looking into analyses that could help identify networks of regions collaborating in carrying out task-related processing and observe their connectivity in different conditions or between groups. There are a number of ways to conduct functional connectivity analysis and published studies vary both in its conceptualization as well as specifics of data preprocessing and analysis. We have developed a processing stream for functional connectivity analysis that combines across-subject mean activity-based computation of correlations reflecting the degree of coactivation of regions during task performance and within-subject timeseries-based computation of correlations reflecting the coupling of regions during task performance. Analyses were applied to compare functional connectivity of core working memory regions during working memory performance between patients with schizophrenia and matched controls.

Methods
The analysis was conducted on functional MRI imaging data of 38 patients with schizophrenia and their matched controls presented in a previous study (1). The data for each subject consisted of two block-design runs (TR = 2.5 sec; 102 frames), of a 2-back working memory task (4x16 trials) and fixation (4, 3x10, 4 frames). Word stimuli were used in one and faces in the other run. After initial preprocessing steps and transformation to atlas space, activational analysis was used to identify the regions of interest (ROI) implicated in working memory processing in both groups and tasks. Individual activational results were used to further constrain the individuals' ROI to 6 most activated voxels within the group defined 12mm spherical ROI. For across-subject analysis functional runs were spatially smoothed and mean task-related activation was extracted to form ROI x subject matrix on which ROI correlations were computed. For within-subject analysis functional runs were further preprocessed by high-pass filtering and removal of nuisance variables (movement parameters, ventricle, white matter and whole brain signal and signal from 8 most variable voxels) using multiple regression. Regions for nuisance signal extraction were defined individually for each bold run. Task related frames were then extracted from residual bold signal and correlation between ROI were computed over resulting task-related timeseries. Group differences were assessed using second level analysis.

Results & Discussion
Across-subject average activity-based connectivity analyses revealed reduced connectivity of right DLPFC to other regions in patients with schizophrenia, which might reflect their inability to recruit the region appropriately, and enhanced connectivity of left DLPFC to other regions, which might be a compensatory effect. Within-subject timeseries-based connectivity analyses revealed reduced prefrontal to parietal connectivity in patients, a subnetwork, which has been considered crucial for executive control, and enhanced connectivity within subcortical regions that could be either a compensatory effect or a consequence of reduced top-down control.

Conclusions
The developed processing stream enables computation of two independent and complementary estimates of functional connectivity, which have proved to be informative in exploring differences in working memory related neuronal processes between patients with schizophrenia and their normal controls.

References
1. D. Barch, et al., J Abnorm Psychol 111, 478-94 (2002)