Unconstrained cross-network directional interactions in schizophrenia

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Introduction: Large-scale intrinsic brain networks have been repeatedly observed to be dysfunctional during task performance in schizophrenia. Effective connectivity studies during cognitive tasks also show reduced causal interactions within the intrinsically organized brain networks. In healthy controls, the existence of a hierarchical causal architecture among the nodes constituting the large-scale networks has been noted even at a 'resting' state, independent of task constraints. In particular the salience network that comprises of the anterior insula and the anterior cingulate cortex, appears to act as a switch between other large-scale networks. Anterior insula appears to have the most significant unidirectional causal influence among a set of 33 nodes examined. It is unclear whether such cross-network causal interactions are affected in schizophrenia.

Methods: We studied this problem by recruiting 38 medicated, clinically stable patients with DSM-IV schizophrenia/schizoaffective disorder (age 34.5(9.1); 9 females) and 35 healthy controls (age 33.5 (9.1), 10 females), group matched for age, gender and parental socio-economic status. 10 minutes resting fMRI was collected in 3T Phillips Achieva scanner with eyes open (dual-echo EPI, 8ch SENSE, TE1/TE2 = 25/53ms, flip 85°, FOV 255 x 255 m, TR=2500ms, 240 time points with 40 contiguous axial slices). Pre-processing included SPM-8 based slice-timing correction, rigid body registration and realignment. Retrospective physiological correction was performed (Retroicor). ArtRepair was used to correct movement artifacts through an interpolation method. Spatial smoothing was done using 8mm FWHM kernel. Variance accounted for by nuisance covariates (6 head motion parameters, global mean signal, white-matter signal and CSF signal) was removed by regression. 8 ROIs corresponding to three resting networks (default mode – ventromedial prefrontal cortex [vMPFC] and posterior cingulated cortex [PCC]; salience network – right and left anterior fronito-insular cortex [FIC] and dorsal anterior cingulate [ACC]; central executive network CEN – right and left posterior parietal [PPC] and right dorsolateral prefrontal [DLPFC]) were based on the nodes reported by Sridharan et al. To identify the ROIs with maximum anatomical likelihood in the present sample, we used functional activation data during a 2-back task performed by all subjects included in the study (2 back minus rest contrast, one sample t-test, FWE corrected p<0.05) and chose the local maxima that were in closest correspondence to Sridharan’s coordinates (Table.1). A 6-mm radius sphere centered on each local maximum was used as the seeds. The extracted fMRI time series first went through a hemodynamic deconvolution, followed by correlation purged granger causality analysis to get the directional connectivity network for each individual subject. A one-tailed T-test was performed between the Schizophrenia group and the control group with a 5% significance level in order to find paths significantly different between the Schizophrenia group and the control group with a 5% significance level in order to find paths significantly different between the Schizophrenia group and the control group with a 5% significance level.

Results and Discussion: Cross-network causal interactions were significantly impaired in schizophrenia even when no external task constraints are placed on the subjects (Fig.1). This diffuse breakdown in effective connectivity is likely to contribute to inefficient cerebral recruitment when task demands are placed, leading to a global cognitive deficit across various domains. Intriguingly, the presence of such disconnectivity despite clinical stability and medicated status suggests that diffuse cross-network disconnectivity is likely to contribute to the core pathophysiology of schizophrenia. Future work focusing on pharmacological/cognitive manipulation of cross network causal interactions could help identify mechanisms through which the diffuse breakdown of effective connectivity could be manipulated.

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