Identification of a Schizophrenia-Related Disease Pattern using Resting State fMRI

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Target Audience Psychiatrists, neuroscientists, psychologists, physicists.

Purpose: Schizophrenia and associated psychotic disorders are serious and often lifelong illnesses. The disease burden gradually rises into early adulthood and peaks between 25 and 50 years of age[1]. Schizophrenia accounts for 7.4% of disability adjusted life years caused by all mental and substance use disorders according to the 2010 Global Burden of Diseases, Injuries, and Risk Factors Study, with the highest disability weight of all disorders[1]. Although prior resting state fMRI studies in schizophrenia have identified individual networks that play a role in disease pathology, they are based mainly on univariate data analysis approaches. In the current study we analyzed resting state fMRI data using multivariate data analysis to derive a schizophrenia disease pattern (SDP) that may serve as a biomarker for schizophrenia in future studies.

Methods: We studied 50 first-episode (36M/14F, mean age = 21.2±5.1 years) and 25 chronic (11M/14F, 45.5±9.9 years) schizophrenia patients with age- and sex-matched control groups (50 controls matched to the first episode patients, 35M/15F, 21.2±5.5 years; 25 controls matched to the chronic patients, 11M/14F, 45.5±8.7 years). The 50 patients in the first-episode group and their respective controls were divided randomly into two independent cohorts that were used for either pattern derivation (training) or verification (testing 1). Chronic patients with schizophrenia and their age- and sex-matched controls were used as a second independent testing dataset. Resting state fMRI (rsfMRI) were acquired on 3T clinical scanner at North Shore University Hospital, that included 150 volumes, FOV = 24 cm, TE = 30 ms, TR = 2 sec, 40 slices of 3 mm in 5 minutes. In addition, a T1-weighted structural image was acquired with FOV = 24 cm, TE = 3.02 ms, TR = 7.8 ms, TI = 650 ms, 216 slices of 1 mm. The rsfMRI preprocessing including motion correction, brain extraction, spatial smoothing and temporal filtering was performed using FMRIB software library (www.fmrib.ox.ac.uk/fsl). The rsfMRI volumes were registered to the subject's structural T1 and then to the Montreal Neurological Institute template. The rsfMRI from the training set of first episode schizophrenia patients and their matched controls were analyzed using spatial group independent component analysis[2] (ICA) with GIFT software in which 40 independent components (ICs) were identified. The subject spatial maps were estimated using dual regression. The number of components was estimated using minimum description length criterion[2]. Subject scores, reflecting the individual expression of each IC, were computed by taking the dot product of the mean group map with the subject's spatial map using a previously described voxel-based computational algorithm[3,4]. Multivariate logistical regression (JMP software) was then utilized to identify a subset of ICs that yielded maximum separation of schizophrenia patient and control subject scores in the training dataset. A schizophrenia disease pattern (SDP) was computed by linearly combining group ICs in this subset according to the parameters estimated through regression analysis. We then assessed SDP expression scores in two independent replication datasets (first-episode and chronic patients).

Results: Two ICs representing independent contributions from the sensory motor cortex, SMA, cingulum, thalamus, putamen, temporal, frontal, hippocampus, and amygdala achieved maximum separation between schizophrenia patients and controls in the first-episode training set ($p < 0.001$). The SDP (Fig. 1) was obtained by using a linear combination of these two ICs. The estimated parameters in using a logistic regression model was subsequently applied to the two replication datasets to compute expression values (subject scores) for each individual. We found that SDP expression scores (Fig. 2) in the first-episode training set were higher ($p<0.001$, Student *t*-test) compared to healthy volunteers. Moreover, prospectively computed SDP expression values were also elevated in the first-episode testing dataset ($p<0.005$, Fig. 2) as well as the chronic patient testing dataset ($p<0.05$, Fig.2) compared to their respective age- and sex-matched healthy volunteer groups.

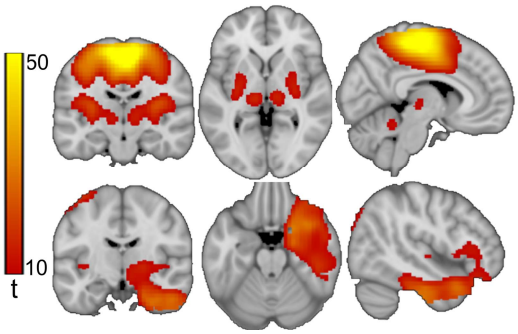

Figure 1 The schizophrenia-related disease pattern (SDP)

Discussion/Conclusions: In this study we have derived a SDP network using rs-fMRI from patients with first-episode schizophrenia compared to healthy volunteers. We have tested this brain network in two independent groups of first-episode and chronic schizophrenia patients. The SDP expression scores were elevated in patients compared to healthy volunteers in each of the three datasets. This SDP may have the potential to serve as a trait-related biomarker in future schizophrenia studies.

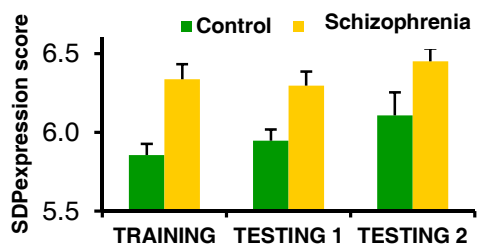

Figure 2 Schizophrenia -related pattern expression scores

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