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Abnormal interactions of verbal- and spatial-memory networks in young people at familial high-risk for schizophrenia

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ABSTRACT

Background: Working memory impairment (especially in verbal and spatial domains) is the core neurocognitive impairment in schizophrenia and the familial high-risk (FHR) population. Inconsistent results have been reported in clinical and neuroimaging studies examining the verbal- and spatial-memory deficits in the FHR subjects, due to sample differences and lack of understanding on interactions of the brain regions for processing verbal- and spatial-working memory.
Methods: Functional MRI data acquired during a verbal- vs. spatial-memory task were included from 51 young adults [26 FHR and 25 controls]. Group comparisons were conducted in brain activation patterns responding to 1) verbal-memory condition (A), 2) spatial-memory condition (B), 3) verbal higher than spatial (A–B), 4) spatial higher than verbal (B–A), 5) conjunction of brain regions that were activated during both A and B (A ∧ B). Group difference of the laterality index (LI) in inferior frontal lobe for condition A was also assessed.
Results: Compared to controls, the FHR group exhibited significantly decreased brain activity in left inferior frontal during A, and significantly stronger involvement of ACC, PCC, paracentral gyrus for the contrast of A–B. The LI showed a trend of reduced left-higher-than-right pattern for verbal-memory processing in the HR group.
Conclusions: Our findings suggest that in the entire functional brain network for working-memory processing, verbal information processing associated brain pathways are significantly altered in people at familial high risk for developing schizophrenia. Future studies will need to examine whether these alterations may indicate vulnerability for predicting the onset of Schizophrenia.

1. Introduction

Schizophrenia is a chronic and heritable mental disorder that is characterized by positive and negative symptoms and neurocognitive impairments (Bang et al., 2015). First-degree relatives (offspring and siblings) of patients with schizophrenia have an almost 10-fold increased risk of developing schizophrenia compared with the general population (Gottesman, 1994). Those first-degree relatives of the schizophrenia patients, who are still within the age range of risk for developing schizophrenia (ages from 13 to 30 defined in Li et al. (2007b))), are considered at heightened risk (FHR). From the literature, FHR subjects for developing schizophrenia have received increased attention in clinical and neuroimaging studies aimed at determining the underlying neurobiological vulnerability that leads to, and predict the onset of schizophrenia.

Clinical studies have suggested that in the FHR individuals, neurocognitive deficits, especially in the verbal- and spatial-working memory domains, exist prior the presentation of positive and negative symptoms, and can be used as strong predictors of schizophrenia (Pukrop and Klosterkotter, 2010; Dickson et al., 2014; Scala et al., 2014; Bang et al., 2015; Hou et al., 2016). Among these studies, Bang et al. found that behavioral performance scores of the tests for verbal- and spatial-working memory in the FHR subjects were intermediate between low risk controls and patients with first-episode schizophrenia (FES) (Bang et al., 2015). A Meta-analysis of 25 studies [published between January 1987 and February 2013, including clinical longitudinal

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data from 905 FES, 560 HR (including both clinical HR and FHR), and 405 healthy controls (HC)] suggested that verbal-memory deficits were already established in the HR subjects before the prodromal phase of psychosis, while no further decline occurred during follow-up assessments (Bora and Murray, 2014). In a new study, Dickson et al. also found verbal- and spatial memory deficits in the FHR subjects when compared to HC; whereas by adjusting statistical analyses for IQ, no significant between-group differences in any neurocognitive domains were remained (Dickson et al., 2014). The inconsistency among these existing neurobehavioral studies may be caused by the heterogeneity of the study samples, different tasks and assessment criteria being used, as well as other factors.

Although the etiology of schizophrenia is still unknown, neuroimaging studies have established that disturbed activities and connectivities in the functional brain networks for sensory and cognitive processing underlie neurocognitive deficits in patients with schizophrenia and the FHR population (Li et al., 2009, 2010, 2012). Several spatial-working memory tasked-based fMRI studies have reported that compared to HC, the FHR subjects had decreased activation in the dorsolateral prefrontal cortex (DLPFC) and the inferior parietal cortex (IPC) (Callicott et al., 2000; Keshavan et al., 2002). One early fMRI study reported that during a verbal-working memory task, the FHR subjects showed greater task-elicited activation in prefrontal cortex (PFC) and anterior cingulate cortex (ACC) (Thermenos et al., 2004). A recent resting-state electroencephalogram (EEG) study demonstrated that compared to HC, FES had increased theta-band resting-state connectivity across midline, sensorimotor, orbitofrontal regions and the left temporoparietal junction, whereas the FHR subjects displayed intermediate theta-band connectivity patterns that did not differ from either FES or HC. Mean theta-band connectivity within the above network partially mediated verbal-working memory deficits in FES and FHR (Andreou et al., 2015).

Of note, as two of the core features of cognitive impairment in schizophrenia, verbal- and spatial-working memory deficits are often observed together, instead of distinctively in the diagnosed patients and even early in the HR status (Scala et al., 2013). However, most of the existing neuroimaging studies investigated the neural mechanisms associated with only verbal- or only spatial working memory processing. Inconsistent results of these studies (partly briefly review in last paragraph) can from sample differences and lack of understanding on interactions of the brain regions for processing verbal- and spatial-working memory. The current study proposed to investigate the pattern of interactions between the verbal- and spatial-working memory processing networks in the FHR population, and its differences from that in a well-match sample of low risk controls.

2. Methods and materials

2.1. Participants

A total of 75 young adults were involved in this study. The 43 non-psychotic FHR subjects had at least one other first-degree relative with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, and at least one 1st, 2nd or 3rd degree relative with a history of psychosis, suicide, psychiatric hospitalization or Axis I disorder. The 32 controls had no family history of a psychosis in 1st, 2nd or 3rd degree relatives. The two diagnostic groups were matched in age, gender, ethnicity and handedness (all right-handed) (Table 1). The FHR participants were recruited from Massachusetts and neighboring New England regions through brochures and advertisements and through the National Alliance on Mental Illness (NAMI). Controls were recruited from the same communities of the HR participants via advertisement. Exclusion criteria for all participants were: lifetime history of DSM-IV psychotic disorder, English not the participant's native language, non-right handed (Smythe and Annett, 2006), neurological illnesses, and IQ below 80 (D, 1999). Control participants were excluded if they had a family history of psychotic disorder, other major psychiatric illness or suicide.

Table 1
Demographic, neuropsychological and clinical characteristics of controls (CON) and young people at familial high-risk for schizophrenia (HR).

Variable	CON ($n = 32$)	HR ($n = 43$)	CON v. HR
	Mean (SD) or %	Mean (SD) or %	t (p) or (p)
Matching variables			
Age at MRI	24.6 (2.8)	25.2 (3.1)	0.93 (0.36)
Gender(% male)	41%	29%	0.88 (0.35)
Ethnicity (% Cauc.)	78%	69%	2.33 (0.80)
Handedness (% right)	100%	100%	–
WRAT-IV[a] reading	109.6 (12.8)	110.9 (12.5)	0.41 (0.69)
Education & IQ			
Education (years)	16.0 (1.7)	15.6 (2.3)	0.99 (0.32)
IQ estimate[b]	117.7 (14.7)	116.8 (11.4)	0.24 (0.81)
POMS[g] T scores			
Tension/anxiety	30.9 (4.9)	34.4 (7.3)	2.32 (0.02)
Depression	36.8 (6.1)	39.5 (7.7)	1.67 (0.10)
Anger/hostility	41.1 (4.9)	44.7 (7.3)	2.37 (0.02)
Vigor	64.1 (9.5)	61.4 (9.1)	1.26 (0.21)
Fatigue	41.4 (4.5)	46.2 (8.8)	2.98 (0.009)
Confusion	33.7 (4.6)	36.2 (9.4)	1.39 (0.17)
SIS[c] scores			
No. of positive scores	2.2 (2.2)	7.8 (7.6)	4.40 (0.00004)
No. of scores > 2	1.1 (1.5)	5.5 (7.0)	3.83 (0.0002)
fMRI task	CON ($n = 26$)	HR ($n = 25$)	CON v. HR
	Mean (SD)	Mean (SD)	t (p)
Ave_ACC_A[d]	0.937 (0.064)	0.859 (0.227)	1.757 (0.089)
Ave_ACC_B[e]	0.919 (0.097)	0.853 (0.222)	1.428 (0.162)
Ave_RT_A[f]	755.6 (111.4)	763.7 (97.1)	-0.291 (0.772)
Ave_RT_B[g,h]	695.8 (112.4)	708.8 (107.1)	-0.445 (0.658)

[a] WRAT-3, Wide Range Achievement Test–Third Edition.
[b] Full scale IQ assessed using the Wechsler Adult Intelligence Scale-III prorated from eight sub-tests.
[c] Structure interview for schizotypy.
[d] Average response accuracy of block A.
[e] Average response accuracy of block B.
[f] Average response time of block A (milliseconds).
[g] Average response time of block B (milliseconds).
[h] Profile of mood states.

Among the total of 75 subjects who participated in this study, 24 were excluded from further fMRI data analyses due to imaging quality issues or heavy head motions. A final group of 26 low risk controls and 25 FHR subjects were included for group level analyses of the imaging data. Based on the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994; Faraone et al., 1996), 9 of the 25 FHR subjects (none of the control subjects) had one or more than one diagnoses of the following conditions: Major Depression, Anxiety Disorder, Attention Deficit Hyperactivity Disorder, Substance Abuse, or Eating Disorder.

The study was approved by the Human Participants Investigation Committee at Harvard Medical School, Beth Israel Deaconess Medical Center, Massachusetts Institute of Technology, Brigham and Women's Hospital and Veterans Administration Boston Healthcare System, Brockton, Massachusetts. All participants provided written informed consent and were compensated for their time of participation.

2.2. Psychiatric and neuropsychological assessments

The DIGS was administered by an experienced interviewer, to establish the lifetime presence of any Axis I or II psychiatric disorder. Diagnoses based on the DIGS were made by the study Principal Investigator (L.E.D.). A medical and substance use history and family pedigree were obtained via interview. Schizotypal traits (magical thinking, ideas of reference, illusions, suspiciousness, psychotic-like symptoms, restricted emotion, social isolation/introversion, schizotypal social

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