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Impaired context processing as a potential marker of psychosis risk state

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ABSTRACT

While structural abnormalities of the dorsolateral prefrontal cortex (DLPFC) may pre-date and predict psychosis onset, the relationships between functional deficits, cognitive and psychosocial impairments has yet to be explored in the at-risk period. An established measure of cognitive control (AXCPT) was administered to demographically matched clinical-high-risk (CHR; $n=25$), first-episode schizophrenia (FE; $n=35$), and healthy control (HC; $n=35$) participants during functional magnetic resonance imaging (fMRI) to investigate these relationships. CHR and FE individuals demonstrated impaired context processing and reduced DLPFC activation relative to HC individuals during increased cognitive control demands. FE and CHR individuals' ability to increase DLPFC activity in response to cognitive control demands was associated with better task performance. Task performance was also associated with severity of disorganization and poverty symptoms in FE participants. These findings support more extensive studies using fMRI to examine the clinical significance of prefrontal cortical functioning in the earliest stages of psychosis.

1. Introduction

Cognitive dysfunction is a core deficit in schizophrenia, and has been consistently linked to poor daily functioning in affected individuals (Green, 1996; Green et al., 2000). Investigation of the "at risk" phase of illness may identify processes contributing to the onset of psychosis (Cannon et al., 2008; Fusar-Poli et al., 2012a; Yung et al., 2003) and clarify associated impairments in cognitive (Wood et al., 2008) and psychosocial functioning (Cornblatt et al., 2007; Niendam et al., 2006, 2007). While clinical neuropsychological studies provided initial evidence for cognitive dysfunction as a predictor of outcome (for reviews, see Fusar-Poli et al., 2011b; Wood et al., 2008), neuropsychological tasks engage a wide range of cognitive and brain systems and hence are not optimal for use in studies that aim to identify specific cognitive and neural mechanisms underlying the at-risk state using fMRI (Carter et al., 2008a). Behavioral and neuroimaging measures from cognitive neuroscience and functional neuroimaging methods hold greater promise in this respect (Cannon et al., 2008; Wood et al., 2008).

Cognitive neuroscience based imaging methods reveal replicable dorsolateral prefrontal cortex (DLPFC) deficits across phases of psychotic illness (Glahn et al., 2005; Minzenberg et al., 2009). The DLPFC plays a crucial role in "cognitive control," a set of higher-order cognitive mechanisms that coordinate thoughts and actions to produce goal-oriented behavior through synchronized activity of functional brain networks (Miller and Cohen, 2001), and reduced DLPFC activation is believed to underlie impairment in cognitive control in schizophrenia (Barch et al., 2001, 2003c; MacDonald and Carter, 2003; Yoon et al., 2008). DLPFC dysfunction in first episode schizophrenia individuals (FE) is accompanied by reduced fronto-parietal functional connectivity reflecting a breakdown in coordinated brain activity necessary for cognitive control (Yoon et al., 2008).

Despite robust findings in schizophrenia individuals, neurobiological mechanisms underlying changes in clinical, cognitive and psychosocial functioning, associated with increased risk for psychosis onset, remain poorly understood. Clinical high risk (CHR) individuals show structural and functional abnormalities, including reduced gray matter density in frontal, temporal and subcortical brain regions (Borgwardt et al., 2007; Fusar-Poli et al., 2011a, 2012b; Hurlemann et al., 2008; Phillips et al., 2002; Witthaus et al., 2008; Wood et al., 2005) and reduced N-acetylaspartate (NAA) in frontal regions (Jessen et al., 2006; Wood et al., 2003). Neuroimaging studies in CHR individuals have identified deficits in the cognitive control network (Allen et al.,

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2011; Broome et al., 2009, 2010; Fusar-Poli et al., 2010a, 2010c; Morey et al., 2005) that are associated with clinical outcome (Fusar-Poli et al., 2011b). Links have also been established between poor psychosocial function and risk for psychosis (Cornblatt et al., 2007; Fusar-Poli et al., 2010b), and between cognition, clinical symptoms, and psychosocial functioning in CHR populations (Niendam et al., 2006, 2007). These findings suggest that cognitive dysfunction may represent a clear risk marker for future deterioration in clinical and psychosocial domains.

The current fMRI study employs the AX version of the Continuous Performance Task (AXCPT; Cohen et al., 1999), an established measure of cognitive control widely studied in individuals with schizophrenia (Barch et al., 2001, 2003a, 2003b; MacDonald and Carter, 2003; Yoon et al., 2008), to examine CHR individuals and determine if cognitive control deficits are present in high risk individuals and if these deficits are associated with clinical symptoms and functional disability. We hypothesize that CHR individuals, relative to healthy controls, have cognitive control impairments accompanied by DLPFC dysfunction that are similar to FE individuals. Further, we hypothesize that reduced DLPFC activation in response to cognitive control demands is associated with poorer task performance and global functioning at baseline in FE and CHR individuals.

2. Methods

2.1. Participants

Thirty-two CHR and 92 FE participants were recruited from the UC Davis Early Diagnosis and Preventative Treatment (EDAPT) clinic (see Table 1). Ninety-five healthy controls (HC) were also recruited. Twenty participants (5 HC, 9 FE, 6 CHR) were excluded for excess movement, seven for poor behavioral performance (2 HC, 5 FE) based on published criteria (Henderson et al., 2012), three (2 FE, 1 CHR) for scanner related artifacts, and two FE for positive urine drug screens at the time of testing. The remaining HC and FE participants were excluded based on demographic variables to create a matched sample for the CHR participants comprised of 35 HC and 35 FE participants. All participants in this analysis were ages 12–25, fluent in English, had a WASI 2-subtest IQ estimate > 70 (WASI; Wechsler, 1999), and had no neurological disorders, current DSM-IV substance abuse/dependence, or contraindications for MRI. CHR participants had no history of psychosis and met criteria for a Structured Interview for Prodromal Syndromes high risk state based on (SIPS; McGlashan, 2001); (1) attenuated psychotic symptoms (APS); (2) brief and self-limited psychotic symptoms (BIPS); (3) substantial drop in functioning over past year with schizotypal personality disorder or first-degree relative with

Table 1
Demographics, clinical characteristics and AXCPT performance across diagnostic groups.

Characteristic	Healthy control (HC, $n=35$)	First episode (FE, $n=35$)	Clinical high risk (CHR, $n=25$)
Age: mean ± S.D.	17.55 ± 3.16	18.27 ± 2.63	16.92 ± 3.85
Gender: male (%)	54	74	56
Ethnicity: Caucasian (%)	49	54	52
Parental education: mean ± S.D.	15.53 ± 2.92	15.33 ± 2.88	14.91 ± 2.21
WASI IQ: mean ± S.D.	109.91 ± 7.67	95.79 ± 12.86	101.25 ± 17.29
GAF: mean ± S.D.	–	46.03 ± 11.08	54.88 ± 9.75
Diagnosis: n (%)			
Schizophrenia	–	30 (86%)	–
Schizoaffective	–	3 (8%)	–
Schizophreniform	–	2 (6%)	–
Primary SIPS syndrome			
% APS	–		23 (92%)
% BIPS	–		2 (8%)
Medication use			
% Unmedicated	–	31	48
% Atypical	–	66	20
% Typical	–	0	0
% Antidepressant	–	3	28
% Missing			4
Symptom severity			
Reality distortion	–	17.35 ± 6.88	10.38 ± 4.67
Disorganization	–	7.55 ± 4.06	6.09 ± 3.01
Poverty symptoms	–	14.47 ± 5.81	12.26 ± 6.08
CHR outcome			
Poor outcome			9 (36%)
Convert to psychosis (CHR+C)			4 (16%)
Persistent APS (CHR+P)			5 (20%)
Good outcome			11 (44%)
Remission of APS (CHR−R)			11 (44%)
Follow up data not available			4 (16%)
Raw AX Error Rates: mean ± S.D.			
AX	0.04 ± 0.04	0.07 ± 0.09	0.09 ± 0.09
AY	0.28 ± 0.22	0.21 ± 0.21	0.27 ± 0.26
BX	0.11 ± 0.10	0.18 ± 0.18	0.19 ± 0.22
BY	0.01 ± 0.03	0.03 ± 0.06	0.02 ± 0.05
d' context	3.21 ± 0.72	2.83 ± 1.02	2.59 ± 1.20
AX Reaction Time: mean ± S.D.			
AX	542.43 ± 128.08	618.48 ± 173.45	595.30 ± 179.93
AY	711.65 ± 145.61	756.51 ± 157.13	721.51 ± 171.34
BX	589.51 ± 192.65	721.64 ± 282.71	659.50 ± 281.57
BY	559.29 ± 158.96	636.91 ± 203.08	616.56 ± 192.80