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Differentiating between clinical and behavioral phenotypes in first-episode psychosis during maintenance of visuospatial working memory

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ABSTRACT

Introduction: We probed the neural basis of working memory in individuals with first episode of psychosis (FEP) and assessed how these neural abnormalities are associated with behavioral performance and/or core to psychosis pathophysiology.
Methods: FEP (N = 35) and matched controls (N = 25) performed a visuospatial working memory task during fMRI acquisition. We isolated neural activity during the maintenance period and examined neural activity within regions typically engaged during a working memory task. Functional connectivity estimates were derived using psychophysiological interaction analysis. We examined correlations between brain function and behavioral performance and clinical symptomatology.
Results: FEP had reduced accuracy and slower reaction times compared to controls ($p < 0.05$, $q < 0.05$). During the maintenance period, FEP exhibited reduced right dorsolateral prefrontal cortex (DLPFC) activation compared to controls ($p = 0.007$, $q = 0.01$), even when behavioral performance was matched between groups ($p = 0.01$, $q = 0.03$). Unlike controls, FEP failed to show increased dorsal anterior cingulate (dACC) activity with increased load level ($p = 0.02$, $q = 0.06$). Compared to controls, FEP showed increased negative DLPFC-dACC coupling during the maintenance period ($p = 0.05$). Increased DLPFC activation was significantly associated with greater negative symptoms ($p < 0.005$, $q = 0.02$), while greater dACC activation was significantly associated with better performance in FEP ($p < 0.05$, $q < 0.17$).
Conclusion: WM impairment in psychosis may be specific to abnormalities in the ability of frontal systems processing executive commands (DLPFC) and monitoring performance (dACC) during the maintenance of information. Our results add to accumulating evidence indicating that DLPFC abnormalities may be core to psychosis psychopathology. We also provide new insights regarding how DLPFC abnormalities may undermine dACC processing during the maintenance of information.

1. Introduction

Impairments in working memory (WM) are considered a core feature of schizophrenia: deficits are better predictors of functional outcome than clinical symptoms (Addington and Addington, 2000; Liddle, 2000; Green, 1996) and impairments in behavioral performance during WM tasks are present during all phases of the illness (Bora and Murray, 2014; Becker et al., 2010; Metzler et al., 2015). Schizophrenia is associated with abnormalities in a distributed cortical network typically engaged during WM tasks (Wager and Smith, 2003; Owen et al., 2005), emphasizing faulty engagement of the prefrontal cortices (PFC) (Glahn et al., 2005; Van Snellenberg et al., 2006; Potkin and Ford, 2009; Van Snellenberg et al., 2016; Minzenberg et al., 2009; Karlsgodt et al., 2009; Jansma et al., 2004; Manoach et al., 2000; Karlsgodt et al., 2007; Barch et al., 2001a; Castner et al., 2004). Open questions remain, however, as to what extent these brain processes are abnormal during

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the first episode of psychosis (FEP) and how these deficits relate to separate WM sub-processes, behavioral performance, and clinical symptoms in this population.

WM deficits in schizophrenia have been found to affect both verbal and visuospatial domains (Lee and Park, 2005; Park and Gooding, 2014; Glahn et al., 2005). WM tasks engage distinct processes including the ability to encode information, sustain information during a delay period, and retrieve information to guide an executive response. Behavioral (Barch and Smith, 2008) and neuroimaging studies (Anticevic et al., 2013; Driesen et al., 2008; Dae et al., 2009; Potkin et al., 2009; Luck et al., 2010) indicate that in schizophrenia WM deficits may be specific to the processes underlying the ability to sustain information online in order to guide behavior. In support of this notion, postmortem human studies in schizophrenia find impairments in pyramidal cells of layer 3 PFC (Glantz and Lewis, 2000) and animal models indicate that these cells are critical for the ability to coordinate the neuronal activity necessary to maintain information online (Goldman-Rakic, 1995; Wang et al., 2013; Wang, 1999). Building on this existing literature, we further probed the nature of WM maintenance impairment in psychosis by assessing (1) neural abnormalities in patients experiencing their first episode of psychosis, and (2) characterizing their association with behavior and clinical symptomatology.

We implemented fMRI during a visuospatial WM task in FEP and healthy controls to investigate activation and connectivity abnormalities in identified WM regions during the maintenance period, and to examine relationships of neural activation/connectivity with behavioral performance and clinical symptomatology/diagnosis. To do this, we included "catch" trials during the task, which provides the opportunity to separate out the different phases of the task (Ollinger et al., 2001; Ruge et al., 2009). While past studies that consider the entire WM trial provide compelling evidence for impairments in core cognitive regions supporting WM including PFC (Glahn et al., 2005), it is not clear which processes of WM are particularly impaired in FEP, limiting our ability to better specify neural mechanisms. In addition, many previous studies did not remove incorrect trials from analyses (e.g.,Anticevic et al., 2013; Cannon et al., 2005; Henseler et al., 2009) or did not match patients and controls on performance (Van Snellenberg et al., 2006), limiting the ability to determine that group differences are due to WM processing and not engagement in performing the task (e.g., distraction, sleep). We analyzed only correct trials, and conducted follow-up analyses that selected a subset of first-episode patients matched in performance to controls to parse apart whether abnormalities was driven by behavioral performance or whether impairments are core to the psychopathology (Van Snellenberg et al., 2006). Furthermore, because previous studies have found that DLPFC activation is altered in individuals with a schizophrenia-spectrum disorder, but not subjects with other psychotic disorders (Barch et al., 2001; MacDonald et al., 2003; MacDonald et al., 2005), we examined whether any significant results were driven by a schizophrenia-spectrum diagnosis. We hypothesized that impaired recruitment of prefrontal cortex would be specific to the schizophrenia-spectrum group. Finally, given that antipsychotic medication use is known to negatively affect visuospatial WM performance in individuals with schizophrenia (Reilly et al., 2006), we were addressed whether identified neural deficits were related to antipsychotic use.

2. Materials and methods

2.1. Participants

Participants were recruited from an ongoing Conte Center study examining neurobiological mechanisms of WM deficits in FEP. The final sample consisted of 60 individuals (35 FEP; 25 Controls, see Table 1 for demographic information, see Supplemental Text for description of participants removed from analyses). Study procedures were approved by the University of Pittsburgh Institutional Review Board and performed in accordance with the Declaration of Helsinki. All subjects or their legal guardians provided written informed consent after study procedures were fully explained.

Table 1
Demographic and clinical information for the final sample examined during the fMRI working memory task (FEP = 35, Controls = 25).

	FEP (N = 35)	Controls (N = 25)	*p*-Value
Mean age in years (±SD)	22.7 (5.1)	22.0 (3.1)	0.55
Range	13.0–35.9	15.7–28.1	
# right handed (%)	29 (83%)	21 (84%)	0.42
# female (%)	10 (29%)	10 (40%)	0.52
# White/African American/Asian Pacific/Hispanic/unknown	21/12/1/0/1	17/5/2/1/0	0.39
Mean WASI IQ (±SD)	106.2 (13.0)	106.1 (9.3)	0.98
# on antispychotics/antipsychotic naiive	24/11	0	NA
# schizophrenia dx/other psychosis dx	23/12	NA	NA
Total symptoms (BPRS)	10.5 (3.5)	NA	NA
Positive symptoms (BPRS)	12.8 (3.8)	NA	NA
Negative symptoms (BPRS)	6.7 (2.5)	NA	NA
Duration of illness (days)	93.6 (136.6)	NA	NA

Exclusion criteria for all participants included: medical illness affecting the central nervous system function, IQ (determined using the Wechsler Abbreviated Scale of Intelligence, Wechsler, 1999) lower than 75, or any MRI contraindications. Inclusion criteria for FEP were as follows: experiencing one's first psychotic episode and seeking help for his/her psychotic symptoms for the first time and antipsychotic naive (N = 11) or prescribed antipsychotic treatment for less than two months (N = 24). Diagnoses were determined using all available clinical information and data gathered from a Structured Clinical Interview for DSM-IV (SCID, First et al., 2002) conducted with a trained clinician. Experienced diagnostician/clinical researchers confirmed diagnoses at consensus meetings. The patient sample was separated into two groups: schizophrenia spectrum (schizophrenia, schizophreniform, or schizoaffective disorder diagnosis) and other psychotic disorders (affective psychosis or psychotic disorder not otherwise specified). Illness duration for each patient was also determined in the consensus conference after a review of historical information about psychosis onset. None of the patients met criteria for a DSM-IV substance abuse disorder currently or within the previous 6 months.

The inclusion criteria for controls were no lifetime history of a major psychiatric disorder or antipsychotic treatment, no first-degree family member with a history of a psychotic disorder, and no significant neurological disorder or head injury or mental retardation as defined by the DSM-IV.

2.2. MRI acquisition

Data were acquired using a Siemens Tim Trio at the University of Pittsburgh Medical Center Magnetic Resonance Research Center using a 32-channel phase array head coil. For the WM task, functional images were acquired using a multiband echo-planar sequence sensitive to BOLD contrast (T2*). Parameters were: TR/TE: 1000/30 ms, flip angle: 55°, voxel size: 2.3 × 2.3 × 2.3 mm (0 gap) in-plane resolution, 60 contiguous axial slices, 360 TRs. A magnetization-prepared rapid gradient-echo sequence (MPRAGE) was also acquired to measure brain structure. MPRAGE parameters were TR: 2530 ms, TI: 1260 ms, multi-echo TE (TE1: 1.74 ms, TE2: 3.6 ms, TE3: 5.46 ms, TE4: 7.32 ms) Flip angle: 7°, voxel size: 1 × 1 × 1 mm, 176 slices. High-resolution spin echo: TR: 5040 ms, TE: 30 ms, 60 slices, 55° flip angle, FOV: 220 × 220 × 138 mm.

2.3. Working memory task

Subjects performed a six-minute event-related spatial WM task during fMRI acquisition. They were instructed to remember the color of one

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