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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

(low load) or three (high load) circles (cue; 700–1400 ms) and, after a variable delay period (delay; 1 s or 3 s), indicate whether a color change occurred with a button press (probe, up to 2 s). Subjects completed two runs of this task and performed 64 full trials (Fig. 1, left). An additional 32 partial "catch" trials (Fig. 1, right) with either the cue alone (N = 16) or cue and delay (N = 16) periods were included to allow for hemodynamic response estimates at each task period.

2.4. Clinical measures

We administered the Brief Psychiatric Rating Scale (BPRS) (Bell et al., 1992; Overall and Gorham, 1962), a widely used measure of clinical psychopathology, which is detailed in the Supplemental Text.

2.5. MRI preprocessing

Processing of functional neuroimaging scans and identification of regions of interest (ROIs) are detailed in the Supplemental Text.

2.6. GLM: task-based activation

To investigate differences in activation in FEP vs. Controls as a function of task phase (encoding, maintenance, retrieval) at each load (low, high), we constructed first-level general linear models (GLM) using the AFNI command 3ddeconvolve. Each individual's GLM included a total of 9 regressors. Six regressors modeled activation during encoding low load, encoding high load, maintenance low load, maintenance high load, retrieval low load, and retrieval high load. Three additional regressors modeled incorrect trials at each phase (encoding, maintenance, retrieval) of the task. Encoding regressors were modeled for the length of the cue presentation (200 ms + variable interval). Maintenance regressors were modeled for the duration of the delay period (short = 1000 ms or long = 3000 ms). Retrieval regressors were modeled using the onset of the target probe and each corresponding RT. All regressors were convolved with a double-gamma hemodynamic response function. Using this GLM, individual maps of parameter estimates were generated for six contrasts of interest: (1) encoding low load > baseline, (2) encoding high load > baseline, (3) maintenance low load > baseline, (4) maintenance high load > baseline, (5) retrieval low load > baseline, (6) retrieval high load > baseline.

Using the AFNI command 3dROIStats, we then extracted the mean parameter estimates for all ROIs for each individual at each contrast.

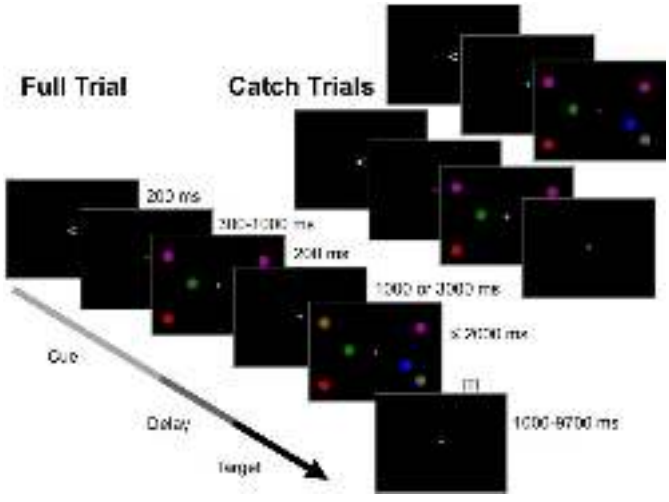

Fig. 1. Subjects completed two runs of a 6-minute event-related visuospatial working memory task during fMRI acquisition. (Left) Subjects were instructed to remember the color of one (low load) or three (high load) circles on one side of the screen (indicated by an arrow). After a variable delay period, subjects were again presented with colored circles and asked to indicate whether a color change occurred. (Right) An additional 32 partial "catch" trials with either the cue alone (top) or cue and delay (bottom) periods were included.

2.7. Psychophysiological interactions

For any ROI that showed a significant effect in task-based activation between FEP and Controls, we then conducted psychophysiological interaction (PPI) analyses with the identified ROI as the seed region. GLMs were constructed that included 9 task-based regressors, one physiological regressor, and two PPI regressors (low & high load). The physiological regressor was the time course extracted from the right DLPFC.

2.8. Statistics

2.8.1. Behavior

A repeated measures analysis of variance (rmANOVA) was used to test group (FEP, control) × load (low, high) interaction of performance (% correct) and reaction time (RT, ms) during the WM task.

2.8.2. Task-based activation

We conducted a rmANOVA of Group (FEP, Controls) × Load (Low, High) × Hemisphere (Right, Left) for each ROI (DLPFC, intraparietal cortex, pre-supplementary motor area, dACC, visual cortex, ventrolateral prefrontal cortex) during the maintenance phase of the WM task. For both behavioral performance and ROI-based activation, we then conducted another set of rmANOVA to determine if there was a diagnostically specific effect of psychotic disorder diagnosis (schizophrenia-spectrum vs. other psychotic disorders vs. controls). Independent samples *t*-tests were run to follow up on any significant main effects or interactions.

In line with previous research showing that equivalent performance ensures that group differences are due to impairment in the target circuitry and/or compensatory mechanisms (e.g., Schlaggar et al., 2002; Potkin et al., 2009), we repeated our analyses with a sub-set of participants that were matched in accuracy.

2.8.3. Activation/connectivity-behavior/symptomatology relationships

For any regions that showed a significant difference between FEP and Controls in the activation- or connectivity-based analyses, we conducted Pearson correlation analyses with these measures and behavioral performance (% correct, RT) in each group separately. We also conducted Pearson correlation analyses between these measures and clinical symptomatology (Positive symptoms, Negative symptoms) within the FEP group.

To ensure that our results were not driven by IQ, duration of psychotic episode, or chlorpromazine equivalents (Andreasen et al., 2010), we conducted confirmatory Pearson correlations.

2.8.4. Correction for multiple comparisons

We had two major aims: 1) examine performance differences in FEP vs. controls and 2) determine regions of sign between working memory brain regions in FEP vs. controls. For the behavioral analysis, False Discovery Rate (FDR) *q*-values (Benjamini and Hochberg, 1995) were used to correct for multiple comparisons accounting for main effects of group and group * load interactions for percent correct and reaction time (i.e., 4 comparisons). For the neuroimaging analysis, FDR *q*-values were used to correct for multiple comparisons accounting for main effect of group, group * load interactions, and group * hemisphere interactions for each of the 5 ROIs (i.e., 16 comparisons). For any significant results, we conducted a post-hoc analysis probing connectivity, diagnosis, or looking at relationships between neural measures and

performance or symptoms. Within each group of post-hoc analyses, we used FDR to correct for multiple comparisons.

3. Results

3.1. Behavior

Performance on the WM task was significantly different between FEP and controls, with respect to accuracy ($F(1,59) = 6.4$, $p = 0.01$, $q = 0.02$) and RT ($F(1,59) = 5.4$, $p = 0.02$, $q = 0.04$, Supplemental Fig. 1). In comparison to controls, FEP exhibited significantly reduced accuracy ($t(58) = -2.7$, $p = 0.008$, $q = 0.02$) and longer RT ($t(58) = 2.4$, $p = 0.019$, $q = 0.02$ Fig. 2). There was also a significant main effect of load (accuracy: $F(1,59) = 120.2$; $p = 9.2e-16$ $q = 5.5e-15$; RT: $F(1,59) = 56.4$, $p = 4.1e-10$, $q = 1.2e-9$). As expected, both patients and controls exhibited lower accuracy and slower RT in the high versus low load condition. There were no interactions between group and load for accuracy ($F(1,59) = 0.004$, $p = 0.9$, $q = 0.9$) or RT ($F(1,59) = 2.1$, $p = 0.15$, $q = 0.18$), indicating that patients exhibited an overall-degree of impairment that was not load dependent. Patients with a schizophrenia-spectrum diagnosis did not significantly differ from individuals with another psychotic disorder in accuracy ($t(33) = 0.5$, $p = 0.60$, $q = 0.6$) or RT ($t(33) = -0.5$, $p = 0.63$, $q = 0.6$).

3.2. Task-based activation

3.2.1. Reduced DLPFC activity in FEP during the maintenance period

During the Maintenance period, there was a significant Group × Hemisphere interaction ($F(1,58) = 7.7$, $p = 0.007$, $q = 0.01$) of the DLPFC, with FEP exhibiting decreased activation in the right DLPFC compared to controls ($t(59) = 2.8$, $p = 0.007$, $q = 0.01$, Fig. 2A) without any significant differences in the left DLPFC compared to controls ($t(59) = -0.08$, $p = 0.94$, $q = 0.94$). Schizophrenia spectrum patients did not significantly differ in activation in the right DLPFC in comparison to patients with other psychotic disorders ($t(33) = 1.5$, $p = 0.17$, $q = 0.17$); both groups exhibited reduced R DLPFC activation compared to controls (schizophrenia-spectrum: $t(46) = -2.1$, $p = 0.04$, $q = 0.06$, other psychotic disorders: $t((35) = -3.0$, $p = 0.006$, $q = 0.02$, Fig. 2B). These findings suggest that there is a generalized, load-independent deficit in DLPFC activation across psychosis-spectrum disorders.

3.2.2. dACC abnormalities in FEP during maintenance

During the maintenance phase of the WM task, there was a Group x Load Interaction in the dACC ($F(1,58) = 5.5$, $p = 0.02$, $q = 0.18$, Fig. 2C). During the high load condition only, controls exhibited significantly greater activation in the bilateral dACC in comparison to FEP ($t(59) = 2.3$, $p = 0.03$, $q = 0.06$). Unlike the DLPFC activation, there were significant differences in dACC activity between schizophrenia-spectrum vs.

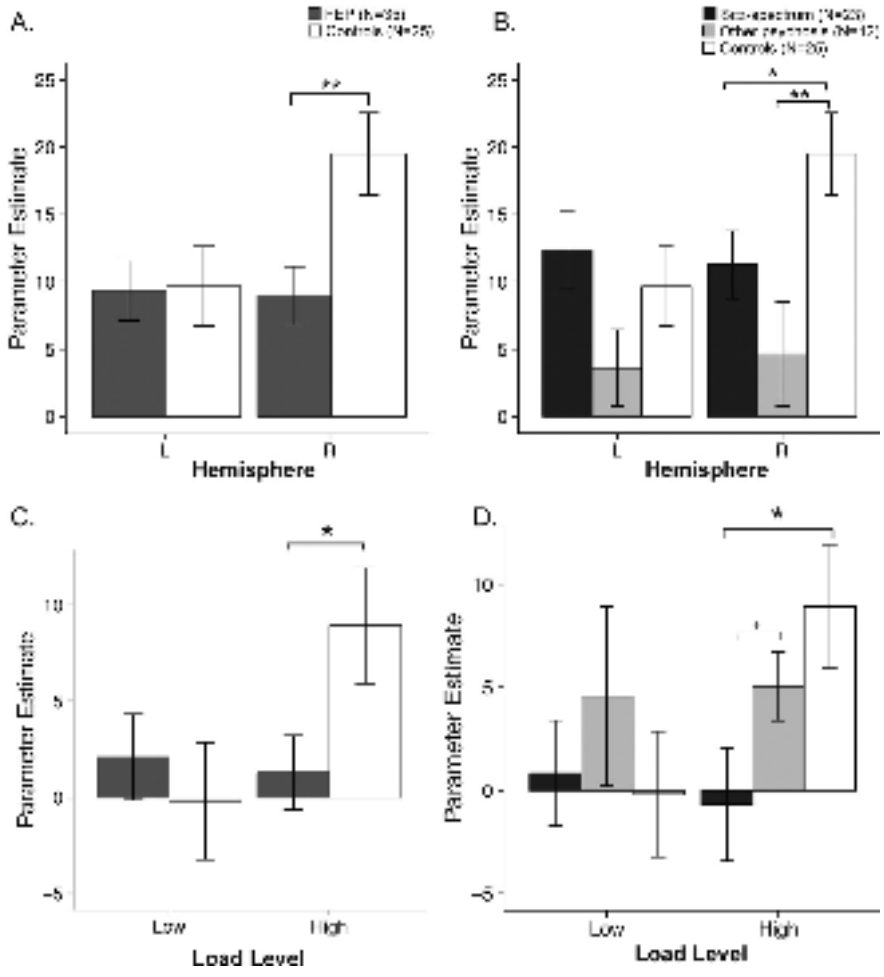

Fig. 2. A) During the maintenance period of the working memory task, patients experiencing their first episode of psychosis (FEP, grey) exhibited reductions in the right dorsolateral prefrontal cortex (DLPFC) compared to control participants (white, $p = 0.007$). B) This reduction did not differentiate between psychosis disorder diagnoses, as both individuals with a schizophrenia-spectrum diagnosis (black, $p = 0.04$) and those with other psychotic disorders (light grey, $p = 0.006$) exhibited reduced right DLPFC maintenance activation. C) During the Maintenance phase of the working memory task, controls exhibited an increase in bilateral dorsal anterior cingulate activation, but FEP failed to show this increase ($p = 0.02$). D) This effect was driven by individuals with a schizophrenia-spectrum diagnosis. ** = $p < 0.01$, * = $p < 0.05$, $^{+}$ = $p < 0.10$.

other psychotic disorders. Individuals with a schizophrenia-spectrum diagnosis showed reduced dACC activity in comparison to controls ($t(46) = -2.36, p = 0.02, q = 0.06$), but those with other psychotic disorders showed equivalent activation ($t(35) = -1.1$, $p = 0.27$, $q = 0.27$). The schizophrenia-spectrum group showed a trend-level reduction in dACC activation in comparison to those with other psychotic disorders ($t(33) = -1.8$, $p = 0.08$, $q = 0.12$, Fig. 2D), suggesting a load-specific deficit in dACC activation in individuals with schizophrenia, but not other psychotic disorders.

3.2.3. Psychophysiological interaction: greater right DLPFC-dACC negative connectivity in FEP during maintenance period

Coupling between the right DLPFC and dACC during the Maintenance period showed a significant main effect of group ($F(1,59) = 3.9$, $p = 0.05$, $q = 0.15$), with FEP exhibiting significantly stronger negative coupling between the right DLPFC-dACC in comparison to controls (Fig. 3A). This result was driven by the schizophrenia-spectrum group showing increased negative right DLPFC-dACC connectivity compared to controls ($t(46) = 2.3$, $p = 0.02$, Fig. 3B) while the group with other psychotic disorders did not differ in their connectivity compared to controls ($t(35) = -0.6$, $p = 0.52$). However, the schizophrenia-spectrum group did not significantly differ in connectivity from those with other psychotic disorders ($t(33) = -1.5$, $p = 0.16$).

3.3. Performance matched

To determine whether any of our results were driven by behavioral performance, we compared a sub-set of participants that were matched in accuracy (overall percent correct: Controls = 87.8% ± 5.8, N = 25, FEP = 86.8% ± 6.6, N = 26, $t(49) = -0.58$, $p = 0.56$). The reduction in right DLPFC activation ($F(1,49) = 7.2$, $p = 0.01$, $q = 0.03$) and increased negative connectivity between the right DLPFC and dACC ($F(1,49) = 4.1$, $p = 0.04$, $q = 0.06$) during the maintenance period in FEP was still observed. However, the group by load interaction for dACC activation was only present at trend level ($F(1,48) = 3.3$, $p = 0.07$, $q = 0.07$).

We used similar methods to examine the other phases of the WM task (Encoding, Retrieval). Importantly, deficits in the DLPFC were not observed. Results are presented in the Supplementary materials.

3.4. Covarying for motion

In comparison to controls, FEP exhibited significantly greater framewise displacement (FD, ($t(58) = 2.6$, $p = 0.01$)) and a trend towards greater DVARS ($t(58) = 1.9$, $p = 0.06$). Thus, we repeated all analyses in which we obtained significant difference between FEP and controls in neural activation or connectivity and included FD and DVARS as covariates in the model. All results remained statistically significant ($p \leq 0.05$) and are reported in S5 Table.

3.5. Brain-behavior relationships

For FEP, greater dACC activation during the high load condition of the maintenance phase resulting in better accuracy ($r = 0.37$, $p = 0.03$, $q = 0.9$ Fig. 4A). This relationship was not present in Controls ($r = -0.08$, $p = 0.7$, $q = 0.8$). We did not observe this relationship when we looked at the relationship between accuracy and activation in the right DLPFC in either group (Controls: $r = 0.009$, $p = 0.97$, $q = 0.97$, FEP: $r = 0.24$, $p = 0.17$, $q = 0.3$). For the connectivity analyses, greater negative DLPFC-dACC connectivity was associated with improved performance in controls ($r = -0.56$, $p = 0.004$, $q = 0.02$) and the same relationship was observed at trend-level for FEP ($r = -0.28$, $p = 0.08$, $q = 0.16$, Fig. 4B). These findings suggest that dACC activation and dACC-DLPFC deficits in FEP were related to WM performance, whereas DLPFC activation was not.

3.6. Relationships with clinical symptomatology

In the FEP, greater right DLPFC activation during the delay period was significantly associated with greater severity of negative symptoms ($r = 0.49$, $p = 0.003$, $q = 0.02$, Fig. 4C), but not positive symptoms ($r = 0.23$, $p = 0.18$, $q = 0.25$). Psychotic disorder diagnosis did not appear to be driving this relationship (schizophrenia-spectrum: $r = 0.40$, $p = 0.06$, $q = 0.1$; other psychotic disorders: $r = 0.58$, $p = 0.05$, $q = 0.1$). The relationship was still present when the "low performing" FEP were omitted from the analysis ($r = 0.51$, $p = 0.008$, $q = 0.03$). We did not observe any significant relationships between dACC activation and clinical symptomatology (all $p > 0.66$), nor any significant relationships between DLPFC-dACC connectivity and clinical symptomatology (all $p > 0.50$). These findings suggest that DLPFC activation, but not dACC activation or dACC-DLPFC connectivity, was related to negative symptoms in first-episode psychosis.

Potential mediators of fMRI activation and connectivity were examined. None of the fMRI variables were significantly associated with IQ (all $p > 0.10$), duration of psychotic episode (all $p > 0.17$), or chlorpromazine equivalent (all $p > 0.19$).

When we examined the relationship between behavioral performance and clinical symptomatology in FEP, we found a trend towards a significant relationship between increased accuracy and increased negative symptoms ($r = 0.30$, $p = 0.06$, $q = 0.24$). There were no

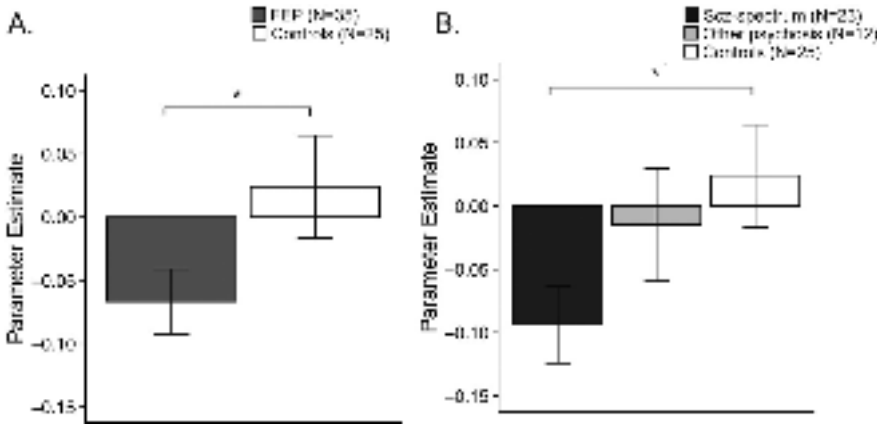

Fig. 3. A) Compared to control participants, patients experiencing their first episode of psychosis (FEP, grey) exhibited greater negative coupling between the right dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate (dACC) during the Maintenance phase of the working memory task ($p = 0.03$). B) This effect was driven by individuals with a schizophrenia-spectrum diagnosis (black, $p = 0.02$). * = $p < 0.05$.

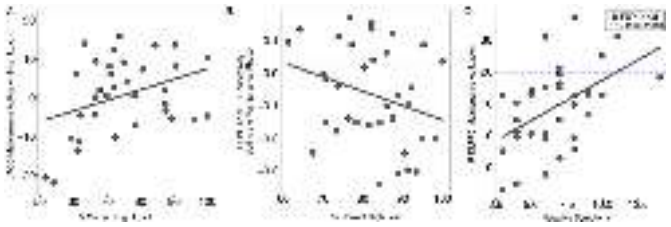

Fig. 4. In patients with a first episode of psychosis (FEP, grey) A) greater activation of the dorsal anterior cingulate (dACC) was associated with better performance in the high load condition ($r = 0.37, p = 0.02$) and B) greater negative coupling between the DLPFC-dACC was marginally associated with better performance on the working memory task ($r = -0.28$, $p = 0.08$). C) Greater activation of the right dorsolateral prefrontal cortex (DLPFC) during the Maintenance phase of the working memory task was associated with greater severity of negative symptoms ($r = 0.49$, $p = 0.003$), In each graph, the blue dotted line represents the control mean of the respective activation or connectivity measure.

significant relationships between positive symptoms and accuracy ($r = -0.09, p = 0.6, q = 0.8$), nor were the any significant relationships between reaction time and clinical symptomatology in FEP (all $p < 0.5$).

3.7. Antipsychotic use (medication naïve versus medicated)

Both antipsychotic naïve ($t(34) = -2.2, p = 0.04, q = 0.06, N = 11$) and those prescribed antipsychotic medications ($t(47) = -2.5$, $p = 0.02$, $q = 0.02$; $N = 24$) exhibited DLPFC deficits in comparison to controls. However, those prescribed antipsychotic medication were driving load-dependent dACC activation deficits (prescribed antipsychotics: $t(47) = -2.6$, $p = 0.01$, $q = 0.02$, antipsychotic naïve $t(34) = -0.7$, $p = 0.5$, $q = 0.5$). Both antipsychotic naïve individuals ($t(34) = -1.7$, $p = 0.09$, $q = 0.14$) and those prescribed medications ($t(47) = -1.6$, $p = 0.12$, $q = 0.14$) exhibited a trend towards greater negative DLPFC-dACC coupling in comparison to controls.

4. Discussion

We examined neural abnormalities during the maintenance phase of a visuospatial working memory (WM) task in first-episode psychosis (FEP) and in controls. Using rigorous methods allowing for the isolation of WM maintenance and controlling for performance-related differences, we found reduced activation in right dorsolateral prefrontal cortex (DLPFC) across task load, along with a reduction in dorsal anterior cingulate cortex (dACC) as memory load increased in FEP vs. controls. We also found that FEP exhibited greater negative DLPFC-dACC connectivity during the maintenance phase in comparison to controls, suggestive of a compensatory mechanism. We found a compelling double dissociation between the DLPFC and dACC: increased right DLPFC, but not dACC, activation was associated with greater negative symptoms, while increased dACC, but not DLPFC, activation was associated with greater accuracy in FEP. Our results provide a novel view of visuospatial WM impairment in FEP, identifying specific neural correlates associated with clinical and behavioral variables, respectively, while also identifying a potential compensatory mechanism for behavioral performance.

4.1. Reduced DLPFC activation during the maintenance phase of the task

Consistent with previous studies of visuospatial WM in schizophrenia (Cannon et al., 2005; Kang et al., 2011), we observed reduced engagement of the DLPFC during a visuospatial WM task that was specific to the maintenance phase of WM. We add to this literature by: (1) examining first episode patients and (2) controlling for performance thus providing evident that impaired recruitment of DLPFC in schizophrenia is specific to the ability to maintain WM information and not to other factors that may influence attention to the task. Results from patients with chronic schizophrenia have found both impaired DLPFC function during the maintenance period (Driesen et al., 2008) and DLPFC impairment that is specific to the encoding period (Anticevic et al., 2013). Taken together, these findings suggest that DLPFC deficits in WM maintenance might be more prominent early in the course of the disorder. These results are further supported by our findings that in a subsample of antipsychotic naïve patients, we still observed decreased DLPFC activity during the maintenance periods, in agreement with previous findings of DLPFC hypofrontality during a verbal WM task in medication naive subjects (Barch et al., 2001). Taken together, these findings suggest that DLPFC dysfunction might be a core and early marker of psychosis. Furthermore, decreased WM maintenance related DLPFC activity was also evident in schizophrenia spectrum and other psychotic disorder groups suggesting that DLPFC hypofrontality may be a general psychosis phenotype. Previously, severity of WM impairments have been associated with the presence of a psychosis history, not driven by affective or schizophrenia-spectrum diagnoses(Frydecka et al., 2014; Martinez-Aran et al., 2008; Savitz et al., 2009; Simonsen et al., 2011; Bora et al., 2007; Glahn et al., 2007; Glahn et al., 2006; Allen et al., 2010; Ivleva et al., 2012). While those with a schizophrenia spectrum diagnosis typically exhibit more severe deficits than affective psychoses, the profile of impairment is similar across groups, possibly reflecting involvement of common neural mechanisms (for a review, see Barch and Sheffield, 2014). Our findings add to the literature suggesting that impairments in the ability for DLPFC to perform complex information processing, such as in maintaining information online to guide executive behavior, may serve as a biological marker for the propensity to develop psychosis, regardless of diagnostic category. However, it is important to note that WM deficits and DLPFC dysfunction is evident across psychopathologies (Brooks et al., 2015; Townsend et al., 2010; Rose and Ebmeier, 2006) and may be a general marker for abnormalities in the executive system in mental illness, although this marker is likely particularly vulnerable in psychosis.

4.2. Load dependent dACC reduction during the maintenance phase

We also observed reduced dACC activation in FEP. The reduced dACC activity in FEP was observed in the high load condition only, suggesting that the difficulty of the WM task plays a critical role in determining the underlying neural mechanisms used to perform the task. To further support this notion, improved behavioral performance was associated with greater activation in the dACC in FEP. The dACC plays a primary role in performance monitoring and signaling to other regions involved in executive functioning (including the DLPFC) to adjust activation, resulting in improved performance (Gehring et al., 1993; Menon et al., 2001; Polli et al., 2005; Carter et al., 1998; Ridderinkhof et al., 2004; Kerns, 2006; Cavanagh et al., 2009).

In line with this body of research and in addition to identifying differences in DLPFC and dACC engagement in individuals with FEP, we found increased negative coupling between the DLPFC-dACC in FEP during the maintenance phase. That is, when DLPFC showed increased recruitment, the dACC was suppressed. Given that we were comparing correct responses in the context of overall poorer performance in patients, greater engagement of DLPFC-dACC may provide a compensatory mechanism allowing correct responses in a system with inherent limitations in the ability to recruit key DLPFC and dACC executive regions. This proposal is supported by our finding indicating that greater DLPFC-dACC negative coupling predict WM performance both in controls and FEP (at trend level). These initial findings on activation and connectivity impairments in the dACC must be followed up in subsequent studies, given that the significant results did not survive correction for multiple comparisons.

4.3. DLPFC-specific relationship with negative symptomatology

Intriguingly, negative symptoms were associated with increased DLPFC activation in FEP. Negative symptoms of psychosis are thought

to reflect, in part, deficits in goal-oriented behavior and motivation. Given prior research implicating the DLPFC in the maintenance of goals(Lopez-Garcia et al., 2016; Barch et al., 1997; Barch et al., 2001; Holmes et al., 2005; Lesh et al., 2013; MacDonald and Carter, 2003; MacDonald et al., 2003; MacDonald et al., 2005; Paxton et al., 2008; Perlstein et al., 2001), this relationship might also reflect a compensatory mechanism of enhanced DLPFC engagement in order for patients with prominent negative symptoms to successfully maintain items in WM. Future work is necessary to investigate how specific deficits in motivation and the initiation of goal-relevant behavior intersects with this relationship between DLPFC engagement and negative symptoms.

4.4. Conclusion

This study uses a rigorous approach allowing us to probe the integrity of processing of DLPFC systems during WM processing in FEP. We found confirmatory evidence of DLPFC hypofrontality and add to this core finding by indicating that this impairment is specific to the ability to maintain information online to direct executive responses. Importantly, we found that these DLPFC impairments were associated with illness severity. Moreover, we found evidence for possible engagement of compensatory brain processing that supports the ability to generate correct WM responses and may inform treatment. Together, these findings suggest that DLPFC impairment in psychosis is a core impairment that is present early in the disorder and may serve as a biological marker for the emergence of psychopathology.

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Author contributions

BL, DS, and WF designed the fMRI working memory task. MJ, WF, and JS participated in data collection and fMRI preprocessing. MJ conceptualized, planned, and executed the analyses, interpreted the data, and wrote the first draft of the manuscript. PLS also completed analyses and assisted in manuscript preparation. VPM assisted in planning, execution of analyses, interpretation, and manuscript editing. BL supervised the current project and had roles in conceptualization, planning, analysis execution, data interpretation, and manuscript writing. All authors contributed to and gave approval to the manuscript.

Conflict of interest

The authors have no conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2017.11.012.

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