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Impaired prefrontal functional connectivity associated with working memory task performance and disorganization despite intact activations in schizophrenia.

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Abstract

Working memory (WM) deficits are key features of schizophrenia and are associated with significant functional impairment. The precise mechanisms of WM and their relationship between WM deficits with other clinical symptoms of schizophrenia remain unclear. Contemporary models propose that WM requires synchronous activity across brain regions within a distributed network, including lateral prefrontal cortex (PFC) and task-relevant posterior sensory cortical regions. This suggests that WM deficits in patients may be due to PFC functional connectivity (FC) impairments rather than activation impairments per se. We tested this hypothesis by measuring the magnitude of FC between lateral PFC and visual cortex and univariate activations within these regions during visual WM. We found decreased FC in patients compared to healthy subjects in the context of similar levels of univariate activity. Furthermore, this decreased FC was associated with task performance and clinical symptomatology in patients. The magnitude of FC, particularly during the delay period, was positively correlated with WM task accuracy, while FC during cue was inversely correlated with severity of disorganization. Taken together, these results suggest that impairment in lateral PFC FC is a key aspect of information processing impairment in patients with schizophrenia, and may be a sensitive index of altered neurophysiology.

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CONTRIBUTORS

Author SC conducted the analyses, statistical analyses, interpretation of data, literature search, and led the writing of the manuscript.
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Author QN assisted with the analyses for the revisions requested by the reviewers.
Author JHY designed the study, wrote the protocol and supervised the analysis and interpretation of the data and writing of the manuscript.

Keywords

Neuroimaging; fMRI; cognition; psychotic disorders; dysconnectivity

1. Introduction

Schizophrenia is a chronic illness that usually begins in late adolescence or early adulthood. It is associated with significant cognitive impairment (Goldman-Rakic, 1994), which often manifests before the onset of psychotic symptoms (Green, 2006; Niendam et al., 2003). Impairments in working memory (WM), which can be defined as the "ability to hold an item of information transiently in mind in the service of comprehension, thinking, and planning" (Goldman-Rakic, 1996), are considered particularly important indications of cognitive dysfunction in patients with schizophrenia (Silver et al., 2003). Consequently, WM is amongst the most commonly studied cognitive processes in patients with schizophrenia. While a variety of brain abnormalities and neural correlates associated with WM deficits in patients with schizophrenia have been documented (Glahn et al., 2005; Schneider et al., 2007), dysfunction of the lateral PFC is often viewed as one of the most critical. However, the mechanisms of how lateral PFC dysfunction translates into WM deficits remains unclear. Furthermore, whether WM related neural deficits could give rise to some of the clinical symptomatology of schizophrenia also remains unclear. A demonstration of an association between WM related neural deficits and clinical symptoms would advance the broader effort to discover the neural mechanisms of schizophrenia in a number of ways. On a conceptual level, it would offer empirical evidence of a link between deficits in the realm of cognition with other domains of clinical symptomatology, potentially offering a common framework with which to conceptualize and study the diverse set of symptoms constituting schizophrenia. The demonstration of an association between WM neural correlates and clinical symptomatology would also validate WM as a useful focus of study in pre-clinical models of schizophrenia.

We undertook this study to both further our understanding of the mechanisms of lateral PFC mediated WM deficits in patients with schizophrenia and to test the possibility that the brain correlates of WM deficits in patients with schizophrenia are associated with clinical symptomatology. In testing for an association with symptomatology, we focused on a category of symptoms referred to as disorganization (Barch et al., 2003; Yoon et al., 2008) since some of the most characteristic clinical features of this illness, such as behavioral disorganization and thought disorder, can be conceptualized as stemming from WM deficits and the inability to maintain on-line mental representations that are necessary to guide behavior (Goldman-Rakic, 1994).

In testing our hypothesis, we adopted a well-established macro-scale brain circuit-based model of WM. Among the distributed network of brain regions engaged by WM (D'Esposito and Postle, 2015; Riggall and Postle, 2012), the lateral prefrontal cortex (PFC) has been proposed to play a central role (Funahashi et al., 1989; Fuster, 1973; Fuster and Alexander, 1971; Kubota and Niki, 1971). However, cognitive processes such as WM are not the result of activity in a singular brain region, but rather are the products of synchronous

activity occurring between two or more brain regions (Mesulam, 1990). This synchronous activity is referred to as functional connectivity (FC) and can be quantified as the magnitude of correlation between fMRI signal time series from two brain regions (Rissman et al., 2004). Numerous basic WM studies with healthy individuals have documented the enhancement of FC of the PFC with task-relevant cortical regions during WM (Gazzaley and Nobre, 2012; Yoon et al., 2007, 2006).These models propose that WM is supported by enhanced FC between the lateral PFC and task-relevant sensory cortical areas, wherein representations of the memoranda are maintained and enhanced under lateral PFC guidance (Curtis and D'Esposito, 2003). This framework offers a number of advantages for clinical translational efforts. It is well-suited to be paired with ROI- to- ROI based FC analytic methods. These methods can be advantageous since they offer enhanced sensitivity due to the reduced need for multiple comparisons correction and better control for Type II errors compared to seed-based, whole brain FC methods. These methods also promote greater scientific rigor since they require *a priori* specification of the specific brain regions to be tested. This rigor would hopefully translate into enhanced reproducibility of results.

The present study builds on prior work that conceptualizes schizophrenia as a disconnection syndrome (Brandt et al., 2015; Collin et al., 2016; Crossley et al., 2015; Friston and Frith, 1995; Mesulam, 1990; van den Heuvel and Fornito, 2014). This prior work has documented the centrality of lateral PFC dysfunction (Andreasen et al., 1999; Glahn et al., 2005; Yoon et al., 2008), and altered FC (Anticevic et al., 2012; Bittner et al., 2015; Deserno et al., 2012; Henseler et al., 2010; Kim et al., 2009; Meda et al., 2009; Meyer-Lindenberg et al., 2001, 2005; Quidé et al., 2013; Schlösser et al., 2003; Tan et al., 2006) associated with WM deficits in patients with schizophrenia. We have designed an experiment inspired by the PFC top-down model of WM. This model suggests that in patients with schizophrenia, there is diminished FC between PFC and task-relevant sensory cortical brain regions accounting for WM impairments. Our study does not aim to find support for the directionality of FC, but rather, to measure the strength of FC between task-relevant regions of the lateral PFC and visual cortex during visual object WM. Furthermore, we addressed the question of task performance and clinical relevance of the hypothesized PFC FC deficit by testing the association of FC with WM task performance and the disorganization symptom in patients with schizophrenia.

The confirmation of these hypotheses would advance our understanding of the neural mechanisms of WM deficits in patients with schizophrenia in a number of ways. PFC - sensory cortex FC appears to be a pervasive mechanism supporting WM and other cognitive processes, having been observed in healthy humans and animals (Zanto et al., 2011). Animal experimental model systems exist to study these phenomena and they have yielded important advances in the basic neurobiological mechanisms underlying WM and related cognitive processes (Bichot et al., 2015; Fuster et al., 1985; Gregoriou et al., 2014; Tomita et al., 1999). Likewise, PFC-sensory cortical FC deficits in WM in patients with schizophrenia could be translated for further study into these experimental model systems, potentially yielding cellular and molecular clues to the neurobiological mechanisms of schizophrenia.

To test our hypotheses, we designed a novel visual object WM fMRI experiment which employs established, unbiased, functional region of interest (ROI) based methods (Gazzaley

et al., 2004; Petrides, 2000; Rissman et al., 2004; Yoon et al., 2006). Using this approach, we identified task relevant functional ROIs in the lateral PFC and visual cortex and derived estimates of the strength of PFC-visual cortex FC to test the hypothesis of PFC FC impairments and their associations with task performance and symptomatology in patients with schizophrenia.

2. METHODS

2.1 Subjects

18 patients with schizophrenia or schizoaffective disorder (SZ) and 19 healthy control (HC) subjects were recruited from the community for this study. Two SZ and one HC subject were excluded due to excessive movement and/or very poor performance on the WM task. Data from 16 SZ and 18 HC subjects were used for further analyses (Table 1). All patients were clinically stable with medications that were unchanged within two weeks of study participation. Master's- and doctoral-level clinicians evaluated subjects with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) to confirm the diagnoses in SZ and to exclude the presence of a major psychiatric illness in HC. All patients were taking antipsychotics at the time of testing. Exclusion criteria for HC were 1) presence of a lifetime diagnosis of an axis I disorder or 2) a first- degree relative with a psychotic disorder. Exclusion criteria for both study groups were: 1) IQ <70, 2) history of drug or alcohol dependence or abuse within three months of study or a positive urine drug screen on day of study, 3) significant head trauma, or 4) any known contraindication to MRI. After complete description of the study was given, written informed consent was obtained from all participants. The study was approved by the University of California Davis Institutional Review Board.

2.2 Cognitive Paradigm

Stimulus presentation and response recordings were conducted with E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA; http://www.pstnet.com). Stimuli were projected onto a screen viewed by participants through a mirror mounted on the head coil. Participants performed the cognitive paradigm displayed in Figure 1.

We designed a novel visual WM paradigm to facilitate the planned unbiased, functional ROI-based fMRI analyses (Gazzaley et al., 2004; Petrides, 2000; Rissman et al., 2004; Yoon et al., 2006). The design of our visual object WM task temporally segregates the phases of cue, delay, and probe. In this manner, this task can be considered a variant of the Sternberg Task. This design was chosen over a traditional N-back task in which the three phases cannot be temporally separated. There were two tasks in this paradigm, which were identical in terms of trial structure, stimulus presentations, order and timing, but differed in WM requirements. The first stimulus presented in both tasks is referred to as the "cue" face. It was displayed for one second and then it was replaced by a crosshair. The color of the crosshair was initially black, but changed color after two seconds. This new color indicated the task of the trial: blue indicated the WM task, which required subjects to maintain the cue face in WM across a 15 s delay period and to make a match discrimination with the face appearing at the end of the delay; red indicated the Gender ID (GID) task, which did not

require WM for task completion but rather for the subjects to make a gender discrimination of the face appearing at the end of the delay period. The faces shown were chosen to be gender ambiguous, so the results from the GID task are not expected to be meaningful. A critical aspect of the design was that the task for a particular trial was revealed only after cue face offset. This design forced subjects to encode into WM a cue face whenever it appeared, even during GID trials. Furthermore, the trial task was revealed two seconds, and not immediately, after cue offset in order to enhance the temporal separation between the engagement of encoding and maintenance related neural processes by the subject. This temporal separation is necessary to disambiguate the BOLD signal reflecting encoding and maintenance related events. Subjects completed 40 trials of each task. There were ten trials within each of eight runs. Trial order was randomly intermixed. To ensure that all subjects were engaged with the task, we imposed a performance criterion of 60% accuracy on the WM task.

We chose a WM task that was not too difficult for both healthy control (HC) and schizophrenia (SZ) groups to accurately complete so that there would be sufficient number of correct trials with which to conduct the FC analyses. A task that was too difficult would likely have yielded a fairly large difference across groups in the number of correct trials. Low correct trial numbers in the patient group would reduce our ability to reliably measure true FC strength and a large group difference in trial numbers could introduce bias in terms of group comparisons. Using this approach, we identified task relevant functional ROIs in the lateral PFC and visual cortex and derived estimates of the strength of PFC-visual cortex FC to test the hypothesis of PFC FC impairments and their associations with task performance and symptomatology in schizophrenia.

2.3 fMRI acquisition and processing

fMRI scans were completed on a Siemens 3T TRIO MR system with an eight channel phased array head coil. fMRI volumes were acquired using the following parameters: 36 3.5-mm oblique axial T2*-weighted gradient-echo EPI slices, with 2000 ms TR, 28 ms TE, 60 degree flip angle and 240 mm × 240 mm field of view in a 64 × 64 matrix. Each functional run was preceded by five images of unanalyzed data to allow steady-state magnetization to be achieved. Preprocessing of fMRI volumes with the Statistical Parametric Mapping, version 8 (SPM8) software package included temporal and spatial realignment, normalization to the EPI template, .001 Hz high-pass filtering and spatial smoothing with 8 mm FWHM Gaussian kernel. We excluded two SZ and one HC subject for exhibiting greater than 4 mm within-run movement. This threshold was chosen as the size of a voxel was 4 mm in plane. A comparison of mean framewise displacement (Power et al., 2014) of included subjects during scanning indicated absence of significant between-group difference in this variable (p=0.292). In addition, we also found no group difference in the frame-by-frame changes in any of the six movement parameters, p>0.13. We also conducted additional post-hoc analyses, described below, to rule out the possibility of head movement confounding our results.

2.4 fMRI analysis

2.4.1 fMRI modeling—fMRI data modeling proceeded under a slow event-related design framework, with the canonical double-gaussian hemodynamic response function convolved with regressors for WM encoding, maintenance and response, corresponding to cue, delay and probe events. The three task phases were modeled in the following manner: encoding—a single covariate during cue presentation at the beginning of the trial (t=0 s); maintenance—a single covariate in the middle of the delay period (t=7 s) and response—a single covariate during probe presentation (t=16 s). We included the first temporal derivative of covariates in the regression matrix to account for potential group differences in BOLD signal temporal dynamics resulting from differences in response times or other variables. We also included the six movement parameters in our models. There were separate covariates for correct and incorrect trials, but only correct trials were analyzed because the number of incorrect trials was too small to produce meaningful results. We included an analogous set of covariates for the GID trials.

2.4.2 Localization of functional ROIs—Given the abundant empirical data implicating the specific brain regions involved in visual WM and the connectivity model of WM with these ROIs, we did not employ a whole brain, voxel-wise analysis and instead we utilized an ROI based approach for hypothesis testing. This approached required specifying *a priori* the ROIs to be analyzed (lateral PFC and ventral visual cortex). We utilized functional ROIs, rather than anatomic ROIs, for hypothesis testing to enhance sensitivity to detect true effects. The lateral PFC is a relatively broad region that encompasses functionally heterogeneous sub-regions. Thus, the use of anatomically defined ROIs of the lateral PFC would likely significantly diminish our ability to detect WM-specific fMRI signal. One of the major challenges in functional localization is the “curse of circularity” (Vul and Kanwisher, 2010). This problem arises when fMRI data that is not independent from the fMRI data to be analyzed is used to identify or define ROIs used in the analysis. We avoided this problem by using scans independent of WM scans, e.g. GID scans, to localize ROIs and used these ROIs to interrogate WM scans. We first generated within-group activation maps (one map for HC and one map for SZ) (Figure 2) which were defined by the contrast of GID cue vs. implicit baseline. These were restricted using anatomic masks from Wake Forest University Pickatlas (http://www.fmri.wfubmc.edu) (Maldjian et al., 2003). The union of the superior and middle inferior gyri and the union of fusiform and lingual gyri served as inclusive masks for the lateral PFC and ventral visual cortex, respectively (Yoon et al., 2007). The size of the functional ROIs was determined by the inclusion of all voxels surviving a voxel-wise FDR threshold of p=0.05 were included in the functional ROIs. There were two sets of PFC and visual cortex ROIs, one set for HC, and another set for SZ. For exploratory analyses, we created left and right ROIs for the PFC and visual cortex in the same manner described above, with the added constraint of hemisphere.

2.4.3 Univariate analysis—We completed two types of univariate analyses– ROI and voxel-wise whole brain. The former was conducted so that we could directly compare univariate and FC ROI data. We obtained spatially averaged beta estimates from univariate fMRI model estimation described above. We also conducted voxel-wise whole brain between-group analyses to explore if regions beyond the functional ROIs exhibited

activation differences. For these analyses, we deliberately chose a liberal threshold of $p<0.01$, uncorrected, in order to maximize the chances of finding any group differences. We also conducted within group voxel-wise whole brain analyses to examine the level of activations in each group. For these analyses, we employed conservative corrected methods for determining activation significance, a cluster-defining threshold of p=0.001 and FDR cluster corrected $p<0.05$.

2.4.4 Functional connectivity—The beta-series correlation method (Gazzaley et al., 2004; Rissman et al., 2004; Yoon et al., 2008) quantified task phase-specific FC between brain regions. This method employs unique covariates for every trial and task epoch to generate trial and task epoch specific estimates of activity for each voxel within the brain (beta series). Beta series of voxels within ROIs (PFC and visual cortex) were spatially averaged to generate PFC and visual cortex beta series, which were then correlated with each other to quantify strength of PFC-visual cortex FC.

2.5 Correlations

The Pearson's *r* was calculated for all correlational analyses. Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), Scale for the Assessment of Positive Symptoms (SAPS), and Global Assessment Scale (GAS) quantified symptoms in patients, and were used for exploratory analyses. Pearson's *r* was calculated to examine their association with a measure of FC. Magnitude of disorganization (distinct from psychotic or negative symptoms) was quantified by combining component item scores listed below from these scales as described elsewhere: BPRS – conceptual disorganization, mannerism and posturing, and disorientation; SANS – global attention; SAPS - global formal thought disorder and global bizarre behavior. (Barch et al., 2003). Pearson's *r* was calculated to test for an association between disorganization and FC.

3. RESULTS

3.1 Demographics

As shown in Table 1, our sample consisted of 16 SZ participants, and 18 HC participants. The mean ages of the SZ group was 26.1 (S.D.=7.8) with a mean education of 13.6 (S.D.=1.6) years. The HC group had a mean age of 29.0 (S.D.=8.5), with mean education of 15.9 (S.D.=1.6) years. The two groups were not significantly different in age ($p=0.205$) or gender composition ($p=0.348$), but were significantly different in education levels ($p<0.001$). This is a common finding in schizophrenia studies. The neurobiological mechanisms that result in WM deficits likely also result in reduced educational attainment. In other words, WM deficits and reduced educational attainment covary and likely share a common etiologic mechanism. Hence, correcting for reduced educational attainment would have the effect of obscuring the ability to detect the brain correlates of WM deficits in patients with schizophrenia. The SZ participants are community-dwelling, relatively stable individuals with established chronic schizophrenia.

3.2 Task Performance Results

Performance accuracy and reaction times of HC and SZ are shown in Figure 3. HC performed more accurately and faster than SZ in the WM task; mean accuracy of HC was 96.08% (S.D. = 3.9), and SZ was 89.84% (S.D. = 7.54), which were significantly different by independent sample t-test, (t=3.23; df=26.521; p=0.003). HC response time (RT) was 930.16 ms (263) and SZ RT was 1209.48 ms (336). RTs were significantly higher in SZ by independent sample t-test, (t=2.9047; df=34.088; p=0.006).

3.3 fMRI Results – Univariate Lateral PFC and Visual Cortex Activity

Group-averaged univariate BOLD signal parameter estimates for the three main WM phases from the lateral PFC and the visual cortex ROIs are shown in Figure 4. An ANOVA of these estimates with factors of Group (HC and SZ) and Task Phase (Cue, Delay and Probe) did not show a main effect of Group in the visual cortex ($F_{(1,96)}$=0.876; p=0.352) or PFC ($F_{(1,96)}$=0.37; p=0.544). There was a main effect of Task Phase in the visual cortex ($F_{(2,96)}$=20.734, p<0.0001) and in the PFC ($F_{(2,96)}$=10.759; p<0.0001). There was no significant Group × Task Phase interaction (p>0.440) for either region. In a separate 3-way ANOVA, there was no significant Group × Task Phase × Region interaction (p=0.571).

To supplement and confirm the ROI univariate results, we completed voxel-wise univariate Generalized Linear Models (GLMs), looking for between group differences in univariate activity across the entire brain. Because our hypotheses involved the lack of a significant difference in univariate activity, we deliberately utilized a relatively liberal threshold e.g., low p value (p=0.01, uncorrected) in the between group contrast maps. This was done so we would be able to detect even relatively small differences in activations between the groups, if they existed. Even at this liberal threshold, we did not find any regions showing group difference in activity for any WM task phase. Within group contrasts for each WM task phase demonstrated comparable activations in both groups, including prominent activation in regions well known to be engaged by visual WM such as the lateral PFC, Anterior Cingulate Cortex (ACC), and visual cortex. A table listing all significant within group activations (Supplemental Table 1) and activation maps of regions showing above threshold activity (Supplemental Figure 1) can be found in the supplement.

While our hypothesis did not involve an effect of laterality, we performed exploratory analyses to determine if there was an effect of laterality. We repeated the ANOVA of the BOLD signal with laterality as an additional factor. This inclusion did not alter the results described above. The factors that were significant prior to the addition of laterality as a factor stayed significant after the addition of laterality, and there were no effects of laterality. (Supplemental Tables 2 & 3).

3.4 MRI Results – PFC-Visual Cortex Functional Connectivity

The quantification of task-evoked FC between the lateral PFC and visual cortex during WM are shown in Figure 4C. ANOVA of the strength of FC (the magnitude of correlation between the two ROIs) with factors of Group and Task Phase showed a significant main effect of Group ($F_{(1,128)}$=14.961; p<0.001), but no significant effect for Task Phase ($F_{(3,128)}$=0.063; p=0.979) or a Task Phase × Group interaction (F(3,128)=0.238; p=0.869).

While the HC group had higher FC in all task phases compared to the SZ group, post-hoc t-tests showed that group differences in FC approached significance only for the delay period, ($F_{(1,32)}$=4.998; p=0.033, uncorrected, p=0.098, Bonferroni corrected). Group difference was non-significant for cue ($F_{(1,32)}$=3.851; p=0.059, uncorrected) and probe ($F_{(1,32)}$=1.849; p=0.183, uncorrected). Both groups exhibited significant FC (above zero) for every task phase as tested by a one-sample t-test, p<0.0001.

We then examined the specificity of these results for the WM task. ANOVA of the strength of FC with factors of Group and Task (WM and GID) showed no significant main effect of Task (p=0.658), or a Task × Group interaction (p=0.098), but only a significant effect of Group (p<0.001). An ANOVA of strength of FC with factors of Group, Task, and Task Phase showed a significant main effect of Group ($F_{(1, 224)}$= 15.795; p<0.001), and the Task × Group interaction was not significant ($F_{(1, 224)}$=2.667; p=0.104). There were no significant main effects for Task or Task Phase (p>0.620), or interaction effects for Task × Task Phase or Task × Task Phase × Group (p>0.594). The results of t-tests also showed no significant difference in PFC FC between the WM and the GID task (p>0.140 for all three phases) in either the SZ or HC sample.

We explored the possibility that the use of antipsychotics by patients could confound our results by correlating chlorpromazine equivalent doses with PFC FC measures. All correlations were associated with p>0.240. We also explored the possibility that head movement during scanning could be confounding our results. We correlated each subject's average framewise displacement with their PFC-visual cortex FC during each WM task phase. This was done for each of the six movement parameters. We found fairly low levels of correlation, with all absolute values of r<0.15 and p>0.420.

As above with the univariate results, we also explored the possibility of the effect of laterality on FC. We found no main effect of laterality (Left vs. Right ROI) (p=0.296), or any significant interactions involving laterality (p>0.480). In addition, the significant effects reported above did not change when laterality was added as a factor (Supplemental Tables 4 & 5).

3.5 Correlation Between Functional Connectivity and Task Accuracy

In patients, the correlations between task performance and FC were significant for delay (r=0.65, p=0.006) and probe (r=0.55, p=0.026) but not for cue (r=0.38, p=0.145) (Figure 5). After applying a Bonferroni correction factor of three, only the delay period correlation remained significant, p=0.018. None of the HC WM task phase correlations were significant, p>0.300 uncorrected. To examine the possibility that this correlation was driven by a single outlier subjects, we re-calculated correlations after excluding single subjects iteratively. The Pearson's r for these correlations ranged between 0.52-0.74 and all associated p-values were <0.05. The correlation between FC and accuracy increased slightly when chlorpromazine equivalents were added as a covariate for delay (r=0.76, p=0.001) and for probe (r=0.62, p=0.016) in the SZ group.

3.6 Correlation Between Functional Connectivity and Disorganization

We next examined the relationship between PFC-visual cortex FC and disorganization. Based on the results of prior studies (Yoon et al., 2008), we predicted that strength of PFC FC would be negatively correlated with severity of disorganization in the present study. Given this clear directional prediction, we utilized a one-tailed alpha level of 0.05 for significance testing. Figure 6 displays correlations for each WM phase. The mean PFC FC during the cue phase was negatively correlated with the magnitude of disorganization (r= −0.54, p=0.015). The correlations during delay and probe were non-significant, r=−0.28, p=0.146 and r=−0.12, p=0.327 respectively. The cue correlation remained significant after Bonferroni correction for multiple comparisons, p=0.045. When chlorpromazine equivalents were used as a covariate, the correlation between mean PFC FC and disorganization during the cue phase stayed significant (r=−0.55, p=0.040). We also conducted exploratory analyses in which we examined the relationship between PFC FC and other symptoms domains (SANS, SAPS, BPRS, and GAS) but no significant correlations were found (p>0.1).

We tested for specificity of WM in these correlations by examining the correlation between disorganization and PFC FC during the GID task (cue: r= −0.417, p= 0.05; delay: r= −0.249, p= 0.180; and probe: r= −0.370, p= 0.080). We did not find specificity for the WM task.

4. DISCUSSION

In this study, we tested the hypothesis of a deficit in FC between the lateral PFC and visual cortex during WM in patients with schizophrenia and examined association of this deficit with task performance and symptomatology. Subjects with schizophrenia were less accurate and responded slower than healthy controls on the WM task. We found decreased lateral PFC-visual cortex FC during WM in SZ compared to HC. In contrast, we found no evidence of significant group differences in univariate activity in lateral PFC, visual cortex or in any other brain region during WM. The strength of lateral PFC-visual cortex FC, particularly during the delay period, was correlated with WM task accuracy in SZ. Lateral PFC-visual cortex FC in the cue phase was also inversely correlated with the magnitude of disorganization in patients. These results suggest that deficits in FC may be an important parameter of lateral PFC dysfunction in patients with schizophrenia, accounting for some of the widespread cognitive and clinically relevant impairments in this disorder.

This study extends the growing literature on lateral PFC FC deficits in patients with schizophrenia in a number of unique ways. To the best of our knowledge, this is the second study to show diminished FC in patients with schizophrenia in the setting of intact lateral PFC activity as measured by fMRI. Nielsen et al. (2017) found evidence of abnormal effective connectivity within the fronto-parietal network in the setting of intact WM task performance and univariate activation. This dissociation between univariate and FC measures of PFC function suggests that the PFC FC impairments are not merely a reflection or an artifact of a failure to engage and activate the PFC and that FC impairments may be a more sensitive or robust indicator of the WM deficits in schizophrenia. This also reinforces the conclusion of others about the unique importance of FC in WM deficits in patients with schizophrenia (Cao et al., 2016).

The divergence between the FC and univariate results should not come as a surprise. FC is a largely orthogonal measure of a brain region's function compared to univariate activity. The former is a bivariate correlation, or some related measure, between two brain regions. Thus, the lateral PFC FC is measured using correlation coefficients and can be largely unrelated to magnitude of univariate activation or group differences in univariate activation. Two time series corresponding to large univariate activity would not yield high correlation values if their covariance across time is low. The converse is also true: two time series with low univariate activity could produce high correlations if their covariance is high across time. The key concept here is that FC indexes a separate dimension of brain function than what is measured by univariate activity.

The significant correlations between FC deficits and decreased accuracy and increased disorganization underscore the clinical relevance of lateral PFC FC deficits. While prior studies have demonstrated impairments in PFC connectivity, only a few have previously identified such an association with cognitive or functional measures (Henseler et al., 2010). Yoon et al. (2008) identified similar findings to the present study in that the magnitude of lateral PFC FC during a cognitive control task was also inversely correlated with severity of disorganization. The absence of an association between WM performance and lateral PFC FC in HC may have been due to the limited variance in performance, as HC subjects demonstrated nearly 96% accuracy on average.

The significant correlations with severity of disorganization represents a validation of the deficit in lateral PFC-visual cortex FC as a clinically relevant phenomenon. As such, it has important implications for future translational research efforts. One of the most significant challenges facing efforts to uncover the neural mechanisms of schizophrenia is the difficulty of modeling the complex clinical features of schizophrenia, such as disorganization, in animal experimental systems. One way to meet this challenge is to rely on clinical neuroscience studies with human subjects afflicted with schizophrenia, such as the present, to identify and validate the neural correlates of the clinical abnormalities of schizophrenia. These neural correlates could then be reverse translated into animal experimental systems for further study. This would avoid the need for modeling complex clinical features within an experimental animal system. The correlation between lateral PFC FC strength and disorganization in patients with schizophrenia represents such an identification and validation. These findings provide the rationale and impetus for the reverse translation of deficits in lateral PFC-visual cortical FC in to animal experimental systems so that the neural mechanism of these deficits could be further explored.

One of the strengths of the present study is the method we employed to evaluate lateral PFC FC. Firstly, our method avoided sampling bias by utilizing a separate set of scans to localize ROIs to derive activation or FC estimates. This method for functional ROI localization may have provided enhanced sensitivity to detect the presence of group differences and associations with task performance and symptomatology. ROIs were chosen based on activation during the cue period of the GID task, which was completed by subjects during the same testing session. The experimental design of the cognitive paradigm ensured that these trials simulated, and therefore, likely engaged the identical brain regions in the lateral PFC and visual cortex compared to the WM trials.

There are important limitations of this current study to keep in mind. Our sample sizes were modest. This raises the possibility that the absence of a significant group difference in the magnitude of univariate activations in the lateral PFC or in the visual cortex represents a Type II error due to insufficient power. While it is an impossibility to prove a negative, power analyses indicate that samples sizes of at least 356 and 156978 would be needed to demonstrate a significant group difference in unvariate activity in the lateral PFC and visual cortex respectively. These estimates are based on the effect sizes we found of < 0.21 in the lateral PFC and < 0.01 in the visual cortex for all three task phases studied (Supplemental Table 6).

Similarly, we did not find specificity for the WM task in the FC results. The absence of a significant difference could be due to a limited sample size, which may lack the power to demonstrate a significant difference between the two tasks. On the other hand, given that the PFC is involved in many basic processes requiring attention, abnormalities in lateral PFC FC may be ubiquitious and not specific for WM or higher order cognitive processes.

A possible reason for the absence of significant group differences in univariate activity may be the WM task utilized in this study. Our task involved low WM load, which, in comparison to ones with high loads, preferentially engage regions of the brain involved in the temporary storage of information (Sreenivasan et al., 2014), rather than regions supporting cognitive control or other cognitive operations required by high WM load such as manipulation of information, which is known to be impaired in patients with schizophrenia (Barch and Sheffield, 2017). However, while decreased univariate activation of the PFC during WM in patients with schizophrenia has been noted by numerous studies as reviewed in Minzenberg et al. (2009), this is not a universal finding and our result showing intact activity is consistent with other reports in the literature.

We only used data from trials where the subjects responded correctly. This further reduced the number of data points and could have led to a reduced correlation between FC and accuracy. This study was by design an *a priori* region-specific study, and so was not intended to address the importance of other networks in the pathophysiology of schizophrenia (e.g., frontal-parietal networks). Our results show a correlation between decreased FC and task performance accuracy as well as with disorganization. This does not prove a causal relationship between these variables. It is possible that the correlation between FC and accuracy and disorganization may be indirect and mediated by another variable. This possibility should be addressed by future studies that are designed to identify such mediating variables.

Another limitation is the inability to infer the directionality of lateral PFC-visual cortex interactions. However, a preponderance of studies, as reviewed by Gazzaley and Nobre (2012) suggest that the likely direction of modulation during WM is from the lateral PFC to the visual cortex. Some of the most compelling evidence comes from studies utilizing interventions capable of demonstrating causal influences. For example, a classic study in monkeys demonstrated that the temporary inactivation of lateral PFC by cooling resulted in the reversible attenuation of neuronal spiking activity in the inferotemporal region during the delay period of a visual WM task (Fuster et al., 1985). A number of human studies utilizing

transcranial magnetic stimulation (TMS) to perturb lateral PFC function observed alterations in activity of occipitotemporal cortex (Feredoes et al., 2011; Higo et al., 2011) or of evoked response potentials thought to emanate from the visual cortex (Zanto et al., 2011).

An ever-present concern in schizophrenia studies is whether a finding is due to antipsychotic medication treatment or the illness itself. We cannot directly address this important concern in the present study since all of our SZ subjects were on psychotropic medication at testing. The effects of these medications on FC in the brain is not clearly understood at this time. However, the absence of a significant correlation between the dependent measures (WM task performance and lateral PFC-visual cortex FC) and chlorpromazine equivalents, suggests that our findings are not confounded by antipsychotic treatment.

In conclusion, our finding of impaired lateral PFC FC in the setting of intact univariate activation of this region during WM, and an association with cognitive performance and clinical symptomatology, suggest that impairment in lateral PFC FC is a key neural mechanism underlying cognitive deficits in patients with schizophrenia and may be a sensitive index of altered neurophysiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Intact activations but deficient DLPFC-visual cortex functional connectivity in patients with schizophrenia
- Functional connectivity deficits correlated with working memory performance in patients with schizophrenia
- Functional connectivity deficits correlated with level of disorganization in patients with schizophrenia

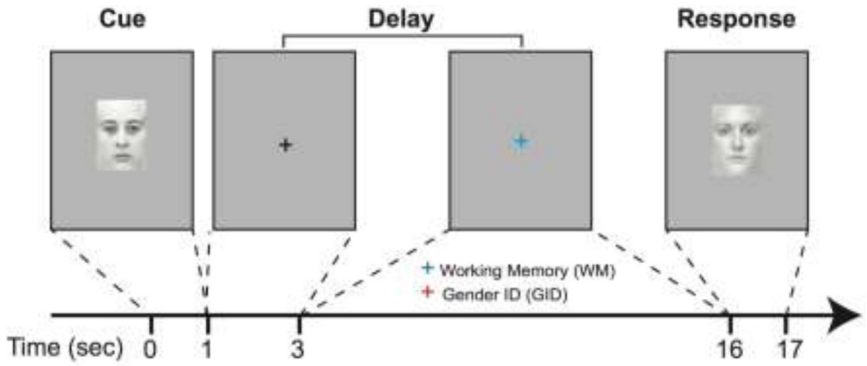

Figure 1.

Cognitive Paradigm. There were two conditions in this paradigm, which differed in requiring WM for task completion but had the identical trial structure and stimulus timing. The cue stimulus was presented for 1 sec. and then it was replaced by a black cross hair. This cross hair changed color after two seconds to either blue or red and the color indicated the condition of the trial: blue - working memory (WM) condition required the subject to maintain the cue face image across the 15 sec. delay period and make a match discrimination with the probe face appearing at the end of the delay; red - functional ROI localization condition did not involve WM and instead required the subject to make a gender discrimination of the probe face presented at the end of the delay period. Trial order was randomized with half of trials being WM trials. NB: The example trial presented above is a WM trial (blue cross hair) but if a GID trial were depicted, the cross hair would have been red.

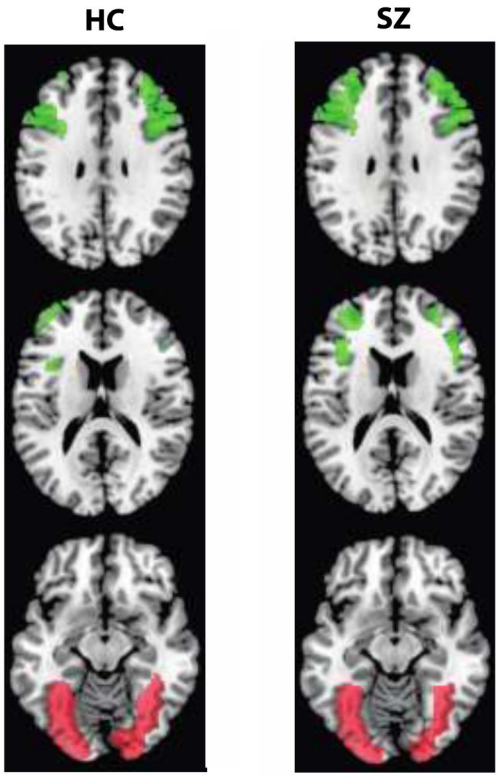

Figure 2.

Regions in the lateral PFC and ventral visual cortex showing above threshold activation in HC and SZ groups during GID cue epoch. Peak coordinates for each region are as follows: Controls, Right: PFC (34,62,4), visual cortex (24,−94,−8); Left: PFC (−42,6,28), visual cortex (−34,−76,−18). SZ, Right: PFC (46,−4,52), visual cortex (26,−92,−8); Left: PFC (−36,20,14), visual cortex: (−34,−52,−18). Masks of these regions we were used to derive estimates of univariate activations and functional connectivity during WM.

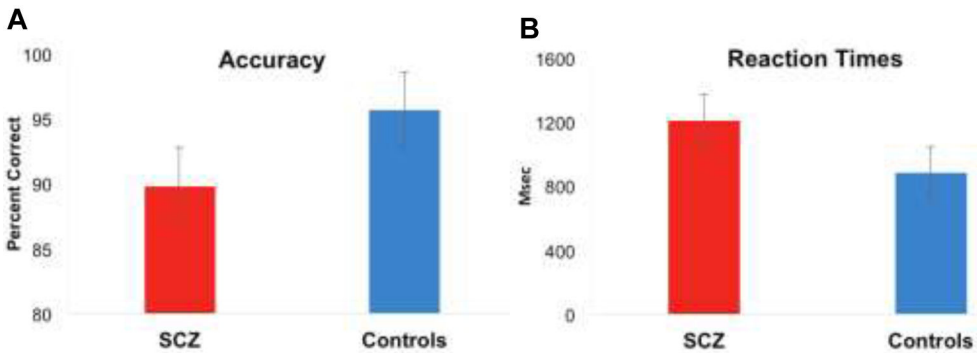

Fig. 3.

Task Performance. A. Task Accuracy. Mean accuracy with SEM on the WM task is displayed for the Schizophrenia (SZ) and Control Group. B. Task Reaction Times. Mean reaction times with SEM on the WM task is displayed for the Schizophrenia (SZ) and Control Group

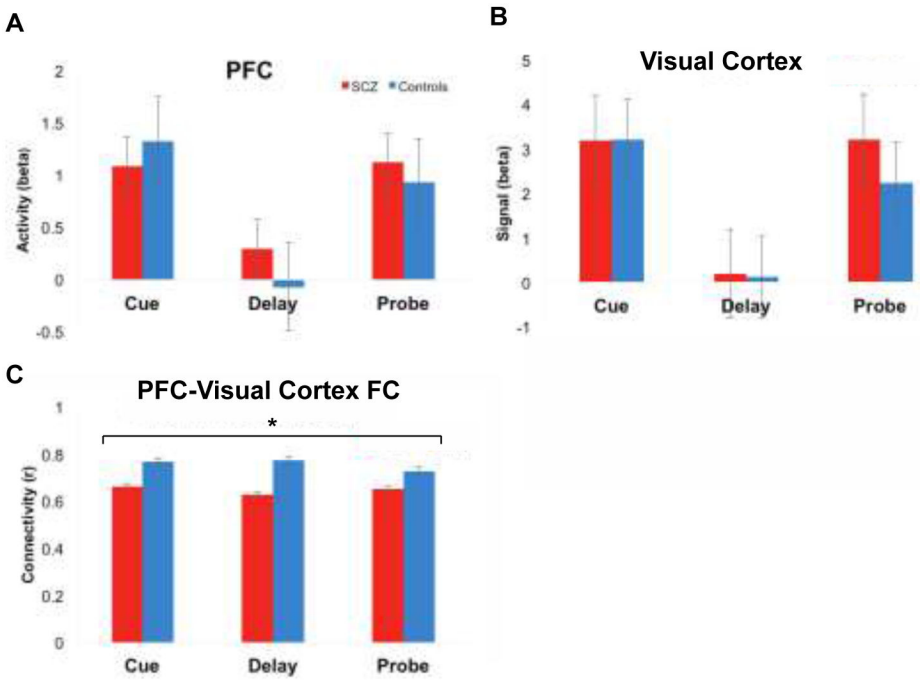

Fig. 4.

Task-Evoked fMRI Results in the PFC and Visual Cortex. The parameter estimates (betas) means for each WM phase are shown for A) PFC and B) visual cortex. C) The trial-wise correlations in BOLD signal between the PFC and the visual cortex in each of the three phases of the WM are shown. *Significant main effect of Group, $p<0.05$. PFC – prefrontal cortex; FC – functional connectivity.

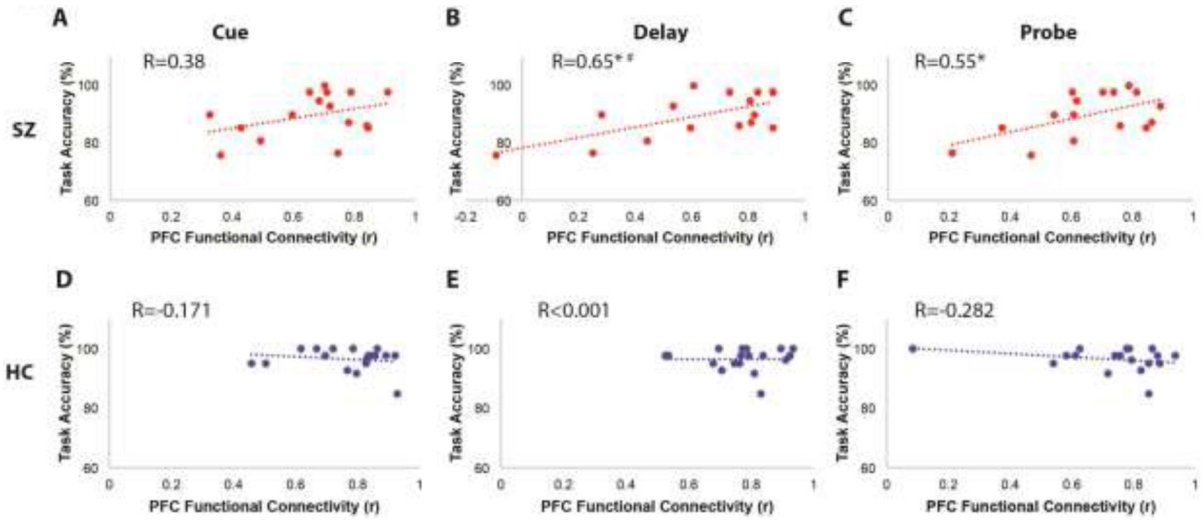

Figure 5.

Correlation Between WM Task Accuracy and PFC-Visual Cortex Functional Connectivity. Correlations are shown for SZ (A-C) and HC (D-F), and for each of the three phases of WM in SZ (C-E). * $p<0.05$, uncorrected, # $p<0.05$, corrected for multiple comparisons.

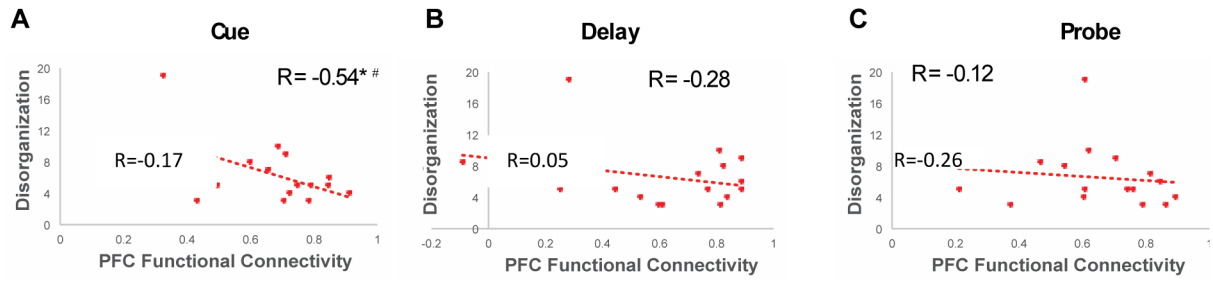

Figure 6.

Correlations Between Disorganization and PFC Functional Connectivity. The WM phase specific correlations are displayed for Cue (A), Delay (B) and Probe (C). *p<0.05, uncorrected, #p<0.05, corrected for multiple comparisons.

Table 1.

Subject demographics, clinical profile and behavioral performance on the cognitive task.

	Patient (*N*=16)		**Control (*N*=18)**		
	Mean	**SD**	**Mean**	**SD**	**p-value**
Age (years)	26.1	7.8	29.0	8.5	0.205
Gender (%male)	78		63		0.3477
Education (years)	13.6	1.6	15.9	1.6	< 0.001
Parental Education (years)	14.6	2.1	15.1	2.3	0.533
Handedness (% R)	94		95		
GAS	52.9	10.1			
Disorganization	6.2	3.7			
SANS Total	8.6	4.2			
SAPS Total	4.8	3.6			
BPRS Total	36.1	11.7			
Anti-Psychotics					
Typical (%)	25				
Atypical (%)	63				
None (%)	12				
CPZ Equivalents	268	334			

Brief Psychiatric Rating Scale (BPRS); Scale for the Assessment of Negative Symptoms (SANS); Scale for the Assessment of Positive Symptoms (SAPS), and Global Assessment of Symptoms (GAS).