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Transdiagnostic Neural Markers of Emotion-Cognition Interaction in Psychotic Disorders

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Abstract

Deficits in working memory (WM) and emotion processing are prominent impairments in psychotic disorders, and have been linked to reduced quality of life and real-world functioning. Translation of knowledge regarding the neural circuitry implementing these deficits into improved diagnosis and targeted treatments has been slow, possibly due to categorical definitions of disorders. Using the dimensional Research Domain Criteria (RDoC) framework, we investigated the clinical and practical utility of transdiagnostic behavioral and neural measures of emotion-related WM disruption across psychotic disorders. Behavioral and functional magnetic resonance imaging data were recorded while 53 participants with psychotic disorders and 29 participants with no history of psychosis performed a modified *n*-back task with fear and neutral distractors. Hierarchical regression analyses showed that psychotic symptoms entered after diagnosis accounted for unique variance in fear versus neutral accuracy and activation in the ventrolateral, dorsolateral, and dorsomedial prefrontal cortex, but diagnostic group entered after psychotic symptoms did not. These results remained even after controlling for negative symptoms, disorganized symptoms, and dysphoria. Finally, worse accuracy and greater prefrontal activity were associated with poorer social functioning and unemployment across diagnostic groups. Present results support the transdiagnostic nature of behavioral and neuroimaging measures of emotion-related WM disruption as they relate to psychotic symptom dimension, irrespective of diagnosis. They also provide support for the practical utility of these markers in explaining real-world functioning. Overall, these results elucidate key aspects of the RDoC construct of WM maintenance by clarifying its transdiagnostic importance and clinical utility in psychotic disorders.

Keywords

emotion; working memory; fMRI; schizophrenia; RDoC

Neural measures such as functional magnetic resonance imaging (fMRI) offer a window into the neurobiology supporting cognitive and emotional processing, as well their disruption in psychotic disorders, creating the potential for better diagnosis and more targeted treatment development (Carter et al., 2011). However, progress in clinical translation of these neural measures has been limited, possibly because psychopathology has traditionally been examined categorically (Ford et al., 2014; Sanislow et al., 2010). Traditional diagnostic categories are based on heterogeneous clusters of symptoms, which limit informational value of the phenotype. Psychotic disorders, for example, may be better conceptualized in terms of behavioral, cognitive, and emotional dimensions that cut across traditionally-defined diagnostic categories (Hill et al., 2013; Kraemer, Noda, & O'Hara, 2004; Markon, Chmielewski, & Miller, 2011; Rosenman, Korten, Medway, & Evans, 2003; Ruocco et al., 2014; Tamminga et al., 2013; von Hausswolff-Juhlin, Bjartveit, Lindström, & Jones, 2009). This dimensional approach is the foundation of the Research Domain Criteria (RDoC; Cuthbert & Insel, 2010; Insel et al., 2010) which proposes to elucidate neural dimensions implementing cognitive and affective domains across categorically defined diagnoses. The RDoC offers a new approach for classifying and defining mental disorders on the basis of dimensions of observable neurobiological and behavioral indices, as opposed to descriptive phenomenology.

The present study utilizes the RDoC framework to examine whether behavioral and neural measures of emotion-cognition interactions relate to symptom dimensions and real-word functioning transdiagnostically, across various psychotic disorders. The importance of emotion-cognition interactions is highlighted by research showing that emotion and cognition are inseparable at neural and behavioral levels (Miller, 1996; Pessoa & Adolphs, 2010; Pessoa, 2008), and their interaction may play a critical role in psychotic disorders (Anticevic & Corlett, 2012; Kring & Caponigro, 2010; Taylor & MacDonald, 2012). While emotion-related distraction can impair a range of cognitive functioning in psychotic disorders (Anticevic, Repovs, & Barch, 2012; Burbridge & Barch, 2002; Calev & Edelist, 1993; Danion, Kazes, Huron, & Karchouni, 2003; M. J. Green, Williams, & Davidson, 2001; Herbener, Rosen, Khine, & Sweeney, 2007; Kerns & Berenbaum, 2000; Mathews & Barch, 2004; Rossell, 2006), we focused on working memory (WM) in the present study since deficits in WM are considered key cognitive impairments in schizophrenia (Barch & Ceaser, 2012; Forbes, Carrick, McIntosh, & Lawrie, 2009; Goldman-Rakic, 1994; M. F. Green, Kern, Braff, & Mintz, 2000; Lesh, Niendam, Minzenberg, & Carter, 2011; Silver, Feldman, Bilker, & Gur, 2003) and are also present in schizoaffective disorder and bipolar disorder with psychotic features (Bellivier et al., 2013; Bora, Yucel, & Pantelis, 2010; Lee & Park, 2005).

Emotional distractors impair WM performance, and alter prefrontal cortex (PFC) recruitment and connectivity in individuals with schizophrenia (Anticevic, Repovs, Corlett, & Barch, 2011; Anticevic, Repovs, Krystal, & Barch, 2012; Becerril & Barch, 2011; Habel et al., 2010; Pauly et al., 2008) or at risk for psychosis (Ladouceur et al., 2013; Mohanty et al., 2005; Pauly et al., 2010). Moreover, neuroimaging studies of emotion-related disruption of WM demonstrate a dissociable pattern of activity between ventral and dorsal prefrontal regions (Dolcos, Iordan, & Dolcos, 2011; Dolcos & McCarthy, 2006; Morey et al., 2009), with greater activity in ventrolateral PFC (VLPFC; Brodmann Areas [BA] 44/45/47; Quidé,

Morris, Shepherd, Rowland, & Green, 2013; Ranganath, 2010; Ranganath, Minzenberg, & Ragland, 2008; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004; Sambataro et al., 2013; Wolf et al., 2009), traditionally involved in emotional processing (Beauregard, Levesque, & Bourgouin, 2001; Lévesque et al., 2003; Markowitsch, Vandekerckhove, Lanfermann, & Russ, 2003; Nakamura et al., 1999; Narumoto et al., 2000; Pelletier et al., 2003; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998) and lower activity in dorsolateral PFC (DLPFC; BA 9/46; Barbey, Koenigs, & Grafman, 2013; Manoach et al., 2000; Petrides, Alivisatos, Evans, & Meyer, 1993; Rajkowska & Goldman-Rakic, 1995), involved in actively maintaining task-relevant information in WM (Banich et al., 2000; Chafee & Goldman-Rakic, 2000; Egner & Hirsch, 2005; Smith & Jonides, 1999). These two regions consistently show altered activity during WM tasks in schizophrenia (Glahn et al., 2005; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Compared to healthy individuals, VLPFC activity is further increased while processing irrelevant (Eich, Nee, Insel, Malapani, & Smith, 2014) and negative emotional stimuli in psychotic disorders (Morris, Sparks, Mitchell, Weickert, & Green, 2012). Furthermore, while individuals with psychotic disorders show decreased DLPFC activity during WM tasks, they show increased DLPFC activity compared to healthy individuals when emotional distractors are introduced in the task (Becerril & Barch, 2011; Mullin et al., 2012). This suggests greater recruitment of cognitive resources to maintain information in WM (Becerril & Barch, 2011; Mullin et al., 2012), potentially due to neurophysiological inefficiency of the DLPFC in psychotic disorders (Jansma, Ramsey, van der Wee, & Kahn, 2004; Manoach, 2003; Potkin et al., 2009; Schneider et al., 2007). Importantly, this emotion-related WM disruption has been linked to positive symptoms in the schizophrenia spectrum (Bentall & Kaney, 1989; Besnier et al., 2011; Epstein, Stern, & Silbersweig, 1999; Fear, Sharp, & Healy, 1996; Leafhead, Young, & Szulecka, 1996; Mohanty et al., 2008).

This understanding of neural processes impaired in emotion-WM interactions has, however, not translated into improved diagnosis and treatments, and little is known about the clinical utility of these measures in psychotic disorders. Specifically, it is unclear whether prefrontal neural markers of emotion-WM interaction are informative regarding illness course, specific symptom dimensions, remission, and real-world functioning. Furthermore, since emotion-related disruption of executive functions and PFC activity is seen in anxiety and depression (Bishop, Duncan, Brett, & Lawrence, 2004; Bishop, 2007; Fales et al., 2008; Kerestes et al., 2012; Wagner et al., 2008), which are highly comorbid with psychotic disorders (Achim et al., 2011; Emsley, Oosthuizen, Joubert, Roberts, & Stein, 1999; Schothorst, Emck, & van Engeland, 2006), it is unclear whether emotion-related WM disruption in psychotic disorders is attributable to comorbid anxiety or depression symptoms. We tested these questions in a diagnostically heterogeneous cohort of individuals with psychotic disorders and never-psychotic adults, using behavioral and fMRI measures of emotion-related disruption of WM. This allowed us to address the following two hypotheses:

Transdiagnostic Hypothesis

Emotion-related WM deficits and PFC dysfunction are seen both in schizophrenia and bipolar disorder with psychosis and are consistently linked with positive symptoms in these disorders (Bentall & Kaney, 1989; Besnier et al., 2011; Epstein et al., 1999; Fear et al.,

1996; Leafhead et al., 1996; Mohanty et al., 2008). Thus, in the present study we hypothesized that increased DLPFC and VLPFC activity due to emotion-related WM disruption will be associated with psychotic symptom dimension even when controlling for groups based on Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (American Psychiatric Association, 1994) categories. Anxiety and depression are highly comorbid with psychotic disorders; however, they have not been found to explain the relationship between psychotic symptoms and disruption of cognitive control from emotional distractors (Mohanty et al., 2008). We examined dysphoria (Watson et al., 2008, 2012), since it taps the common core of depression and anxiety, and hypothesized that the relationship between emotion-related WM measures and psychotic symptoms will remain even after controlling for dysphoria.

Practical Utility Hypothesis

Since WM deficits and DLPFC impairment are strongly related to worse occupational and social functioning in schizophrenia and bipolar disorder with psychosis (Bowie et al., 2008; Dickerson et al., 2004; Hofer et al., 2005; Huang et al., 2013; Mattson, Berk, & Lucas, 1997; Pantelis, Stuart, Nelson, Robbins, & Barnes, 2001), we hypothesized that behavioral and neural measures of emotion-related WM disruption will be associated with worse occupational and social functioning, and that this relationship will exist even after controlling for diagnostic groups.

Method and Materials

Participants

The present sample is a subset of the Suffolk County Mental Health Project (Bromet et al., 1992, 2011), a 20-year longitudinal epidemiologic study of first-admission psychosis. Data were collected from 53 individuals with a history of psychosis – 26 with schizophrenia spectrum disorders (SZ; schizophrenia and schizoaffective disorder) and 27 with other psychotic disorders (OP; mood disorders with psychotic features, substance induced psychosis, and psychotic disorder not otherwise specified). The current assessment (including imaging) was carried out 20 years after first admission. Since differential diagnosis between psychotic disorders is prone to misclassification (Bromet et al., 2011), lifetime diagnosis was made by longitudinal consensus of study psychiatrists who reviewed six assessments spanning 20 years, which included face-to-face assessments by masters-level clinicians using the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 2012) with significant others, and review of medical records collected at 6 time points spanning 10 years (first admission, 6-month, 2-year, 4-year, 10-year, and 20-year). See Supplemental Methods for further details.

The groupings (SZ and OP) of DSM diagnostic categories were made based on previous work with this cohort (Roman Kotov et al., 2013; Reichenberg et al., 2009) as well as other work (Daban et al., 2006; Krabbendam, Arts, van Os, & Aleman, 2005) showing that schizophrenia spectrum disorders are characterized by more severe symptoms, worse course, and greater cognitive impairment than other psychotic disorders. Although substance-induced psychosis may involve a different etiology compared to other psychotic disorders,

individuals with this diagnosis were included in our present sample based on self-reports of elevated positive and negative symptoms at the time of the study. This was consistent with our focus on transdiagnostic relationships between behavioral and neural measures of emotion-cognition interactions and symptom dimensions. Additionally, an age and gender matched comparison group of 29 participants with no history of psychosis (NP) was recruited from the same zip codes as patients. The procedures for obtaining informed consent were approved annually by the Committees on Research Involving Human Subjects at Stony Brook University.

Procedure

After informed consent was obtained, participants completed the diagnostic interviews and their eligibility for fMRI was confirmed with a brief screening questionnaire. The participants then completed practice trials designed to acquaint them with the experimental tasks outside the scanner. The scan session began with an anatomical localizer, followed by a field inhomogeneity shim, and a high-resolution 3D structural scan using a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence. Next, the participants performed the current (i.e., emotion-related WM) task, followed by an emotional face processing task and a functional localizer task in separate runs using the same scanning parameters as the current task (described later). Finally, resting-state fMRI and Diffusion Tensor Imaging (DTI) data were acquired for each participant. The entire scan session which included structural, functional, resting-state, and DTI scans lasted about an hour and the participants were given breaks between each run, or as needed.

Clinical and Functional Measures

Clinical measures were obtained for each participant concurrent with fMRI scanning. Participants were assessed with the SCID (First, Spitzer, Gibbon, & Williams, 2012) the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). Based on prior factor analysis (Roman Kotov, Guey, Bromet, & Schwartz, 2010), the SANS was scored as a single index, and the SAPS as two symptom subscales: psychotic (hallucinations, delusions) and disorganized (bizarre behavior, thought disorder). The SAPS consists of 31 items tapping 4 symptom domains and a global rating for each domain. Consistent with prior studies, we used individual items but not the global items (Peralta & Cuesta, 2001; Stuart, Pantelis, Klimidis, & Minas, 1999; Toomey et al., 1997). Common factor analysis supported the established structure in the present data. We removed 3 items that had consistently poor loadings in these analyses: SANS item 13 (inattentiveness during mental status testing), SAPS item 9 (persecutory delusions), and SAPS item 10 (delusions of jealousy). The final SAPS psychotic composite consisted of 16 items ($\alpha = .79-.85$), and SAPS disorganized of 13 items ($\alpha = .71-.76$). The interrater reliability of these ratings was very good (average interrater $r = .72$) (Brown, Susser, Jandorf, & Bromet, 2000).

Remission was defined according to the consensus criteria (Andreasen et al., 2005), and medication usage was recorded for antipsychotics, antidepressants, and mood stabilizers. Antipsychotic medication status for each participant was determined based on the presence or absence of antipsychotic medication use in the past month, separately for first and second

generation medications. Real-world functioning assessment included Global Assessment of Functioning (GAF) reflecting past month, employment status (employed vs. unemployed), and social functioning, a composite of social activity, social initiative, and socio-sexual relations ratings on the Quality of Life Scale (Heinrichs, Hanlon, & Carpenter, 1984). Participants also completed the Dysphoria scale of Inventory of Depression and Anxiety Symptoms, expanded version (IDAS-II; Watson et al., 2012) which taps common elements of anxiety and depression (Watson et al., 2008). Master's-level interviewers conducted the assessments with high interrater reliability ($r = 0.83$).

Experimental Task

Participants completed a 1-back version of the n -back task, modified to include fear, neutral, and no distractors (Figure 1). The task required participants to view a series of houses and, for each house, indicate whether or not it matched the house that immediately preceded it by pressing buttons corresponding to a “Yes” or “No” response. In between the images of houses, participants were presented with distractors - fear face or neutral face - or no distractor (fixation cross). The task stimuli included 15 black and white images of Victorian houses, which were similar in size and shape. Distractors were 15 fear and 15 neutral faces selected from the NimStim Face Stimulus Set (Tottenham et al., 2009). Facial expression stimuli represented male actors, from different ethnic groups (Caucasian and African-American). The images were cropped and converted to gray-scale, adjusted for brightness, luminance, and contrast. The three distractor conditions – fear, neutral, and no distractor - were counterbalanced across blocks for each participant. Each trial consisted of presentation of the picture of a house (500 ms), followed by a fixation cross (500 ms), followed by the distractor image (1500 ms), and another fixation cross (500 ms), culminating in a trial length of 3 seconds. The trials were grouped into five blocks for each distractor type, with 18 trials in each block, resulting in a total of 270 trials. Accuracy and reaction times were recorded during the scan sessions via button press. The experiment was coded in Python 2.7 (<http://www.python.org>) and presented using PsychoPy software (Peirce, 2007, 2009). To minimize performance differences, all participants practiced the task (only with neutral trials, to minimize practice effects) until they achieved at least 75% accuracy. The main task was conducted across 5 scanning sessions with three blocks each. Behavioral measures of accuracy and response time were collected during scanning.

Image Acquisition

Structural and Blood-Oxygen-Level-Dependent (BOLD) data were acquired on a 3 Tesla Siemens TIM Trio whole body scanner. Functional volumes were acquired with an interleaved echoplanar imaging (EPI) sequence using the following parameters: 2000 ms repetition time (TR), 30 ms echo time (TE), 34 axial slices, slice thickness: 3.5 mm, in-plane resolution: 3.1×3.1 , field of view (FOV): 210 mm, flip angle: 90 degrees, and total number of volumes collected: 480. Structural images were acquired via sagittal magnetization prepared rapid gradient echo (MPRAGE) sequence (TR = 1900 ms, TE = 2.53 ms, flip angle = 9° , slice thickness = 1 mm, in-plane resolution = 1×1 mm).

Behavioral Data Analysis

Emotion-related WM disruption was calculated as the difference between Neutral and Fear accuracy (Neutral>Fear accuracy).

Transdiagnostic hypothesis—To test our transdiagnostic hypothesis, we first conducted bivariate correlations between Neutral>Fear accuracy and the three symptom dimensions – psychotic, negative, and disorganized. Next, two sets of hierarchical regression analyses predicting Neutral>Fear accuracy were conducted. In the first regression, variables were entered in the following order: (1) demographic variables, negative symptoms, disorganized symptoms (2) psychotic symptoms, (3) diagnostic group, and (4) psychotic symptoms × diagnostic group interaction. A second hierarchical regression was conducted with psychotic symptoms and diagnostic group entered in the reverse order, with the remaining variables entered in the same order. The demographic variables included age, gender, medication status – first and second generation, current occupation, race, education, and parental education. Of primary interest was the increment in variance accounted for (R^2) by symptom dimensions and diagnostic group when added second, as a means of evaluating the unique variance contributed by each. To assess the role of dysphoria (anxiety and depression) in the relationship between Neutral>Fear accuracy and psychotic symptoms, a second set of hierarchical regressions similar to the ones described above were conducted. In the first regression, variables were entered in the following order: (1) demographic variables (2) psychotic symptoms, (3) dysphoria, and (4) psychotic symptoms × dysphoria interaction. In the second regression, symptoms and dysphoria were entered in a reverse order, while the remaining variables were entered in the same order.

Emotion-related disruption of WM in psychotic disorders—Since our hypotheses focused on the relationship of psychotic symptom dimension with Neutral>Fear accuracy, we also examined whether Neutral>Fear accuracy in individuals who are currently psychotic (CP; N=23; based on current delusions or hallucinations endorsed on SAPS) is actually impaired compared to never-psychotic individuals by conducting a 2 (groups: CP vs. NP) × 2 (conditions: Fear vs. Neutral) repeated measures analysis of variance (rmANOVA).

Practical utility hypothesis—To assess practical significance of behavioral measures of emotion-related WM disruption, we computed bivariate correlations between Neutral>Fear accuracy and measures of real-world functioning, including employment status, social functioning, remission, and GAF scores across patients. In addition, we computed partial correlations between the above variables, controlling for diagnostic group (SZ and OP).

fMRI Data Analyses

Subject-level fMRI Data Preprocessing and Statistical Analysis—Using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK), functional images for each participant were corrected for slice timing, and were then spatially realigned, spatially normalized using the Montreal Neurological Institute (MNI) EPI brain template, and smoothed with an isotropic Gaussian kernel of full-width half-maximum (FWHM) of 8 mm³. The ArtRepair toolbox (<http://cibsr.stanford.edu/tools/>

[ArtRepair/ArtRepair.htm](#)) was used to correct motion artifacts by replacing affected volumes with a volume interpolated from the nearest unaffected volumes.

For each participant, a general linear model (GLM) was estimated with functional images across sessions. Blood oxygenation level-dependent (BOLD) hemodynamic response function (HRF) was modeled separately for each distractor condition (Fear and Neutral) using stick (delta) functions convolved with the canonical HRF resulting in per-voxel parameter estimate (β) maps representing the magnitude of activation associated with each distractor condition. The model included a 128 sec high-pass filter to remove low-frequency fluctuations and an autoregressive (1) model to account for temporal non-sphericity due to autocorrelations. Contrasts comparing Fear > Neutral distractor conditions β were computed for each participant and used for second-level group analyses.

Regions of interest (ROI) selection—Given our strong *a priori* predictions regarding the role of DLPFC and VLPFC in emotion-related WM disruption, we applied small-volume correction for all analyses using a single mask that included these ROIs. DLPFC traditionally comprises of BA 9 and 46 (Barbey et al., 2013; D. S. Manoach et al., 2000; Petrides et al., 1993; Rajkowska & Goldman-Rakic, 1995), while VLPFC comprises of BA 44, 45, and 47 (Quidé et al., 2013; C. Ranganath, 2010; Charan Ranganath et al., 2008; Ridderinkhof et al., 2004; Sambataro et al., 2013; Wolf et al., 2009). ROIs were defined bilaterally as 11mm spheres centered around activation peaks in DLPFC ($\pm 36,32,28$; BA 9) and VLPFC ($\pm 44,8,28$; BA 44), identified in a prior meta-analysis (Minzenberg et al., 2009) and converted to MNI space (<http://bioimagesuite.yale.edu/mni2tal/>). ROI definition in this manner ensured independence between our ROI selection process and subsequent testing of contrasts between experimental conditions. For further hypothesis testing, these ROIs were combined to create a single bilateral mask using the MarsBar toolbox (Brett, Anton, Valabregue, & Poline, 2002). To control for multiple voxelwise statistical testing in the ROI mask we used the AlphaSim toolbox (AFNI; Ward, 2000). For ROI analyses we used a cluster extent of 157 contiguously activated voxels (derived via Monte Carlo simulations) to achieve a corrected significance level of $p < .05$. For the whole brain analyses, we used a minimum cluster extent of 112 contiguously activated voxels to achieve a more stringent corrected significance level of $p < .005$.

Identifying task-sensitive regions—We examined whether our hypothesized regions showed differences in activity during Fear versus Neutral distractors across all patients by conducting a one-sample *t*-test on subject-level Fear>Neutral contrast maps, which resulted in a group-level Fear>Neutral contrast map.

Transdiagnostic hypothesis—To examine our hypothesis that Fear>Neutral activity is associated with psychotic symptoms, we first screened for symptom dimensions (psychotic, negative, and disorganized) that are associated with Fear>Neutral activity by conducting voxelwise correlation analyses between Fear>Neutral activity and the three symptom dimensions across all patients. Using the correlated symptom dimensions as independent variables and Fear>Neutral activity as the dependent variable, we followed the same analysis plan as for behavioral data to determine whether activity is sensitive to: a) symptom dimensions controlling for diagnostic group (SZ and OP), or b) diagnostic group controlling

for symptom dimensions, while also controlling for demographic variables. Demographic variables included age, gender, and antipsychotic medication status – first and second generation. We also examined the relationship between symptom dimensions and Fear>Neutral activity, while controlling for symptoms \times diagnostic group interaction. Finally, given that anxiety and depression are also associated with WM disruption due to emotional distractors, we examined whether the relationship between symptom dimensions and Fear>Neutral brain activity remained after controlling for dysphoria. Similar to the regression analyses reported above, we conducted ROI-based and whole-brain voxelwise multiple regression analyses with symptoms, dysphoria, and demographic variables predicting Fear>Neutral activation.

Emotion-related disruption of WM in psychotic disorders—Since our hypotheses focused on the relationship of psychotic symptom dimension with Fear>Neutral activity, we also examined whether Fear>Neutral activity in CP individuals is significantly altered compared to NP using a 2 (groups: CP vs. NP) \times 2 (conditions: Fear vs. Neutral) voxelwise rmANOVA.

Practical utility hypothesis—To examine whether Fear>Neutral activity is also associated with measures of real-world functioning, including social functioning, employment status, remission, and GAF, a series of separate ROI-based and whole-brain correlation analyses were conducted, each controlling for diagnostic group.

Conjunction Analysis—While the correlation analyses help determine voxels in which Fear>Neutral activity correlates with symptom dimensions, diagnosis or real-world functioning, it is not clear if this activity is also sensitive to our Fear versus Neutral task-manipulation. To confirm that the voxels are sensitive to clinical measures and task-manipulation we applied a mask of the Fear<Neutral contrast to the map correlating symptoms or real-world functioning with Fear>Neutral activity such that the resulting conjunction revealed regions of conjoint significance.

The individual contrasts included in the conjunction for the ROI-based analyses were analyzed at a corrected threshold of $p < 0.05$ (such that the conjoint probability of the conjunction analysis, using Fisher's estimate, was $p < 0.0025$; Fisher, 1950; Giovanello, Kensinger, Wong, & Schacter, 2010; Knutson, Adams, Fong, & Hommer, 2001; Lazar, Luna, Sweeney, & Eddy, 2002). For whole-brain analyses, $p < 0.01$ was used as threshold for the Fear>Neutral contrast and $p < 0.005$ for the regression contrast, such that the conjoint probability of the conjunction analysis was $p < 0.0005$.

Results

Sample Characteristics

Sample demographics and clinical variables for patients and age and gender matched never-psychotic individuals are presented in Table 1. Compared to NP, patients showed worse social functioning, had lower GAF scores, and were less likely to be employed. Among the SES-related variables, the two groups did not show a significant difference in race, but they differed significantly in current occupation and education.

Behavioral Results

Transdiagnostic hypothesis—Across all patients, Neutral>Fear accuracy correlated significantly with psychotic ($r = .29, p = .05$), marginally with disorganized ($r = .28, p = .06$), but not with negative symptoms ($r = .23, p = .11$). Analyses with the reaction times recorded during the task did not show any correlation with any of the symptoms dimensions – psychotic ($r = .16, p = .30$), disorganized ($r = -.04, p = .81$), or negative ($r = -.01, p = .93$). We, therefore, used accuracy instead of RT as our dependent measure for all further analyses.

Hierarchical regression analyses (Table 2) showed that psychotic symptoms entered after diagnostic group (SZ and OP) accounted for a significant increase in variance in Neutral>Fear accuracy, but diagnostic group entered after psychotic symptoms did not. The interaction between symptoms and diagnostic group did not account for significant additional variance in Neutral>Fear accuracy. Furthermore, psychotic symptoms ($\beta = .386, p = .034$), but not negative ($\beta = -.137, p = .619$) or disorganized symptoms ($\beta = .188, p = .280$), accounted for significant variance in the model. Additionally, our regression results remained even after controlling for the two facets of SANS - anhedonia-avolition and alogia-blunted affect (Blanchard & Cohen, 2006; Kotov et al., in press). Furthermore, regression analyses with dysphoria showed that psychotic symptoms entered after dysphoria, but not dysphoria entered after psychotic symptoms, accounted for a significant increase in variance in Neutral>Fear accuracy (Supplemental Table 1). The interaction between psychotic symptoms and dysphoria did not account for significant additional variance in Neutral>Fear accuracy. Consistent with the hierarchical regression analysis, accuracy differences between SZ and OP were not significant after controlling for psychotic symptoms (see Supplemental Results).

Emotion-related disruption of WM in psychotic disorders—After establishing that psychotic symptoms accounted for significant variance in Neutral>Fear accuracy, we examined whether CP performed worse than NP in Fear versus Neutral condition. Results of the 2×2 rmANOVA, revealed main effects of group, $F(1, 48) = 23.87, p < .001, \eta_p^2 = .33$, condition, $F(1, 48) = 5.99, p < .05, \eta_p^2 = .11$, and group \times condition interaction, $F(1, 48) = 6.40, p < 0.05, \eta_p^2 = .12$, indicating that CP performance was significantly lower than NP, though more so for Fear compared to Neutral condition (Figure 2). This was confirmed with simple effects tests conducted to probe this interaction. CP showed lower accuracy than NP for both Fear, $F(1, 48) = 27.58, p < .001, \eta_p^2 = .37$, and Neutral, $F(1, 48) = 15.69, p < .001, \eta_p^2 = .25$, conditions, though the effect size was greater for the fear condition. Furthermore, Fear accuracy was lower than Neutral accuracy for CP, $t(1, 22) = -2.74, p < .05, d = -.57$, but no difference was seen for NP, $t(1, 26) = .08, p = .94, d = .02$.

Practical utility hypothesis—Neutral>Fear accuracy was associated with being employed ($r = -.34, p = .02$), higher GAF ($r = -.33, p = .03$), and remission of symptoms ($r = -.31, p = .03$), indicating that this measure is a good index of the real-world functioning in patients. However, partial correlations of Neutral>Fear accuracy with these functioning measures controlling for diagnostic group (SZ and OP) did not yield any significant effects.

fMRI Results

Task-sensitive prefrontal regions—ROI analysis showed significant Fear>Neutral activation in DLPFC and VLPFC across all patients (Figure 3 and Table 3). With whole-brain analysis, additional regions, including inferior frontal gyrus, precentral gyrus, amygdala, and superior temporal gyrus, showed significant Fear>Neutral activation (Table 4). All figures show activation only in *a priori* ROIs at $p < .05$, corrected.

Transdiagnostic hypothesis—Voxelwise ROI analysis showed that Fear>Neutral activity in DLPFC and VLPFC correlated with psychotic and negative, but not disorganized symptoms. In whole-brain analyses, psychotic symptoms were correlated with additional regions including dorsomedial PFC (DMPFC) and middle temporal gyrus (MTG). A multiple regression performed across all patients showed that greater psychotic symptoms were associated with higher Fear>Neutral activity in DLPFC and VLPFC, even after controlling for negative symptoms, diagnostic group, and demographic variables (Figure 3 and Table 3). Whole-brain analysis showed this association in regions including DMPFC and MTG (Table 4). Conjunction analysis (Figure 3) revealed that voxels in the DLPFC, VLPFC, and DMPFC that are sensitive to Fear>Neutral distractors also correlate with psychotic symptoms. With the exception of VLPFC, results of the above ROI and whole-brain regression analyses remained significant even after controlling for behavioral accuracy by adding it as a predictor in the regression model. Furthermore, negative symptoms were not significantly associated with Fear>Neutral activity, when controlling for psychotic symptoms, diagnostic group, and demographic variables in regions identified in the above regression analyses. Finally, in a separate regression, symptoms \times diagnostic group interaction did not account for unique variance in activity in the regions showing an association with psychotic symptoms.

Confirming our hypothesis regarding the relationship between symptoms and brain activity controlling for anxiety and depression, regression analysis showed that association between Fear>Neutral activity in the above mentioned prefrontal regions and psychotic symptoms remained significant even after controlling for dysphoria (Supplemental Figure 1). Finally, direct comparison between SZ and OP showed no differences in DLPFC and VLPFC activity for Fear>Neutral contrast, while whole-brain analysis indicated difference between the two groups in regions other than those implicated in regression analyses above (see Supplemental Results; Supplemental Table 2).

Emotion-related disruption of WM in psychotic disorders—After establishing the relationship between psychotic symptoms and Fear>Neutral DLPFC and VLPFC activity, we examined whether DLPFC and VLPFC activity for CP differed more from NP in Fear versus Neutral conditions. An ROI-based voxelwise rmANOVA showed a significant group \times condition interaction. As in the behavioral data, NP showed no difference in DLPFC and VLPFC activity between Fear and Neutral conditions whereas CP showed a significantly higher DLPFC and VLPFC activity for Fear versus Neutral conditions. Furthermore, CP showed significantly lower DLPFC and VLPFC activation compared to NP for Neutral condition but no such difference was seen for the Fear condition (Figure 2). The rmANOVA conducted at whole-brain level showed significant group \times condition interaction in

additional regions including DMPFC, middle frontal gyrus, precentral gyrus, thalamus, and cerebellum.

Practical Utility Hypothesis—Worse social functioning and being unemployed were associated with higher Fear>Neutral DLPFC and VLPFC activity, and lower GAF was associated with greater Fear>Neutral DLPFC activity (Figure 4 and Table 3). Conjunction analyses showed that voxels in the DLPFC and VLPFC ROIs correlating with these measures of real-world functioning were also sensitive to Fear>Neutral distractors (Figure 4). The correlation of Fear>Neutral DLPFC activity with unemployment and worse social functioning and Fear>Neutral VLPFC activity with unemployment remained even after controlling for diagnosis (Supplemental Figure 2). At the whole-brain level, worse GAF was associated with greater Fear>Neutral activity in DMPFC and MTG and worse social functioning was associated with greater activity in DMPFC and middle frontal gyrus, even after controlling for diagnosis (Table 4).

Discussion

Using a transdiagnostic approach recommended by RDoC (Cuthbert & Insel, 2010; Insel et al., 2010), we show that worse behavioral accuracy and greater DLPFC and VLPFC activity due to emotion-related disruption of WM is associated with the psychotic symptom dimension even after controlling for diagnostic group, demographics, dysphoria (anxiety and depression) symptoms, and medication. Furthermore, greater DLPFC and VLPFC activity due to emotion-related WM disruption was associated with worse social functioning and unemployment, even after accounting for diagnostic groups. Overall, our results provide strong support for the transdiagnostic nature of behavioral and neuroimaging markers of emotion-related WM disruption in tracking psychotic symptoms and their practical utility for explaining real-world functioning.

WM maintenance during emotional distraction involves interactions between VLPFC and DLPFC (Dolcos & McCarthy, 2006). The VLPFC has been identified as the “circuit breaker” of ongoing cognitive activity, directing attention to salient or threatening task-irrelevant events (Corbetta & Shulman, 2002). In the presence of salient distractors, the current attentional set is broken and attention is redeployed to these distractors. While this circuit breaking function can be an adaptive in preventing salient events from escaping notice, it can be maladaptive when attentional set must be maintained to complete a task. The VLPFC has also been implicated directly in emotion processing (Beauregard et al., 2001; Lévesque et al., 2003; Markowitsch et al., 2003; Nakamura et al., 1999; Narumoto et al., 2000; Pelletier et al., 2003; Sprengelmeyer et al., 1998). Taken together, in individuals with higher psychotic symptoms, increased VLPFC activity during fear condition could indicate a hyperactive circuit breaker that interferes with goal maintenance by redirecting attention to task-irrelevant emotional stimuli. This is consistent with studies showing greater interference from irrelevant but salient threatening or non-threatening stimuli in individuals with positive symptoms (Bentall & Kaney, 1989; Carter et al., 2011; Fear et al., 1996; Green et al., 2001; Hahn et al., 2010; Moritz & Laudan, 2007) and with imaging studies showing greater VLPFC activity while processing irrelevant (Eich et al., 2014) and negative emotional stimuli (Morris et al., 2012) in psychotic disorders.

Psychotic symptoms in the present study were also associated with increased DLPFC activity for fear versus neutral distractors. The DLPFC plays an important role in the maintenance of task-relevant information in WM (Banich et al., 2000; Chafee & Goldman-Rakic, 2000; Egnér & Hirsch, 2005; Smith & Jonides, 1999) as well as inhibition of task-irrelevant information (Chao & Knight, 1998; Funahashi, Bruce, & Goldman-Rakic, 1993; Shimamura & Shimamura, 2000). Reduced DLPFC activation has been associated with increased distractibility (Suzuki & Gottlieb, 2013) and decreased goal-maintenance (Barch & Smith, 2008). Similarly, in the presence of salient emotional distractors, reduced DLPFC activity is associated with worse task maintenance (Dolcos & McCarthy, 2006) and increased DLPFC activity is associated with better task maintenance (Compton et al., 2003). Thus, it was somewhat surprising that we found increased DLPFC during emotional distraction as a function of psychotic symptom severity. However, given that increased DLPFC activity in cognitive control tasks is associated with enhanced effort (Cazalis et al., 2003; Donohue, Wendelken, & Bunge, 2008; Wagner, Maril, Bjork, & Schacter, 2001), increased DLPFC activity during emotional distractors in individuals with psychotic disorders may indicate that they needed to recruit greater cognitive resources to remain task-focused. Indeed, despite increased DLPFC activity for fear distractors, no performance benefits were observed, possibly due to inefficiency of the WM neural system in psychotic disorders (Jansma et al., 2004; D. Manoach, 2003; Potkin et al., 2009; Schneider et al., 2007).

Inefficiency of cortical activation (evidenced by ‘hyperfrontality’ with no performance benefits) during WM task performance has been found to extend to the DMPFC in schizophrenia (Callicott et al., 2003; Tan, Callicott, & Weinberger, 2007). Using the n-back task, several studies have reported greater activation of the DMPFC in individuals with schizophrenia relative to controls (Pomarol-Clotet et al., 2008, 2010; Whitfield-Gabrieli et al., 2009). It has been argued that the hyperfrontality seen in the MPFC in schizophrenia actually represents a failure to deactivate this region of the default mode network (Whitfield-Gabrieli et al., 2009), which is typically active at rest but deactivates during task performance (Raichle et al., 2001). Moreover, positive and negative symptoms in schizophrenia have been found to be positively correlated with higher activity in the DMPFC during WM performance (Pomarol-Clotet et al., 2008). Additionally, the DMPFC has been shown to be involved in monitoring difficulty posed due to competition between choices (Matthew M Botvinick, 2007; Matthew Michael Botvinick, Braver, Barch, Carter, & Cohen, 2001; Pochon, Riis, Sanfey, Nystrom, & Cohen, 2008; Shenhav & Buckner, 2014), including monitoring of emotion-related competition (Davis et al., 2005; Egnér, Etkin, Gale, & Hirsch, 2008; Shenhav & Buckner, 2014; Wittfoth et al., 2010) as well as emotional evaluation (Heinzel et al., 2005; Mataix-Cols et al., 2008). In the present study, correlation between greater Fear>Neutral activity in the DMPFC and psychotic symptoms may, thus, indicate that individuals with greater symptoms experience greater competition between emotional distractors and task-relevant stimuli in our n-back task, and therefore, show greater recruitment of the MPFC.

Anxiety and depression are highly comorbid with psychotic disorders and may contribute to cognitive impairments observed in psychotic disorders (Achim et al., 2011; Emsley et al., 1999; Schothorst et al., 2006). Anxiety is associated with higher allocation of attentional

resources towards potential threats (Williams, Watts, MacLeod, & Mathews, 1997), worse WM maintenance in the presence of emotional distractors (Ladouceur et al., 2005, 2009), and increased VLPFC and DLPFC activity during emotional distractors. However, we found that the transdiagnostic associations between psychotic symptoms and worse WM accuracy and higher VLPFC and DLPFC activity during fear versus neutral distractors exist even after controlling for effects of anxiety and depression.

In real-world situations, in which cognitive and emotional demands are personally relevant and exceed those experienced in the lab, emotion-related WM disruption may be even more pertinent to occupational and social functioning. Indeed, WM deficits and DLPFC impairment on tasks using relatively neutral stimuli are strongly related to worse occupational and social functioning within specific psychotic disorders (Bowie et al., 2008; Dickerson et al., 2004; Hofer et al., 2005; Mattson et al., 1997; Pantelis et al., 2001). Our study demonstrates the significance of measures of emotion-related WM impairment in explaining real-world functioning transdiagnostically across psychotic disorders. It is conceivable that in psychotic disorders, worse WM in the presence of emotional distractors contributes to difficulty in social and work-related situations.

While our study focused on transdiagnostic relationships between psychotic symptoms and emotion-related WM deficits in the psychotic group, we also wanted to determine whether the currently psychotic group showed more emotion-related WM deficit than the never psychotic control group. Due to the low difficulty level of the task conditions, it is not surprising that behavioral performance for Fear and Neutral conditions does not differ in the NP group. Rather, this provides support for the idea that, even though the fear and neutral conditions are not inherently different in the present task, the CP group performs worse than NP for Fear versus Neutral conditions. While the behavioral findings may be limited by the likely ceiling effect in the NP group, the fMRI results align quite well with the idea that the two conditions are very similar. Importantly, we show that the CP group shows poorer performance than the NP, more so in Fear than Neutral condition. Consistent with worse behavioral performance for Neutral condition, DLPFC and VLPFC activity was lower for CP compared to NP group (Glahn et al., 2005). However, we did not see the same reduction in activity for CP compared to NP group for the Fear condition. Rather, equivalent activity in the CP group for Fear condition may indicate greater reactivity to emotional stimuli and the need to recruit cognitive resources to greater extent without yielding the performance benefits due to inefficiency of PFC (Jansma et al., 2004; D. Manoach, 2003; Potkin et al., 2009).

Certain limitations in the current study must be acknowledged. While an ROI approach allowed focus on regions that are theoretically driven and well-established for emotion-WM interactions, it was at the cost of examining interactions at the whole-brain level. Exploratory whole-brain analyses, however, showed that patterns of fear versus neutral neural activity in our *a priori* ROIs were similar to patterns of whole-brain activity. While a block design allowed us to obtain robust neuroimaging findings, an event-related design may have been more helpful in identifying specific components of WM (e.g., encoding, maintenance, retrieval) that are impaired by emotional distractors. The sample size was limited, and larger samples are needed to confirm our findings. Most patients in our study

were receiving medication and our sample size was insufficient to confirm observed effects in medication-free participants. Instead, we statistically controlled for medication effects and hypothesized effects remained. Finally, we employed only fear stimuli and future work should be expanded to examine the full range of emotional expressions to determine if the distractor effect is emotion or threat specific.

The present study attempted to bridge the gap between basic neuroscience research on emotion-cognition interaction and clinical research in psychosis. Biological correlates of WM have been recommended as candidates for biomarker development by Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS; Barch & Smith, 2008) initiative, and our findings suggest that emotion-related WM measures may have some utility in this regard. We found an association between emotion related-WM impairment and psychotic (but not negative or disorganized) symptoms that cut across traditional diagnostic boundaries of psychotic disorders, consistent with the transdiagnostic and dimensional framework suggested by the RDoC. Hence, these cognitive and neurobiological dimensions offer potential ways of understanding the structure of mental disorders that are not based on traditional DSM diagnostic criteria. Furthermore, these behavioral and neural correlates were associated with employment and social functioning across different diagnostic categories, indicating their clinical utility in predicting real-world functioning that transcends diagnostic categories. Overall, identification of these transdiagnostic measures is an important first step towards development of affective/cognitive and neural markers for better diagnosis and treatment development. Unified treatment protocols that capitalize on commonalities and target risk and maintenance factors that cut across diagnostic boundaries have been shown to hold important practical and clinical advantages over interventions designed to treat specific disorders (McEvoy, Nathan, & Norton, 2009). These include greater efficiency with comorbid disorders, lower cost and training requirements, adherence to evidence-based treatments, and ease of disseminating effective treatments (Addis, Wade, & Hatgis, 1999; Barlow, Allen, & Choate, 2004; McEvoy et al., 2009; McHugh, Murray, & Barlow, 2009). Additionally, these transdiagnostic behavioral and neural markers, if validated as endophenotypes, could be useful for further investigation by genetic methods. Although further research is required, the current findings show promise of a window into the pathophysiology of psychosis that can be translated into more effective transdiagnostic intervention approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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General Scientific Summary

Our findings provide support for clinical and practical utility of dimensional measures of emotion-related working memory impairment by showing that these behavioral and neural measures are associated with more severe psychotic (but not negative or disorganized) symptoms and worse real-world functioning, irrespective of psychotic disorders diagnoses.

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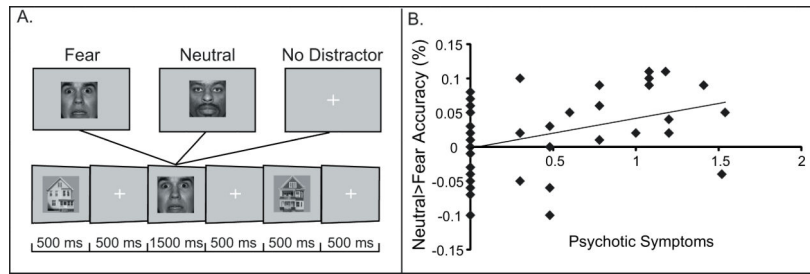


Figure 1. (A) *n*-back task showing different trial components and the timeline, and (B) correlation between Neutral>Fear accuracy and psychotic symptoms (log transformed) across all patients.

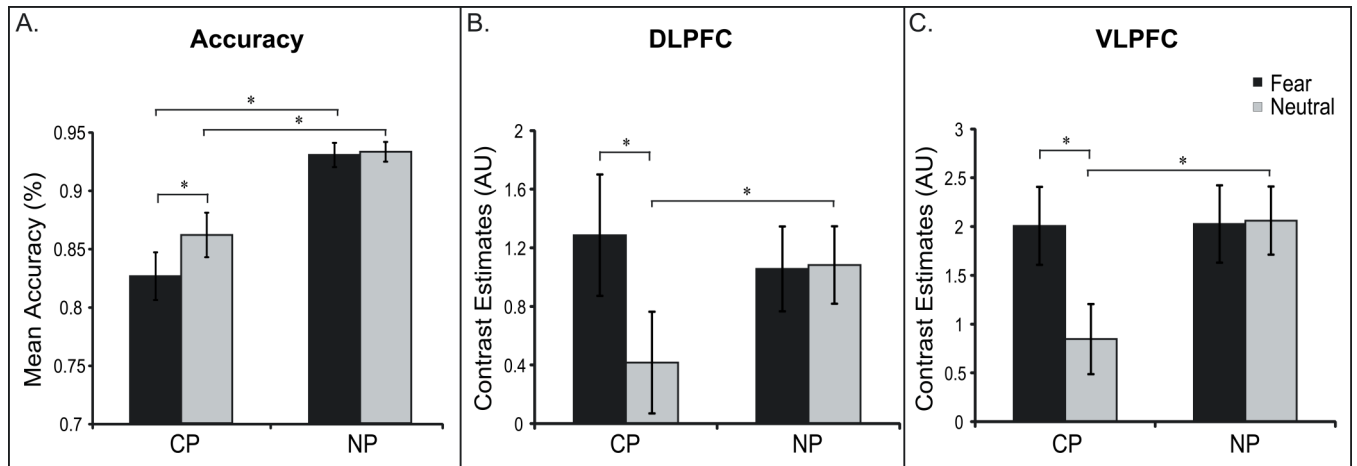


Figure 2.

(A) Mean WM accuracy, and contrast estimates for fear and neutral distractor conditions for (B) Dorsolateral Prefrontal Cortex (DLPFC; $x=42, y=40, z=30$) and (C) Ventrolateral Prefrontal Cortex (VLPFC; $x=46, y=16, z=26$) for currently psychotic (CP; $N=23$) compared to never psychotic (NP; $N=27$) individuals.

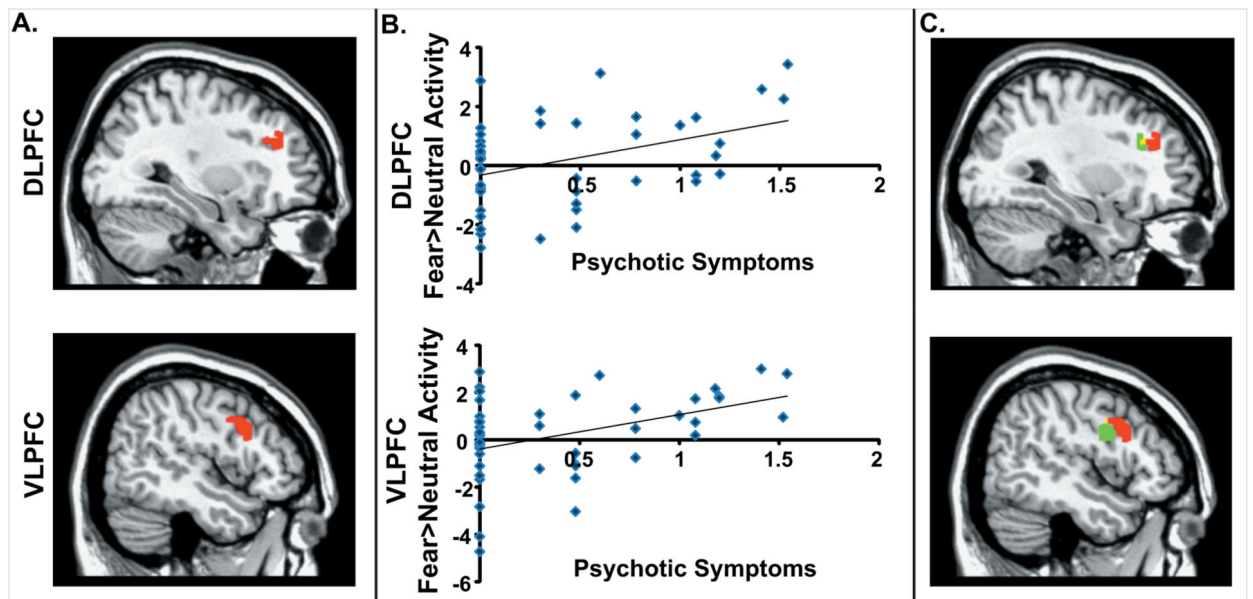


Figure 3.

(A) Fear>Neutral activity in Dorsolateral Prefrontal Cortex (DLPFC) and Ventrolateral Prefrontal Cortex (VLPFC) across all patients (red), (B) Correlation between Fear>Neutral activity in DLPFC and VLPFC and psychotic symptoms (log transformed), and (C) Overlaps between voxels sensitive to Fear>Neutral activity in DLPFC and VLPFC (red) and psychotic symptoms controlling for negative symptoms, diagnosis, and demographic variables (green).

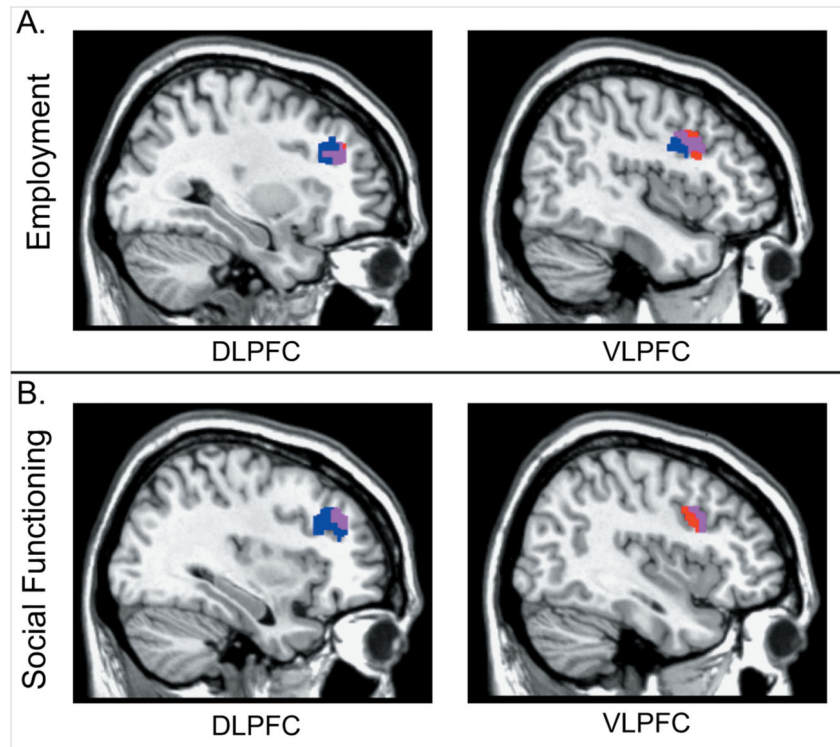


Figure 4. Correlation of Fear>Neutral activity in Dorsolateral Prefrontal Cortex (DLPFC) and Ventrolateral Prefrontal Cortex (VLPFC) (red) with (A) employment (blue) and (B) social functioning (blue).

Table 1

Sample characteristics

	Psychotic Disorder group (n = 46)		Never-Psychotic group (n = 27)		Group Comparison	Cohen's <i>d</i>
	<i>n</i>	%	<i>n</i>	%		
<i>Gender</i>					$\chi^2(2) = .13$.08
Male	27	58.70	17	63.00		
Female	19	41.30	10	37.00		
<i>Medication</i>						
Antipsychotic – 1st generation	7	15.94				
Antipsychotic – 2nd generation	21	45.65				
<i>Remission status</i>						
Remitted	20	43.50				
Unremitted	26	56.50				
<i>Employment status</i>					$\chi^2(2) = 7.19^b$.66
Employed	25	54.30	23	85.20		
Unemployed	21	45.70	4	14.80		
<i>Current Occupation</i>					$\chi^2(2) = 18.02^c$	1.15
Blue collar or below	38	82.61	9	33.33		
White collar	8	17.39	18	66.67		
<i>Education</i>					$\chi^2(2) = 6.43^a$.62
High School graduate and below	26	56.52	7	25.93		
Some college education and above	20	43.48	20	74.07		
<i>Parental Education</i> *						
Completed high school	34	73.91				
Didn't complete high school	11	23.91				
<i>Ethnicity</i>					$\chi^2(2) = 0.14$.09
Caucasian	39	84.78	22	81.48		
Other	7	15.22	5	18.52		
	Mean	SD	Mean	SD		
Age	44.76	7.43	47.11	6.98	$t(1,71) = 1.33$.33
<i>Symptoms</i>						
Negative	18.28	14.55				
Psychotic	4.57	8.23				
Disorganized	5.04	6.01				
IDAS Dysphoria	17.24	6.70	15.17	6.66	$t(1,70) = -1.27$.31
Social Functioning	10.61	4.42	13.19	2.94	$t(1,71) = 2.70^a$.66
GAF functioning past month	50.85	17.59	71.96	11.87	$t(1,80) = 5.53^a$	1.34

^a $p < .05$

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^b
 $p < .01$

^c
 $p < .001$

* Parental education details were not available for never-psychotic group and one participant from the psychotic disorder group

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Table 2

Summary of hierarchical regression analysis for symptom dimensions and diagnostic group predicting Neutral>Fear accuracy

Predictors	R ²	R ²	F of	<i>p</i>
Regression 1				
<i>Step 1</i>	.229	.229	1.01	.454
Demographic variables				
Negative symptoms				
Disorganized symptoms				
<i>Step 2</i>	.020	.250	.899	.350
Diagnosis				
<i>Step 3</i>	.100	.349	4.90	.034
Psychotic symptoms				
<i>Step 4</i>	.000	.349	.008	.929
Psychotic symptoms × Diagnosis				
Regression 2				
<i>Step 1</i>	.229	.229	1.01	.454
Demographic variables				
Negative symptoms				
Disorganized symptoms				
<i>Step 2</i>	.113	.342	5.67	.023
Psychotic symptoms				
<i>Step 3</i>	.007	.349	.351	.558
Diagnosis				
<i>Step 4</i>	.000	.349	.008	.929
Psychotic symptoms × Diagnosis				

Note: Demographic variables include age, gender, antipsychotic medication status – first and second generation, race, current occupation, education, parental education

Table 3

Coordinates of peak activation in regions of interest sensitive to task manipulation (Fear>Neutral distractor condition), symptom dimensions, and measures of real-world functioning in patients, identified using ROI-based analysis.

Region	Brodmann Area (BA)	Peak MNI coordinates		
		<i>x</i>	<i>y</i>	<i>z</i>
Fear > Neutral distractors				
DLPFC (Right)	9	34	38	32
VL PFC (Right)	44	40	14	28
Psychotic symptoms (controlling for diagnosis, negative symptoms, age, gender)				
DLPFC (Right)	9	34	24	26
VL PFC (Right)	6 [*]	52	6	28
Real-world Functioning Measures				
<i>Employment</i>				
DLPFC (Right)	9	34	26	26
VL PFC (Right)	44	52	8	28
<i>Social Functioning</i>				
DLPFC (Right)	9	36	22	28
DLPFC (Left)	9	-38	34	18
VL PFC (Right)	44	40	16	32
VL PFC (Left)	44	-42	0	22
<i>Global Assessment of Functioning</i>				
DLPFC (Right)	9	34	30	38
DLPFC (Left)	9	-40	40	24

MNI, Montréal Neurological Institute; DLPFC, Dorsolateral Prefrontal Cortex; VL PFC, Ventrolateral Prefrontal Cortex

*The majority of the cluster falls in BA 44, however, the peak lies in BA 6

Table 4

Coordinates of peak activation in regions sensitive to task manipulation (Fear>Neutral distractor condition), symptom dimensions, and measures of real-world functioning in patients, identified using whole-brain analysis.

Region		Peak MNI coordinates		
		x	y	z
Fear>Neutral				
Inferior Frontal Gyrus	L	-48	36	-4
Superior Temporal Gyrus	L	-64	-48	14
Amygdala	L	-32	-4	-12
Precentral Gyrus	R	50	-10	44
Positive symptoms (controlling for diagnosis, and demographic variables)				
Medial Prefrontal Cortex	L	-10	38	30
Middle Frontal Gyrus	L	-42	22	38
Middle Temporal Gyrus	L	-64	-44	-8
Middle Occipital Gyrus	L	-36	-64	26
Insula	L	-26	28	10
Middle Cingulate	L	-12	18	38
Cerebellum	R	32	-68	-42
Caudate	L	-8	2	2
Real-world Functioning (controlling for diagnosis)				
<i>Social Functioning</i>				
Medial Prefrontal Cortex	R	10	48	6
Middle Frontal Gyrus	L	-36	52	12
<i>Global Assessment of Functioning</i>				
Medial Prefrontal Cortex	R	10	48	4
Middle Temporal Gyrus	L	-60	-18	-22

MNI, Montréal Neurological Institute