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PERCEPTION

Neural markers of emotional face perception across psychotic disorders and general population

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Abstract

There is considerable variation in negative and positive symptoms of psychosis, global functioning, and emotional face perception (EFP), not only in schizophrenia but also in other psychotic disorders and healthy individuals. However, EFP impairment and its association with worse symptoms and global functioning have been examined largely in the domain of schizophrenia. The present study adopted a dimensional approach to examine the association of behavioral and neural measures of EFP with symptoms of psychosis and global functioning across individuals with schizophrenia spectrum (SZ; N=28) and other psychotic (OP; N=29) disorders, and never-psychotic participants (NP; N=21). Behavioral and functional magnetic resonance imaging data were recorded as participants matched emotional expressions of faces and geometrical shapes. Lower accuracy and increased activity in early visual regions, hippocampus, and amygdala during emotion versus shape matching was associated with higher negative, but not positive symptoms and lower global functioning across all participants. This association remained even after controlling group-related (SZ, OP, and NP) variance, dysphoria, and antipsychotic medication status, except in the amygdala. Furthermore, negative symptoms mediated the relationship between behavioral and brain EFP measures and global functioning. This study provides some of the first evidence supporting the specific relationship of EFP measures with negative symptoms and global functioning across psychotic and never-psychotic samples, and transdiagnostically across different psychotic disorders. Present findings help bridge the gap between basic EFP-related neuroscience research and clinical research in psychosis, and highlight EFP as a potential symptom-specific marker that tracks global functioning.

General Scientific Summary: Present study shows that behavioral and neural measures of emotional face perception (EFP) are associated with negative symptoms and global functioning across non-clinical and clinical samples, and transdiagnostically across different psychotic disorders, highlighting the importance of EFP measures as symptom-specific markers that track global functioning dimensionally.

Key words: fMRI, schizophrenia, transdiagnostic, negative symptoms, global functioning

Neural markers of emotional face perception across psychotic disorders and general population

Schizophrenia is characterized by prominent emotional face perception (EFP) deficits (Edwards, Jackson, & Pattison, 2002; Kohler, Walker, Martin, Healey, & Moberg, 2010; Mandal, Pandey, & Prasad, 1998). The National Institute of Mental Health (NIMH) Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative has identified EFP as a priority for developing biomarkers that can inform better diagnosis and treatment development in schizophrenia (Carter et al., 2009). Most existing research has emphasized how EFP in schizophrenia differs from other disorders and healthy individuals (Addington & Addington, 1998; Gaebel & Wölwer, 1992; Kohler et al., 2010). However, there is increasing evidence that EFP impairment and its neural markers are not limited to individuals with schizophrenia but are also found in mood disorders with psychosis, schizoaffective disorder, and individuals with schizotypal traits (Gur & Gur, 2016; Phillips & Seidman, 2008; Ruocco et al., 2014). EFP deficits are found in unaffected relatives of people with schizophrenia (Bediou et al., 2007; Kee, Horan, Mintz, & Green, 2004) and others vulnerable to psychosis (Phillips & Seidman, 2008).

Variation in EFP performance is also seen in healthy individuals and is related to individual differences in psychosis-proneness, social-cognitive abilities, personality traits, biological sex, as well as genetic and environmental factors in the general population (Corden, Critchley, Skuse, & Dolan, 2006; Germine & Hooker, 2011; Hamann & Canli, 2004; Wilhelm et al., 2010; Yovel, Wilmer, & Duchaine, 2014). Additionally, these individual differences are associated with negative symptom dimensions across psychotic disorders and in general population (Harvey, Koren, Reichenberg, & Bowie, 2006; Lencz, Smith, Auther, Correll, &

Cornblatt, 2004; Lindamer, Lohr, Harris, McAdams, & Jeste, 1999; Lysaker, Bell, Kaplan, Greig, & Bryson, 1999; Owen, Craddock, & Jablensky, 2007; Ross, Lutz, & Bailey, 2002; Sergi et al., 2007; Simons, Jacobs, Jolles, van Os, & Krabbendam, 2007). Thus, rather than being specific to particular diagnoses, neural and behavioral EFP deficits may relate to negative symptoms dimensions that are transdiagnostic and present even in the general population. In the present study, we used functional magnetic resonance imaging (fMRI) and an EFP task to examine clinical and functional dimensions associated with neural and behavioral measures of EFP across individuals with schizophrenia spectrum and other psychotic disorders, as well as never-psychotic participants.

Face perception is supported by a distributed neural network in which information is first processed in early visual cortex, followed by a core network that includes occipital face area (OFA) and fusiform face area (FFA) for processing invariant features of faces such as the individual's identity, and superior temporal sulcus (STS) for processing dynamic aspects of faces such as gaze direction and expression (Haxby, Hoffman, & Gobbini, 2000; Ishai, Schmidt, & Boesiger, 2005; Pitcher, Walsh, & Duchaine, 2011). Additionally, an extended network includes amygdala and insula for perception of emotion in faces (Haxby et al., 2000) and hippocampus for recognition of faces (Fried, MacDonald, & Wilson, 1997; Leveroni et al., 2000). The amygdala has been found to be both hypoactive (Li, Chan, McAlonan, & Gong, 2009) and hyperactive (Kosaka et al., 2002; Rauch et al., 2010) for emotional faces in schizophrenia, and this discrepancy is attributed primarily to whether the emotional faces are compared to neutral faces or non-face stimuli, respectively (Hall et al., 2008; Holt et al., 2006).

Furthermore, deficits in face perception in schizophrenia have been attributed to difficulty in basic visual functions of perceptual organization and integration of visual

information (Silverstein & Keane, 2011). While non-emotional face processing is associated with hypoactivity in early visual cortex in patients compared to controls (Silverstein & Keane, 2011), EFP in schizophrenia is associated with hyperactivity in early visual areas, such as calcarine sulcus and cuneus (Delvecchio, Sugranyes, & Frangou, 2012; Taylor et al., 2012). It has been hypothesized that abnormalities in early visual processing, particularly in the magnocellular pathway, may contribute to higher-order EFP deficits in schizophrenia (Butler et al., 2009; Johnston, Stojanov, Devir, & Schall, 2005; Turetsky et al., 2007), particularly because the magnocellular pathway is important for processing low spatial frequency information (Merigan & Maunsell, 1993), which is utilized in EFP (Vuilleumier, Armony, Driver, & Dolan, 2003). Studies of face and object perceptual organization in schizophrenia also show increased activity in FFA and temporal regions, which has been hypothesized to compensate for face processing deficits in early visual areas. During EFP, however, activity in the core face perception network, including OFA, FFA, and STS, has been found to be lower in schizophrenia than in controls (Habel et al., 2010; Johnston et al., 2005; Seiferth et al., 2009), and is negatively correlated with negative symptoms (Mendrek, Jiménez, Mancini-Marie, Fahim, & Stip, 2011; Michalopoulou et al., 2008).

The specificity of EFP deficits in schizophrenia in comparison with other types of facial discrimination (e.g. identity, age, gender) is an area of ongoing investigation, and it is yet to be determined whether these deficits are confined to emotion perception or whether they are representative of a general impairment in face processing. Studies that have used psychometrically matched emotion and non-emotion face perception tasks have shown both, generalized face processing deficits (Edwards et al., 2002) as well as differential deficit in EFP (Schneider et al., 2006). Overall, given mixed behavioral and neural evidence implicating several

aspects of face processing in schizophrenia, it has been recommended to examine the entire range of the visual processing hierarchy from early visual cortex to the core (OFA, FFA, and STS) and extended (amygdala, insula, and hippocampus) neural network supporting face processing (Chen & Ekstrom, 2015; Li et al., 2010, Chen & Ekstrom, 2015; Li et al., 2010). Given that these neural abnormalities may be present not only in schizophrenia but also in other psychotic disorders and the general population, it is critical to examine which transdiagnostic symptom dimensions may explain these neural EFP deficits.

Similar to the dimensional nature of EFP function, negative and positive symptoms are not specific to schizophrenia, or even to psychotic disorders. Studies show that negative and positive symptoms occur in several psychotic disorders including schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, and schizotypal personality (Johns & Van Os, 2001; Linscott & van Os, 2013; Tamminga et al., 2013; Toomey, Faraone, Simpson, & Tsuang, 1998). Even after accounting for individuals with clinically diagnosed psychotic disorders, sub-threshold forms of positive symptoms are present in almost 7% (Linscott & van Os, 2013) and negative symptoms are present in 20.1% (Werbeloff et al., 2015) of the general population. Deficits in global functioning, including work and social functioning, too are seen in different psychotic disorders as well as in normal controls (Corral, Rodríguez, Amenedo, Sánchez, & Díaz, 2006; Healey, Brodzinsky, Bernstein, Rabinovitz, & Halperin, 2010; Möller, Bottlender, Wegner, Wittmann, & Straub, 2000; Sommer et al., 2010).

Overall, there is substantial evidence establishing the dimensional nature of EFP function, negative and positive symptoms, and global functioning. Studies that have investigated the association of neural and behavioral measures of EFP with symptoms of psychosis have generally reported an association with negative symptoms (Addington & Addington, 1998;

Baudouin, Martin, Tiberghien, Verlut, & Franck, 2002; Michalopoulou et al., 2008; Mueser et al., 1996; Gabriele Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004; van 't Wout et al., 2007). The stronger relationship between negative symptoms and EFP deficits may be attributed to an exaggerated emotional reactivity towards unpleasant stimuli (Cohen & Minor, 2010; Horan, Green, Kring, & Neuchterlein, 2006; Schlenker, Cohen, & Hopmann, 1995; Strauss & Gold, 2012) and increased amygdala activity indicative of increased emotional reactivity (Gur et al., 2007; Rauch et al., 2010) as well as aberrant basic visual cortical processing (Doniger, Silipo, Rabinowicz, Snodgrass, & Javitt, 2001; Kéri, Kiss, Kelemen, Benedek, & Janka, 2005; Spencer et al., 2004) that impacts facial expression processing in case of negative symptoms. Consistent with the idea that negative symptoms are associated with increased emotional reactivity towards unpleasant stimuli, studies show that EFP deficits tend to be specific to negatively-valenced, as opposed to positively-valence facial expressions (Edwards et al., 2002; Mandal et al., 1998; Morrison, Bellack, & Mueser, 1988; Tremeau, 2006). Finally, EFP is a critical component of nonverbal communication, and related to social judgement (Said, Haxby, & Todorov, 2011), social competence (Hooker & Park, 2002; Ihnen, Penn, Corrigan, & Martin, 1998; Mueser et al., 1996; Penn et al., 2000; Vauth, Rüscher, Wirtz, & Corrigan, 2004) as well as work functioning and independent living (Kee, Green, Mintz, & Brekke, 2003) in schizophrenia and non-psychotic individuals, leading us to hypothesize that EFP would be associated with global functioning across psychotic disorders.

Worse EFP in schizophrenia is linked with impairment in occupational, social, and global functioning (Hofer et al., 2009; Hooker & Park, 2002; Irani, Seligman, Kamath, Kohler, & Gur, 2012; Kee, Green, Mintz, & Brekke, 2003). In fact, negative symptoms have been found to mediate the relationship between social-cognitive measures (including EFP) and global

functioning in schizophrenia (Lin et al., 2013; Ventura, Helleman, Thames, Koellner, & Nuechterlein, 2009). However, to our knowledge, no single study so far has examined whether behavioral and neural measures of EFP relate differentially to positive and negative symptom dimensions of psychosis or to global functioning in non-clinical and clinical samples, and transdiagnostically across different psychotic disorders.

In the present study, we evaluated EFP (dys)function across individuals with schizophrenia spectrum and other psychotic disorders as well as control participants. We measured behavioral performance and fMRI activity while participants matched geometrical shapes and emotional expressions of faces. The contrast between emotional faces and geometrical shapes has frequently been used to study emotional face perception and has been shown to reliably activate core and extended neural network supporting EFP (Fakra, Salgado-Pineda, Delaveau, Hariri, & Blin, 2008; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; Kleinhans et al., 2010), allowing us to examine in which of these areas emotional face-related activity was most sensitive to worsening negative symptoms or global functioning. Based on the evidence detailed above, our first hypothesis was that there would be increased activity in regions of the core and extended face processing neural network and the early visual cortex for emotion vs. shape matching across all participants. Our second hypothesis was that (1) lower accuracy, (2) increased activity in limbic and early visual areas, and (3) reduced activity in core face network during emotion vs. shape matching will be associated with higher negative symptoms and lower global functioning across all participants, even after controlling for positive symptoms, mood-related symptoms, and group-related variance. Our third and final hypothesis was that the relationship between behavioral and neural measures of EFP and global functioning will be mediated via negative symptoms across all participants. An examination of our

hypotheses will clarify the relative specificity and utility of the RDoC domain of EFP, providing support for its behavioral and neural measures as symptom-specific markers that can aid identification of targets for novel and more effective treatment.

Methods

Participants

The present sample is a subset of the Suffolk County Mental Health Project (Bromet et al., 1992, 2011; see Supplementary Methods for details). Data were collected from 55 individuals with a history of psychosis – 26 with schizophrenia spectrum disorders (SZ; schizophrenia and schizoaffective disorder) and 29 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. These groupings (SZ and OP) of the diagnostic and statistical manual of mental disorders (DSM) diagnostic categories are based on previous work with this cohort (Roman Kotov et al., 2013; Reichenberg et al., 2009) and other work (Daban et al., 2006; Krabbendam, Arts, van Os, & Aleman, 2005) showing that schizophrenia spectrum disorders are characterized by worse symptom severity, course, and cognitive impairment than other psychotic disorders.

Additionally, an age and gender matched comparison group of 29 never-psychotic participants (NP), without a current or past diagnosis of any psychotic disorder, was recruited from the same zip codes as the patients using random-digit dialing. After exclusion of participants due to poor task-performance and fMRI artifacts the final sample consisted of 78 (21 SZ, 28 OP, and 29 NP) participants. The study was approved by the Institutional Review Board at Stony Brook University. Demographic information is presented in **Table 1**. See supplementary methods for further details on the selected sample and exclusion criteria.

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 an emotion-related working memory task, followed by the current task (i.e. 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 15 minutes, and the participants were given breaks between each run, or as needed.

Clinical and Functional Measures

Clinical measures obtained for each participant concurrent with fMRI scanning included: (1) Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1997), (2) Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), (3) Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), (4) Dysphoria scale of the Inventory of Depression and Anxiety Symptoms, expanded version (IDAS-II; D. Watson et al., 2012) which taps common elements of anxiety and depression (Watson et al., 2008) to assess mood symptoms, and (5) Social and Occupational Functioning Assessment scale (SOFAS), to assess participants' overall level of functioning in the past year across social and occupational domains (Goldman, Skodol, & Lave, 1992). Antipsychotic medication status for each participant

was determined by asking participants to bring their pill bottles or a list of all medications and dosages. See supplementary methods for details regarding measures.

Emotional Face Perception Task

The emotional face perception task (Hariri et al., 2002), a well-utilized task in schizophrenia (Fakra, Salgado-Pineda, Delaveau, Hariri, & Blin, 2008; Johnston et al., 2005; Kosaka et al., 2002), involved three conditions of interest, presented in a blocked design (**Figure 1A**). In the emotion-matching condition, participants viewed a set of three emotional faces (angry or fearful; all different actors) and were asked to select one of the two probe faces whose emotional expression matched that of the target face. The shape-matching condition required participants to match one of the two probe geometric shapes to the target shape. In the neutral face identity-matching condition, participants matched the identity of one of the two probe faces to the target face. Given the elevated amygdala response to neutral faces in schizophrenia (Hall et al., 2008; Holt et al., 2006; Kohler et al., 2010; Williams et al., 2004), the use of neutral faces as the baseline condition may underestimate the magnitude of amygdala activation for emotional faces. We, therefore, used geometrical shape matching as our baseline condition instead of neutral face matching. See Supplemental Results for more details regarding our baseline condition selection.

All conditions of the emotional face perception task consisted of sets of 3 stimuli (faces or shapes) presented in a triangular formation - one at the top and two at the bottom. The participants were required to indicate, with a button press, which of the two at the bottom (left or right) matched the one at the top. The face stimuli consisted of 18 forward-facing images displaying fear or anger emotions, and 18 forward-facing neutral faces drawn from the Radboud Faces Database (Langner et al., 2010). The images were cropped and converted to gray-scale,

adjusted for brightness, luminance, and contrast. Three blocks of each condition were counterbalanced across participants. Each block began with an instruction for 2 seconds, and consisted of 6 trials presented sequentially for 5 seconds, culminating in a total block length of 32 seconds. Behavioral measures of accuracy and response time were collected during scanning. The experiment was coded in Python 2.7 (<http://www.python.org>) and presented using PsychoPy software (Peirce, 2007, 2009).

Behavioral Data Analyses

EFP accuracy. We first examined accuracy for the EFP task across all participants by conducting paired-sample t tests comparing emotion and shape matching accuracy.

EFP and symptoms of psychosis. To examine whether EFP accuracy (calculated as shape minus emotion accuracy) is associated with symptom dimensions (positive and negative), we conducted separate partial correlations of symptoms with EFP accuracy across all participants, controlling for group-related (SZ, OP, and NP) variance. To control for group-related variance in all analyses, we used two dummy variables to represent the three groups. The first variable was coded 1 for SZ and 0 for all others, and the second variable was coded as 1 for OP and 0 for all others. We also computed the correlations separately for patients and never-psychotic participants. Next, to determine whether deficits in EFP are specific to negative symptoms, we conducted a hierarchical regression with negative symptoms, dummy variables for group, positive symptoms, dysphoria, and antipsychotic medication usage entered in the first step, and group x negative symptom interactions in the second step, predicting EFP accuracy. The group x symptom interaction terms were computed as products of the dummy variables and negative symptoms. To examine specificity of our findings to EFP, we also conducted the

correlation and regression analyses outlined above with shape minus neutral face accuracy and emotional minus neutral face accuracy.

EFP and global functioning. With our next set of analyses, we assessed the practical significance of EFP accuracy measure by conducting a partial correlation between global functioning and EFP accuracy across all participants, while controlling for group-related differences. We also computed the correlations separately for patients and never-psychotic participants. Next, to determine specificity of the association between global functioning and EFP performance, we conducted a hierarchical regression with global functioning, dummy variables for group, **positive symptoms**, dysphoria, and antipsychotic medication usage in the first step and global functioning x group interaction in the second step, predicting EFP accuracy.

Mediation analysis. Finally, to test our hypothesis that negative symptoms mediate the relationship between EFP function and global functioning, we conducted the standard three-variable path model (Baron & Kenny, 1986) (**Supplementary Figure 1**) and tested the statistical significance of mediation with bootstrapping (Preacher & Hayes, 2004). For the bootstrapping test, unstandardized indirect effects were computed for each of 5,000 bootstrapped samples, and the 95% confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles.

fMRI Data Analyses

Image acquisition and data preprocessing. Structural and functional data were acquired on a 3 Tesla Siemens TIM Trio whole body scanner and Statistical Parametric Mapping (SPM12; <http://www.fil.ion.ucl.ac.uk/spm/>) was used to preprocess and analyze the fMRI data. Functional images for each participant were corrected for slice timing, spatially realigned, spatially normalized, smoothed, and corrected for motion artifacts. A general linear model was

estimated for each participant with functional images across sessions for all conditions. The β s corresponding to each condition were contrasted, yielding contrasts maps comparing the emotion matching condition to shape matching and neutral face matching conditions. See supplementary methods for details of data acquisition and preprocessing.

To correct for multiple voxelwise statistical testing in the t tests and regression analyses, we used the 3DFWHMx and 3DClustSim toolbox (updated May 2016, AFNI; Ward, 2000) which takes into account the voxelwise and cluster-volume thresholds to establish a p-value that protects against false-positive detection of activation clusters (Forman et al., 1995). Since the focus of the present study was specifically on the core and extended network of face processing regions described above, we examined our results within these hypothesized ROIs. For this purpose, we created an ROI mask comprising of regions involved in the face processing network – FFA, OFA, posterior STS (pSTS), early visual cortex, insula, and hippocampus. Since the FFA, OFA, and pSTS are typically defined functionally, we used the Face vs. House contrast of a localizer task to identify these regions (see Supplementary Methods for details). The primary visual cortex, insula, and hippocampus were defined anatomically using the Wake Forest University (WFU) PickAtlas Toolbox for Statistical Parametric Mapping (SPM12; Maldjian, Laurienti, Kraft, & Burdette, 2003). For the amygdala, ROI analyses were conducted separately to determine activation, given its importance for our hypotheses, and because activation in this small region may not survive a contiguity threshold determined for the ROI mask comprising regions of the entire face processing network. See supplementary methods for details on correction for multiple comparisons and ROI analyses.

Neural correlates of EFP. We first determined task-sensitive voxels by conducting group-level voxelwise t tests across all for EFP activity (Emotion vs. Shape related activity).

EFP correlation with symptoms of psychosis. Next, we determined whether EFP activity was associated with the two symptom dimensions by conducting separate regression analyses with negative and positive symptoms predicting neural activity across all participants, controlling for group-related variance. We also computed the correlations separately for patients and never-psychotic participants. To determine whether the voxels correlating with negative symptoms were also the ones sensitive to our EFP task manipulation, we conducted a conjunction analysis. The strategy of identifying task-sensitive voxels, symptom-sensitive voxels, and the overlap between the two via conjunction analyses was adopted to avoid any issues of non-independence. Problems associated with non-independence can arise even when orthogonal contrasts are used to define the ROI from which data are extracted (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009) for further analyses of another contrast. We, therefore, adopted the most conservative and unbiased approach to showing that there exists a joint relationship between our variables of interest. Finally, in order to examine our hypothesis that EFP-related neural activity is associated specifically with negative symptoms, we conducted a regression analysis using negative symptoms, dummy variables for group, positive symptoms, dysphoria, and antipsychotic medication usage as predictors, and EFP activity as the dependent variable. An additional regression was conducted to examine whether symptoms x group interaction accounted for unique variance in activity in our ROIs over and above main effects of negative symptoms. To examine specificity of our findings to EFP, we also conducted the correlation and regression analyses outlined above with neutral face vs. shape activity and emotional vs. neutral face activity.

EFP correlation with global functioning. Voxelwise regression analyses were conducted to examine whether neural activity for EFP is associated with global functioning,

controlling for group-related variance. The correlations were also conducted separately for the patients and never-psychotic participants. To determine whether voxels correlating with global functioning are also sensitive to our EFP task manipulation, we conducted a conjunction analysis. To further confirm the specificity of this association between global functioning and EFP activity, we conducted a voxelwise regression analysis with global functioning, dummy variables for group, positive symptoms, dysphoria, and antipsychotic medication usage and as predictors and EFP activity as the dependent variable.

Mediation Analysis. Finally, as with our behavioral data, we examined the hypothesis that negative symptoms mediate the relationship between EFP activity in our ROIs and global functioning.

Results

Sample Characteristics

Sample demographics and clinical ratings for SZ, OP, and NP groups are presented in **Table 1**. Overall, 93.88% patients and 46.94% never-psychotic participants showed negative symptoms, and 71.43% patients and 24.14% never-psychotic participants showed positive symptoms. The three groups differed in the severity of positive and negative symptoms as well as global functioning. However, there were no group differences in demographic variables like age, gender, and ethnicity.

Behavioral Results

EFP accuracy. The internal consistency of the EFP task was high for both conditions, with a Cronbach's alpha of .90 for the Emotion condition, and .89 for the Shape condition. The true score variance for the Emotion and Shape conditions were .36 and .32, respectively, indicating similar discriminatory power (Chapman & Chapman, 1978). Across all participants,

accuracy for emotion matching ($M = .92$; $SD = .12$) was lower than accuracy for shape matching ($M = .99$; $SD = .05$), $t(77) = -5.14$, $p < .001$, $d = .77$, 95% CI [.75, .78] (**Figure 1B**).

EFP correlation with symptoms of psychosis. Results of partial correlation analyses, controlling for group-related variance, showed a positive correlation between EFP accuracy (shape minus emotion accuracy) and negative ($r = .35$, $p < .01$), but not positive ($r = .10$, $p = .40$), symptoms across all participants (**Figure 1C**). This correlation was driven by the relationship of negative symptoms with emotion accuracy ($r = -.28$, $p < .05$) as opposed to shape accuracy ($r = .12$, $p = .32$). Correlation between EFP accuracy and negative symptoms remained significant when the analysis was conducted separately for the patients ($r = .46$, $p < .01$) and for never-psychotic participants ($r = .58$, $p < .01$), and using permutation tests in never-psychotic participants (see Supplementary Results). Finally, regression analysis examining whether EFP deficits are specific to negative symptoms showed that, in Step 1, negative symptoms ($\beta = .44$, $p < .01$), but not dummy variables for group ($\beta = .08$, $p = .69$ and $\beta = -.04$, $p = .73$), positive symptoms ($\beta = .04$, $p = .78$), dysphoria ($\beta = -.11$, $p = .30$), or antipsychotic medication status ($\beta = .02$, $p = .89$) accounted for significant variance in EFP performance. Additionally, in Step 2, the group x symptom interactions did not account for a significant increase in variance ($\Delta R^2 = .02$, $p = .33$). Finally, the relationship between symptoms and functioning was not seen for neutral face accuracy alone, but remained the same for emotional vs. neutral face accuracy (see Supplementary results).

In order to assess for effects of multicollinearity between the independent variables, the variance inflation factor (VIF) was calculated. The VIF values were found to be relatively low (1.04 – 3.58); we, thus, assumed limited effect of multicollinearity on the results of the regression analysis. The same regression conducted with the two facets of SANS – avolition-

asociality and inexpressivity (Blanchard & Cohen, 2006; Kotov et al., in press) – entered as separate scores within the model, indicated that the avolition-asociality dimension ($\beta = .31, p = .05$) accounted for marginally significant variance in EFP performance. However, the inexpressivity dimension ($\beta = .19, p = .15$), dummy variables for group ($\beta = .08, p = .69$ and $\beta = -.04, p = .73$), positive symptoms ($\beta = .03, p = .82$), dysphoria ($\beta = -.11, p = .31$), or antipsychotic medication status ($\beta = .02, p = .89$) did not account for any significant variance in the model. The above results remained significant even after the addition of age and gender in the model.

EFP correlation with global functioning. Partial correlation analyses showed a negative correlation between EFP accuracy and global functioning ($r = -.32, p < .01$; **Figure 1D**) across all participants, while controlling for group-related differences, indicating that EFP performance is an informative index of real-world functioning. This correlation was driven by the relationship of global functioning with emotion accuracy ($r = .34, p < .01$) as opposed to shape accuracy ($r = .06, p = .64$). Correlation between EFP accuracy and global functioning remained significant when the analysis was conducted separately for the patients ($r = -.46, p < .01$) and for never-psychotic participants ($r = -.38, p < .05$), and using permutation tests in never-psychotic participants (see Supplementary Results). Regression analysis, conducted to determine specificity of the association between global functioning and EFP performance, revealed that global functioning ($\beta = -.47, p < .01$), but not dummy variables for group ($\beta = .09, p = .66$ and $\beta = -.09, p = .49$), positive symptoms ($\beta = -.02, p = .89$), dysphoria ($\beta = -.15, p = .16$), or antipsychotic medication status ($\beta = .03, p = .82$) accounted for significant variance in EFP performance. Additionally, in Step 2, the group \times global functioning interactions did not account for a significant increase in variance ($\Delta R^2 = .00, p = .98$). The VIF values, calculated to assess

for effects of multicollinearity, were found to be relatively low (1.06 – 3.51); we, thus, assumed limited effect of multicollinearity on the results of the regression analysis.

Mediation Analysis. Analyses examining whether negative symptoms mediate the relationship between EFP accuracy and global functioning across SZ, OP, and NP showed that, after controlling for negative symptoms, the significant association between EFP accuracy and global functioning were not significant, suggesting that negative symptoms mediate the relationship between EFP accuracy and global functioning (**Figure 4A**). The bootstrapped unstandardized coefficient for the indirect effect was -62.55, 95% CI [-92.95, -41.80], indicating a statistically significant indirect effect.

fMRI Results

Neural correlates of EFP. Across all participants, significant EFP activation in regions involved in EFP including hippocampus, FFA in the fusiform gyrus, OFA in the inferior and middle occipital gyrus, and early visual cortical areas (**Table 2**). Additionally, significant activation was observed in left amygdala for EFP using ROI analysis (**Table 2**).

EFP correlation with symptoms of psychosis. Regression analyses showed positive correlation between EFP activity and negative symptoms in the insula, hippocampus, and early visual cortical areas including calcarine sulcus while controlling for group-related variance (**Table 2; Figure 2**). Results also showed that EFP activity in the amygdala was positively correlated with negative symptoms (**Figure 2**). This correlation was driven by the relationship of negative symptoms with emotion-related activity as opposed to shape-related activity. Conjunction analysis showed overlaps between clusters of voxels sensitive to EFP and correlation with negative symptoms in the hippocampus and early visual cortex (**Figure 2; Table 2**) indicating that the voxels correlating with negative symptoms were also the ones sensitive to

our EFP task manipulation. Correlation between EFP activity in early visual areas and negative symptoms was also observed in analyses conducted separately for patients ($r = .33, p < .05$) and never-psychotic participants ($r = .36, p = .05$), and using permutation tests in never-psychotic participants (see Supplementary Results). No correlation was found between positive symptoms and EFP activity. Furthermore, the relationship between symptoms and functioning were not seen for neutral face activity alone, but was replicated for emotional vs. neutral face activity (see Supplementary results).

Regression analyses examining symptom-specificity of EFP deficits to negative symptoms showed that EFP activity in early visual cortical areas and insula remained significantly associated with negative symptoms even after controlling for group-related variance, positive symptoms, dysphoria, and antipsychotic medication status. However, EFP activity in the amygdala did not remain significantly correlated with negative symptoms after controlling for the aforementioned variables. In an additional regression conducted to examine interaction effects, symptoms x group interaction did not account for unique variance in activity in these limbic and visual regions over and above main effects of negative symptoms. The above results remained significant even after the addition of age and gender in the model. No significant correlations were observed in any brain regions between EFP activity and positive symptoms. The same regression was conducted with the two facets of SANS – avolition-
asociality and inexpressivity – entered as separate scores within the model. Results indicated that the avolition-asociality dimension, but not the inexpressivity dimension, group membership, positive symptoms, dysphoria, or antipsychotic medication status, was associated with EFP activity in the visual cortical areas.

EFP correlation with global functioning. Regression analyses showed negative correlations between global functioning and EFP activity in the amygdala, hippocampus, insula, and early visual cortex (**Figure 3; Table 2**), even after controlling for group-related variance. We also confirmed that this association between global functioning and EFP was driven by its association with emotion-related activity and not shape-related activity. Conjunction analyses showed overlaps between clusters of voxels sensitive to EFP and correlation with global functioning (controlling for group) in the hippocampus and early visual cortex (**Table 2**). Significant correlation between EFP activity in early visual areas and global functioning was also observed in analyses conducted separately for patients ($r = -.41, p < .01$) and never-psychotic participants ($r = -.41, p < .05$), and using permutation tests in never-psychotic participants (see Supplementary Results). Further confirming the relative specificity of this association between global functioning and EFP activity, voxelwise regression analysis showed that despite controlling for the dummy variables for group, positive symptoms, dysphoria, and antipsychotic medication status, global functioning remained significantly associated with EFP activity in the early visual cortex and insula. In an additional regression conducted to examine interaction effects, global functioning x group interaction did not account for unique variance in activity in these limbic and visual regions over and above main effects of negative symptoms.

Mediation Analysis. Finally, we examined the hypothesis that negative symptoms mediate the relationship between EFP activity in our ROIs and global functioning. Results showed that, after controlling for negative symptoms, the significant association between EFP activity and global functioning were not significant in the amygdala (**Figure 4B**), hippocampus (**Figure 4C**), and calcarine sulcus (**Figure 4D**) suggesting a mediation effect of negative symptoms. The bootstrapped unstandardized indirect effects for EFP activity in amygdala, -

11.84, 95% CI [-21.78, -3.52], calcarine sulcus, -17.40, 95% CI [-32.47, -4.19], and hippocampus, -15.19, 95% CI [-26.60, -5.29] showed that the indirect effects were statistically significant in all three cases.

Discussion

There is considerable research indicating that symptoms of psychosis as well as EFP impairment and global functioning exist in individuals with and without diagnoses of psychotic disorders. Despite their dimensional presentation, most research has examined these constructs and their relationship largely within the realm of schizophrenia. The present study adopted a dimensional approach to examine the association of EFP with symptoms of psychosis and global functioning across a heterogeneous sample comprising individuals with and without psychotic disorders. As predicted, lower EFP accuracy correlated with higher negative symptoms and lower global functioning across all participants, and in the psychotic and never-psychotic groups separately. Neurally, greater EFP-related activity in limbic regions including the amygdala, insula, and hippocampus, as well as in early visual regions was associated with greater negative symptoms and lower global functioning across all participants. Behaviorally and neurally, in early visual areas and hippocampus, the association of EFP measures with negative symptoms and global functioning existed even after controlling for group-related variance, positive symptoms, dysphoria, and antipsychotic medication status. The correlation between EFP and early visual activity was also seen for both psychotic and never-psychotic groups separately. The interaction between groups and symptoms did not account for additional variance in EFP, indicating that relationship between EFP measures and symptoms or global functioning did not vary by diagnosis.

Overall, using a face processing model firmly grounded in the cognitive neuroscience literature, our study provides the first evidence establishing the clinical specificity (for negative but not positive symptoms) and practical utility (for global functioning) of both behavioral and neural EFP measures transdiagnostically. We identify regions in the face processing hierarchy that are sensitive to greater severity of negative symptoms and worse global functioning. Furthermore, we show consistent effects for behavioral and neural emotion vs. shape measures, such that these effects are driven by the emotion (and not shape) condition, are not seen for neutral vs. shape condition, but replicate for emotion vs. neutral face condition, thereby indicating effects specific to the emotional nature of faces. More broadly, our study provides strong evidence supporting the specificity, utility, and dimensional nature of RDoC domain of emotional face perception in psychotic disorders.

The observed pattern of behavioral performance and brain activation for EFP in the present study was largely consistent with that reported in basic affective neuroscience literature (Johnston, Devir, & Karayanidis, 2006; Kohler et al., 2000). Across all participants, our EFP task activated early visual areas as well as regions comprising the core (OFA, FFA, STS) and extended (amygdala and hippocampus) face perception network (Haxby et al., 2000; Ishai et al., 2005; Pitcher et al., 2011). The amygdala is well-established for its role in EFP (Adolphs et al., 1999; Kosaka et al., 2002; Li et al., 2009; Rauch et al., 2010), and the hippocampus, too, has been implicated in EFP due to its reciprocal anatomical connections to (Pitkänen, Pikkarainen, Nurminen, & Ylinen, 2000), and concurrent activation with (Gur et al., 2002; Williams et al., 2001), the amygdala. While our EFP task activated the expected neural regions across all subjects, the relationship of this activation with negative symptoms and global functioning was seen only for a subset of the regions, including, early visual cortex, amygdala and hippocampus.

In schizophrenia, evidence of limbic involvement in EFP is mixed, showing both hyperactivity (Holt et al., 2005, 2006; Kosaka et al., 2002; Rauch et al., 2010; Taylor, Phan, Britton, & Liberzon, 2005) and hypoactivity (Gur et al., 2002; Hempel et al., 2003; Li et al., 2009; Schneider et al., 1998) in amygdala and hippocampus for emotional vs. neutral faces. This discrepancy may be due to amygdala hyperactivity to neutral faces in schizophrenia (Hall et al., 2008; Holt et al., 2006), since studies that have used a baseline condition other than neutral faces (e.g., shapes) show increased EFP-related amygdala activity (Fakra et al., 2008; Johnston et al., 2005; Kosaka et al., 2002). Using a shape matching baseline condition, we too observed an association between EFP-related amygdala/hippocampus hyperactivity and more severe negative symptoms. We also confirmed that increased emotional face-related activity (as opposed baseline shape-related activity) was associated with greater severity of negative symptoms. These increases in amygdala activity may have an impairing effect on task performance, since increased activity is associated with incorrect, rather than correct EFP responses in schizophrenia (Gur et al., 2007; Morris, Weickert, & Loughland, 2009).

We also examined the relationship of negative symptoms with regions of the EFP visual processing hierarchy. Negative symptoms did not impact activity in the core face processing regions (OFA, FFA, and STS) but were associated with hyperactivity in early visual cortex. These findings are in line with evidence of early visual processing deficits (Butler, Silverstein, & Dakin, 2008; Kim, Zemon, Saperstein, Butler, & Javitt, 2005) as well as EFP-related hyperactivity in early visual areas such as cuneus, calcarine, and lingual gyrus in schizophrenia (Delvecchio et al., 2012; Taylor et al., 2012). Deficits in the magnocellular visual processing pathway, which projects to V1 and V2 and is involved in EFP (Vuilleumier et al., 2003) are typically associated with negative rather than positive symptoms (Butler et al., 2002; Kéri et al.,

2005; Slaghuis, 2004). Furthermore, early visual processing deficits in schizophrenia are associated with worse community (Butler et al., 2005), social (Sergi & Green, 2003), and real-world functioning (Brenner, Lysaker, Wilt, & O'Donnell, 2002).

Our results demonstrate the relative specificity of EFP-related limbic and early visual cortex hyperactivity to negative (but not positive) symptoms and worse global functioning, and extend these findings to other psychotic disorders as well as never-psychotic participants. The association of EFP measures with negative, but not positive, symptoms is consistent with past studies that have demonstrated a specific relationship between EFP and negative symptoms (Addington & Addington, 1998; Baudouin et al., 2002; Michalopoulou et al., 2008; Mueser et al., 1996; Gabriele Sachs et al., 2004; van 't Wout et al., 2007). Since EFP has also been shown to be associated with aberrant visual cortical activity, the lack of association between EFP and positive symptoms in our study may be attributable to the relatively intact early visual cortical functioning related to positive symptoms (Doniger et al., 2001; Kéri et al., 2005; Spencer et al., 2004). Amongst negative symptoms, EFP-related amygdala hyperactivity has been particularly associated with blunted affect (Gur et al., 2007; Rauch et al., 2010). However, studies that have reported an association between EFP deficits and negative symptoms did not directly compare the two facets (avolition-asociality and inexpressivity) of negative symptoms (Germine & Hooker, 2011; Kohler et al., 2003). Our results show that, when examined in the same model, behavioral and neural measures of EFP were associated with the avolition-asociality facet of negative symptoms, not the inexpressivity facet.

The present study also demonstrates that the relationship between behavioral and neural EFP measures and global functioning is mediated by negative symptoms across all participants. This finding corroborates past research showing that negative symptoms mediate the relationship

between behavioral measures of social cognition and functional outcomes in schizophrenia (Harvey, Green, Bowie, & Loebel, 2006; Lin et al., 2013) and shows a similar mediation for neural measures across psychotic disorders and healthy individuals.

Some limitations of the present study must be acknowledged. About half the participants in the sample were taking antipsychotic medications, which may interact with task performance and neural activity. However, our behavioral and neural results remained even after controlling for medication status. Moreover, a substantial proportion of individuals with psychotic disorders are chronically medicated and it is important to assess their functioning in their typical state. Another limitation is that we used only two types of negative emotion – fear and anger - for our EFP task, which limits the generalizability of our findings to other emotion types, such as sadness or happiness. Additionally, there may be a difference in the relationship of negative symptoms with these two emotions, but the design of the current study did not allow us to parse out these differences. Future studies examining the full range of emotional expressions with larger samples will help to further clarify the nature of the association between EFP and symptoms of psychosis.

Humans depend heavily on visual EFP skills in their interpersonal interactions. Individuals who have enduring negative symptoms may have limited skills and experience with the interpretation of emotional expressions (Bryson, Bell, Kaplan, Greig, & Lysaker, 1998; Gabriele Sachs et al., 2004). Furthermore, the inability to correctly interpret and respond to social information, particularly cues about the internal states of others, may lead to consistent failures in daily living (Bryson et al., 1998), thereby impacting overall quality of life and functioning in individuals with more severe negative symptoms. The present study provides some of the first evidence indicating the specific relationship of behavioral and neural EFP

deficits and negative symptoms and global functioning that cut across traditional diagnostic boundaries of psychotic disorders. Studying these constructs as dimensions across non-clinical and transdiagnostic clinical samples offers potential ways of understanding the structure of mental disorders that are not based on traditional DSM diagnostic criteria. Identification of these transdiagnostic measures is an important first step towards development of affective and neural markers that can aid identification of targets for novel and more effective treatment development and also serve as potential diagnostic and prognostic markers. Unified treatment protocols that capitalize on commonalities that cut across diagnostic boundaries have important practical and clinical advantages over interventions designed to treat specific disorders including lower costs, ease of dissemination of effective treatments, and adherence to evidence-based treatments (Addis, Wade, & Hatgis, 1999; Barlow, Allen, & Choate, 2004; McEvoy, Nathan, & Norton, 2009; McHugh, Murray, & Barlow, 2009). Indeed, studies using training programs with a specific focus on EFP have been shown to influence activity in brain regions involved in EFP (Habel, Koch, et al., 2010). Moreover, these training programs have shown improvement in social and community functioning as well as in negative symptoms in individuals with schizophrenia spectrum disorders and bipolar disorder, indicating transdiagnostic benefits (Combs et al., 2007; Kurtz & Richardson, 2012; Lahera et al., 2013; Roberts et al., 2014; G. Sachs et al., 2012).

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Table 1
Sample characteristics

	Schizophrenia (N = 21)		Other Psychoses (N = 28)		Never-Psychotic (N = 29)		Group Comparison	p
	n	%	n	%	n	%		
<i>Gender</i>							$\chi^2(2) = 60$.741
Female	9	42.9	9	32.1	11	37.9		
Male	12	57.1	19	67.9	18	62.1		
<i>Medication status</i>							$\chi^2(2) = 2.02$.364
Typical antipsychotic	6	28.6	1	3.6	0	0		
Atypical antipsychotic	13	61.9	9	32.1	1	3.4		
<i>Ethnicity</i>							$\chi^2(2) = .21$.902
Caucasian	17	81	24	85.7	24	82.8		
Other	4	19	4	14.3	5	17.2		
	Mean	SD	Mean	SD	Mean	SD		
<i>Age</i>	45.14	7.71	45.64	8.20	46.38	7.07	$F(2,77) = .16$.850
<i>Symptoms</i>								
Negative	27.67	11.55	10.97	11.65	5.21	4.98	$F(2,77) = 34.08$	<.001
Positive	16.86	13.41	3.97	6.25	.93	2.17	$F(2,77) = 26.09$	<.001
<i>Global functioning</i>	39.52	11.84	59.54	16.52	73.03	12.77	$F(2,77) = 34.82$	<.001
<i>IDAS dysphoria</i>	18.90	8.06	17.37	7.24	15.68	7.07	$F(2,76) = 1.17$.315
<i>Mean task accuracy</i>								
Shape	.97	.08	.98	.05	.99	.01	$F(2,77) = 2.16$.122
Emotion	.82	.17	.94	.09	.97	.07	$F(2,77) = 10.82$	<.001

IDAS, Inventory of Depression and Anxiety Symptoms

Table 2

Coordinates of peak activation in brain regions sensitive to emotional faces versus shapes (EFP), negative symptoms, and global functioning, across all participants.

Region		Peak MNI coordinates			
		Z	x	y	z
EFP					
Amygdala	L	3.62	-26	-4	-14
	R	2.73	30	-10	10
Fusiform Gyrus	L	6.38	-40	-64	-18
	R	5.88	38	-50	-12
Middle Occipital Gyrus	R	4.65	26	-90	4
Superior Temporal Gyrus	R	4.61	56	-48	16
Hippocampus	L	4.05	-30	-8	-12
	R	4.62	32	-14	-8
Insula	L	3.52	-28	26	0
	R	3.12	34	20	4
Calcarine	R	3.63	12	-70	8
EFP correlation with negative symptoms (controlling for group)					
Amygdala	L	2.42	-28	-8	-16
Insula	L	3.89	-36	-14	22
Calcarine	R	3.64	30	-58	10
Hippocampus	L	3.12	-22	-38	4
Conjunction (EFP and negative symptoms)					
Calcarine	R	3.33	32	-72	8
Hippocampus	L	3.80	-28	-36	4
EFP correlation with global functioning (controlling for group)					
Amygdala	L	2.30	-28	-2	-22
	R	2.31	28	-10	-10
Calcarine	R	5.48	28	-60	10
Hippocampus	L	3.76	-16	-38	6
	R	3.32	28	-36	6
Insula	L	3.61	-36	-14	22
Conjunction (EFP and global functioning)					
Calcarine Sulcus	R	3.13	30	-72	8
Hippocampus	L	3.36	-26	-36	2
	R	3.32	28	-36	6

Figure Captions

Figure 1. (A) Emotional face perception (EFP) task showing the emotion and shape conditions, (B) mean accuracy for emotion and shape matching, (C) correlation between EFP accuracy and negative symptoms across all participants, and (D) correlation between EFP accuracy and global functioning, across all three groups – schizophrenia (SZ), other psychoses (OP), and never-psychotic participants (NP).

Figure 2. Greater Emotional Face Perception (EFP) related activity (blue) positively correlates with negative symptoms (red) in calcarine sulcus ($y = -69$), hippocampus ($y = -36$), and amygdala ($y = -6$), across all three groups – schizophrenia (SZ), other psychoses (OP), and never-psychotic participants (NP). Overlaps (pink) indicate that task-sensitive voxels are also sensitive to negative symptoms.

Figure 3. Greater Emotional Face Perception (EFP) related activity (blue) negatively correlates with global functioning (green) in calcarine sulcus ($y = -69$), hippocampus ($y = -36$), and amygdala ($y = -8$), across all three groups – schizophrenia (SZ), other psychoses (OP), and never-psychotic participants (NP). Overlaps (cyan) indicate that task-sensitive voxels are also sensitive to global functioning.

Figure 4. Standardized regression coefficients and p values showing that negative symptoms mediate relationship of global functioning with (A) Emotional Face Perception (EFP) accuracy, and EFP related activity in (B) calcarine sulcus, (C) hippocampus, and (D) amygdala.