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Lateral prefrontal cortex activity during cognitive control of emotion predicts response to social stress in schizophrenia

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ABSTRACT

LPFC dysfunction is a well-established neural impairment in schizophrenia and is associated with worse symptoms. However, how LPFC activation influences symptoms is unclear. Previous findings in healthy individuals demonstrate that lateral prefrontal cortex (LPFC) activation during cognitive control of emotional information predicts mood and behavior in response to interpersonal conflict, thus impairments in these processes may contribute to symptom exacerbation in schizophrenia. We investigated whether schizophrenia participants show LPFC deficits during cognitive control of emotional information, and whether these LPFC deficits prospectively predict changes in mood and symptoms following real-world interpersonal conflict. During fMRI, 23 individuals with schizophrenia or schizoaffective disorder and 24 healthy controls completed the Multi-Source Interference Task superimposed on neutral and negative pictures. Afterwards, schizophrenia participants completed a 21-day online daily-diary in which they rated the extent to which they experienced mood and schizophrenia-spectrum symptoms, as well as the occurrence and response to interpersonal conflict. Schizophrenia participants had lower dorsal LPFC activity (BA9) during cognitive control of task-irrelevant negative emotional information. Within schizophrenia participants, DLPFC activity during cognitive control of emotional information predicted changes in positive and negative mood on days following highly distressing interpersonal conflicts. Results have implications for understanding the specific role of LPFC in response to social stress in schizophrenia, and suggest that treatments targeting LPFC-mediated cognitive control of emotion could promote adaptive response to social stress in schizophrenia.

1. Introduction

Interpersonal conflicts are emotionally difficult and require regulation of negative affect and behavior for successful resolution (Arriaga and Rusbult, 1998; Lopes et al., 2011). These self-regulatory mechanisms are reliant on cognitive control processes mediated by the lateral prefrontal cortex (LPFC; Heatherton and Wagner, 2011; Ochsner et al., 2012). LPFC dysfunction in cognitive control is a well-established neural impairment in schizophrenia (Barch, 2005; Manoach, 2003; Minzenberg et al., 2009) that is associated with worse symptoms (Goghari et al., 2010; MacDonald et al., 2005; Menon et al., 2001; Nishimura et al., 2011; Perlstein et al., 2001; van Veelen et al., 2010) and global functioning deficits (Sanz et al., 2009; Yoon et al., 2008). However, there is a paucity of research examining *how* LPFC dysfunction contributes to illness severity. Consistent with the diathesis–stress model, one proposal is that LPFC dysfunction is a biological vulnerability that, in the presence of an interpersonal stressor, contributes to symptom exacerbation via impaired cognitive control of emotion (Hooker et al., 2010; Krabbendam et al., 2014; Kring and Werner, 2004).

Cognitive control of emotion comprises the dual processes of explicit and effortful control of the experience and expression of internal emotional states (emotion regulation) and the implicit and more automatic control of how external emotional information influences behavior (Gyurak et al., 2011; Gross and Thompson, 2007, Ochsner et al., 2005; Quirk et al., 2006). The LPFC, comprising both dorsolateral (DLPFC) and ventrolateral (VLPFC) regions, is consistently implicated in laboratory assessed cognitive control of emotion (Ochsner and Gross, 2005; Ochsner et al., 2012; Pessoa, 2008), including paradigms assessing explicit emotion regulation (e.g. reappraisal paradigms) as well as paradigms assessing implicit cognitive control of external and/or irrelevant emotional information (e.g. emotional Stroop, emotional flanker tasks) (Gyurak et al., 2011).

Evidence suggests that response to interpersonal stressors may be mediated by LPFC function. Lower VLPFC activity during social exclusion predicts higher self-reported distress (Eisenberger et al., 2003). Similarly, lower VLPFC activity when viewing negative facial expressions predicts increased negative mood and maladaptive behavior following

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interpersonal conflicts (Hooker et al., 2010). In schizophrenia, interpersonal conflicts, especially conflicts characterized by criticism, predict symptom exacerbation and higher relapse rates (Hooley, 2007), and symptom exacerbation in response to interpersonal criticism is related to poor working memory and cognitive control (Rosenfarb et al., 2000) — neurocognitive processes known to be mediated by the LPFC (Aron et al., 2004; Curtis and D'Esposito, 2003) and to predict functional outcome (Milev et al., 2005). Collectively, these data suggest that compromised LPFC function is a vulnerability for symptom exacerbation and functional difficulties in response to interpersonal conflict.

However, research attempting to connect LPFC activity, interpersonal conflict, and schizophrenia symptomatology is sparse. To date, studies have primarily focused on the direct relationship between the LPFC and symptoms (Goghari et al., 2010; MacDonald et al., 2005; Menon et al., 2001; Nishimura et al., 2011; Perlstein et al., 2001; van Veelen et al., 2010). To our knowledge, only one study has examined the interaction between LPFC activation, symptoms, and real-world social interactions. In a sample of healthy individuals characterized along the schizophrenia-risk dimension social anhedonia, individuals at high-risk for schizophrenia (i.e. those with high social anhedonia) with low LPFC activation had worse symptoms of paranoia on days with distressing interpersonal conflicts compared to days without distressing interpersonal conflicts (Hooker et al., 2014). To date, no study has examined this relationship in individuals with schizophrenia. The scarcity of studies directly linking LPFC function to social interactions and subsequent symptoms in schizophrenia may result from limitations inherent in the currently available and commonly used methods.

First, the tasks traditionally used to assess LPFC function, such as response inhibition or working memory tasks (Barch, 2005), although robust activators, may not be the most sensitive measures for assessing how LPFC activity relates to real-world social functioning because they do not directly capture cognitive control of emotional information. Given the inherently affective nature of social interactions and the accompanying need for self-regulation (Arriaga and Rusbult, 1998), tasks assessing the *interaction* between LPFC mediated cognitive control and emotional information may provide a more accurate reflection of the inhibitory demands of real-world social contexts. By using "cold cognitive" tasks and not assessing LPFC mediated cognitive control in relation to emotional information, previous studies may have lacked the sensitivity necessary to identify the role of the LPFC in individuals' response to social conflict.

Second, prior research has primarily assessed social interactions using laboratory-based one-time retrospective measures of functioning. Although these provide an overview of an individual's general level of functioning, they are not well suited for capturing the multidimensional nature of social interactions in daily life, and rarely provide the context in which they occur (Trull and Ebner-Priemer, 2009). Social interactions do not occur in a vacuum; day-to-day changes in social behavior may be prompted at a specific time, in a specific setting, or in the context of a particular interpersonal relationship. One-time retrospective evaluations of social functioning miss these nuances, calling into question their ecological validity (Yager and Ehmann, 2006). Experience sampling methods (ESM), a technique in which assessments are collected in the person's natural environment and repeated over time, have revealed a nuanced relationship between changes in the social environment, particularly social stressors, and symptoms (Myin-Germeys et al., 2009; Oorschot et al., 2009), Thus, using ESM in conjunction with neuroimaging techniques may provide a more sensitive and ecologically valid approach to understanding the contribution of LPFC dysfunction to social deficits in schizophrenia.

The present study addressed these prior limitations by combining fMRI and ESM to test whether people with schizophrenia have LPFC deficits in cognitive control of negative emotional information, and, if so, whether these LPFC deficits are related to changes in mood and symptoms following interpersonal conflict. Individuals with schizophrenia and demographically-matched healthy controls completed an adapted version of the Multi-Source Interference Task (MSIT), a cognitive control task specifically designed to activate the cingulo–frontal–parietal cognitive control network (Bush and Shin, 2006). In our adapted version, the MSIT-Emotion, MSIT stimuli are superimposed on a negative emotional scene that is irrelevant to the central task demand. Thus, rather than requiring explicit manipulation of emotional material and/or the explicit regulation of internal emotional states (i.e. emotion regulation through reappraisal/suppression), the task requires participants to engage cognitive control mechanisms to inhibit the effect of irrelevant emotional information in the external environment on task performance. This process is thought to more accurately reflect the interaction of emotion and cognitive control in real-world social contexts (Silbersweig et al., 2007), and considered to be a form of implicit cognitive control of emotion (Gyurak et al., 2011). Our measure of cognitive control of emotional information was LPFC activity when inhibiting the effect of irrelevant emotional information during high interference trials (when cognitive control skills are most challenged). Stimuli were also superimposed on neutral pictures, included to test the specificity of schizophrenia participants' LPFC deficits for controlling emotional information. Following the scan, schizophrenia participants completed an online, structured daily-diary questionnaire of mood and symptoms every evening for 3 weeks. End-of-the-day reports provide data on daily events and day-to-day symptom fluctuations whilst minimizing interference with participants' daily experience. Participants rated the extent to which they experienced mood and schizophrenia-spectrum symptoms, as well as the occurrence of interpersonal conflict and associated distress. We hypothesized that: 1) schizophrenia participants would show reduced LPFC activity during cognitive control of emotional information compared to healthy participants; and 2) among schizophrenia participants, LPFC activity during cognitive control of emotional information will predict changes in mood and symptoms following interpersonal conflict. Specifically, we expect that schizophrenia participants with low LPFC activity will have an increase in negative mood and psychotic symptoms the day after highly distressing interpersonal conflict.

2. Material and methods

2.1. Participants

23 individuals with schizophrenia or schizoaffective disorder and 24 healthy controls were recruited from the Greater Boston area. Groups were matched for gender, age, education, and IQ (Table 1). Inclusion criteria for all participants were: age 18–65, primary English speaker, no neurological or major medical illness, no head trauma history, no substance abuse within 6 months, and no current/past substance dependence. Inclusion criteria for schizophrenia participants were: diagnosis of schizophrenia or schizoaffective disorder, no comorbid axis I disorders, and no history of electroconvulsive therapy. Inclusion criteria for healthy participants were: no current/past axis I disorders, no first-degree relative with a psychotic disorder, scores within 1.5 standard deviations of the population mean on five measures of schizotypal personality (perceptual aberration scale (Chapman et al., 1978), magical ideation scale (Eckblad & Chapman, 1983), referential thinking scale (Lenzenweger et al., 1997), physical anhedonia scale (Chapman et al., 1976), and revised social anhedonia scale (Eckblad et al., 1982)). Psychopathology was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 2002); symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987); social functioning was assessed with the Social Adjustment Scale – Self-Report (SAS-SR; Weissman et al., 1978) and the Global Functioning: Social scale (GF:S; Auther et al., 2006); positive and negative mood were assessed using the Positive And Negative Affect Schedule (PANAS; Watson et al., 1988). Clinical assessments were conducted by trained PhD-level clinical psychologists (LMT, SHL) and supervised by a licensed clinical psychologist (CIH).