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Weak dorsolateral prefrontal response to social criticism predicts worsened mood and symptoms following social conflict in people at familial risk for schizophrenia

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ABSTRACT

Understanding the specific mechanisms that explain why people who have relatives with schizophrenia (i.e., people at familial high risk; FHR) are more likely to develop the disorder is crucial for prevention. We investigated a diathesis-stress model of familial risk by testing whether FHR individuals under-recruit brain regions central to emotion regulation when exposed to social conflict, resulting in worse mood and symptoms following conflict. FHR and non-FHR participants listened to critical, neutral, and praising comments in an fMRI scanner before completing 4 weeks of daily-diary records. Compared to non-FHR individuals, FHR individuals under-recruited the bilateral dorsolateral prefrontal cortex (DLPFC)—a region strongly implicated in cognitive emotion regulation—following criticism. Furthermore, within FHR participants, weak DLPFC response to criticism in the laboratory task was associated with elevated negative mood and positive symptoms on days with distressing social conflicts in daily-diary assessments. Results extend diathesis-stress models of schizophrenia by clarifying neural and environmental pathways to dysregulation in FHR individuals.

1. Introduction

Schizophrenia is a devastating and highly heritable illness (Goldman et al., 2009; McGuffin et al., 1984; Tsuang et al., 2001). People who have family members with schizophrenia—i.e., people at familial high risk (FHR)—are 7–10 times more likely than the general population to develop schizophrenia (Gottesman, 1991; MacDonald et al., 2009; Rasic et al., 2014). The diathesis-stress model of schizophrenia suggests that the disorder emerges when genetic or acquired *diatheses* (i.e. vulnerabilities) interact with environmental *stressors* (Corcoran et al., 2003; Fowles, 1992; Rosenthal, 1970; Walker and Diforio, 1997; Walker et al., 2008). Although converging evidence suggests that atypical activity in the lateral prefrontal cortex (LPFC) may be a biomarker of latent diatheses in those at familial and clinical high risk for schizophrenia (Lawrie et al., 2008; Waters-Metenier and Toulopoulou, 2010), the mechanisms through which this neural vulnerability interacts with environmental stressors to produce symptoms remain unclear. Here, we tested whether FHR individuals under-recruit the dorsolateral prefrontal cortex (DLPFC) during emotion regulation and if this diathesis produces exacerbated mood and psychotic symptoms following social stress.

LPFC deficits are a core feature of schizophrenia-spectrum pathology (Barch, 2005). People with schizophrenia exhibit reduced lateral prefrontal activity during cognitive control tasks (Davidson and Heinrichs, 2003; Minzenberg et al., 2009), and this deficit is associated with worse functional outcomes (Nishimura et al., 2011; Van Veelen et al., 2010). However, the DLPFC is also implicated in emotion regulation, a social-cognitive skill that is necessary to control the impact of stressful events (Buhle et al., 2014; Ochsner et al., 2002; Ochsner et al., 2012). Parallel to the cognitive control literature, people with schizophrenia show reduced LPFC activity and atypical limbic-prefrontal coupling during emotion regulation tasks (Morris et al., 2012; Tully et al., 2014; van der Meer et al., 2014), and these deficits are associated with worse reactions to social conflict outside of the laboratory (Tully et al., 2014).

Structural and functional LPFC abnormalities are also observed in

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individuals at familial risk for schizophrenia, even if they do not have the disorder. For example, FHR individuals suffer from deficits in LPFC-mediated cognitive skills, such as working memory and cognitive control (Lawrie et al., 2008). LPFC dysfunction may also contribute to poor emotion regulation in FHR. Both people with schizophrenia and FHR relatives demonstrate reduced ventrolateral prefrontal activity when regulating their emotions using cognitive reappraisal (van der Meer et al., 2014). Similarly, individuals at clinical high risk for schizophrenia (i.e., people with early signs of schizophrenia symptoms), exhibit atypical LPFC activity and cortical–limbic coupling during emotion regulation, as well as reduced tendencies to regulate emotions in daily life (Gee et al., 2012; van der Velde et al., 2015). Additionally, atypical LPFC activity is found in individuals with personality or trait markers of schizophrenia risk (i.e., schizotypy or high social anhedonia; Fisher et al., 2004; Hooker et al., 2014; Mohanty et al., 2005).

Although these findings suggest that FHR participants struggle to regulate emotions—and that this difficulty may be associated with LPFC function—little is known about the real-world implications of this process in FHR. This represents an obvious dearth in understanding, given that effective emotion regulation is vital for psychological health (Aldao et al., 2010). In fact, substantial evidence suggests that effective emotion regulation may be especially important for FHR individuals, who appear to be highly sensitive to the impact of negative emotions aroused by *social stress*. Prior research shows that social stress is a potent environmental risk factor for schizophrenia (Hooley and Gotlib, 2000; Jones and Fernyhough, 2007; Krabbendam et al., 2014). Indeed, early research on schizophrenia outcomes focused on *expressed emotion*, a measure of familial criticism, hostility, and emotional over-involvement (Butzlaff and Hooley, 1998; Hooley, 2007; Kavanagh, 1992). This line of research revealed that familial criticism—one form of social stress—is robustly associated with schizophrenia relapse (Butzlaff and Hooley, 1998). Furthermore, this line of work converges with diathesis-stress models of schizophrenia, as one study demonstrated that adverse family environments are associated with schizophrenia onset *specifically* for FHR individuals (Tienari et al., 2004). In this study, familial risk and family environment interacted to predict schizophrenia onset: Conversion rates were especially high in FHR individuals exposed to family stressors. These data suggest that FHR individuals may be particularly vulnerable to the negative effects of social conflict, and although this finding is illuminating, it remains unknown whether this pattern of results may be connected to FHR-related LPFC deficits described above.

Taken together, prior work suggests that weak DLPFC-mediated emotion regulation may be a *diathesis* that renders FHR individuals vulnerable to psychiatric symptoms when exposed to the *stress* of social conflict. We tested this hypothesis using a joint fMRI/daily-diary paradigm. FHR and non-FHR participants listened to critical comments while undergoing fMRI scanning. Participants then completed 28 days of daily questionnaires on their mood, symptoms, and social conflicts. As in our previous work on schizophrenia and FHR, joint fMRI/daily-diary methods allowed us to both discover underlying neural differences in FHR populations and to test how these differences relate to real-world outcomes (Dodell-Feder et al., 2014; Dodell-Feder et al., 2016; Hooker et al., 2014; Hooker et al., 2010; Tully et al., 2014). We hypothesized that FHR individuals would demonstrate reduced DLPFC activity following exposure to social criticism and that this deficit would predict worse mood and increased schizophrenia symptoms on days marked by the stress of social conflict.

2. Material and methods

2.1. Participants

Twenty-one FHR and 20 non-FHR individuals enrolled in the study and completed the fMRI task. We excluded 1 non-FHR participant due to excessive motion. All non-FHR participants and 17 FHR participants then completed 4 weeks of daily-diary questionnaires. Consequently, for fMRI analyses, $N_{FHR} = 21$ and $N_{non\text{-}FHR} = 19$. For daily-diary analyses, $N_{FHR} = 17$ and $N_{non\text{-}FHR} = 19$ (see Table 1 for participant details).

FHR participants were required to be between 15 and 32 years of age and have a relative or relatives diagnosed with psychotic disorders. All FHR participants had at least one first-degree relative with schizophrenia or schizoaffective disorder, and all but 2 had a second first-degree relative with one of these disorders. Non-FHR participants had no family history of psychotic disorders, psychiatric hospitalization, or suicide. Exclusion criteria for both FHR and non-FHR participants included past/current treatment with anti-psychotics or mood stabilizers, IQ < 70, being a non-native English speaker, fMRI contraindication, and past or current DSM-IV Axis-I psychotic disorders (i.e., schizophrenia, schizoaffective disorder, psychosis-NOS, substance-induced psychosis, or bipolar/major depressive disorder with psychotic

Table 1
Participant characteristics.

	FHR	Non-FHR	Group differences
N	21	19	
Gender (male/female)	7/14	5/14	$\chi2(1, N = 40) = 0.02$, $p = .89$
Age	27.33 (3.88)	26.00 (3.93)	$t(38) = 1.08$, $p = .29$
Education (years)	15.95 (1.53)	16.21 (0.79)	$t(38) = -0.66$, $p = .51$
IQ[a]	117.85 (9.65)	117.16 (12.22)	$t(37) = 0.20$, $p = .85$
BDI-II[b]	5.55 (5.37)	2.11 (3.32)	$t(36) = 2.34$, $p = .02$*
STAI-State[b]	27.00 (7.01)	25.67 (5.48)	$t(36) = 0.65$, $p = .52$
STAI-Trait[b]	33.55 (8.84)	28.94 (7.12)	$t(36) = 1.76$, $p = .09$#
Lifetime Axis-I diagnosis[c] (number of participants)	10	1	$\chi2(1, N = 35) = 6.65$, $p = .01$**
MDD	4	0	–
ADHD	1	0	–
Substance abuse	0	1	–
Comorbid diagnoses	5[d]	0	–
SIPS[b,e]			
Positive	0.55 (0.49)	0.06 (0.15)	$U = 297.5$, $p < .001$***
Negative	0.33 (0.37)	0.05 (0.16)	$U = 270$, $p = .002$**
Disorganized	0.48 (0.39)	0.14 (0.26)	$U = 275.5$, $p = .003$**
General	0.46 (0.53)	0.08 (0.17)	$U = 262$, $p = .008$**
Expressed emotion task			
Critical affect rating	4.45 (0.92)	4.63 (0.52)	$t(38) = -0.75$, $p = .46$
Neutral affect rating	2.67 (0.60)	2.74 (0.40)	$t(38) = -0.43$, $p = .67$
Praise affect rating	1.13 (0.28)	1.25 (0.44)	$t(38) = -1.03$, $p = .31$

Notes: When applicable, values represent means with standard deviations in parentheses.
[a] Data not collected from 1 FHR participant.
[b] Data not collected from 1 FHR participant and 1 non-FHR participant.
[c] Data not collected from 2 FHR participants and 3 non-FHR participants.
[d] Individuals counted in the comorbid category are not repeated in counts of other conditions (i.e., counts for each category are mutually exclusive); two individuals met criteria for MDD and ADHD, 2 individuals met criteria for MDD and an anxiety disorder, and 1 individual met criteria for MDD, an anxiety disorder, ADHD, and substance abuse.
[e] Due to lack of normality in data, we used Mann–Whitney U tests to compare groups.
IQ = Intelligence Quotient, BDI = Beck Depression Inventory, STAI = State–Trait Anxiety Inventory, MDD = Major Depressive Disorder, ADHD = Attention-Deficit Hyperactivity Disorder, SIPS = Structured Interview for Prodromal Symptoms.
* $p < .05$.
** $p < .01$.
*** $p < .001$.
# $p < .10$.