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Cortical thickness of neural substrates supporting cognitive empathy in individuals with schizophrenia

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ABSTRACT

Background: Cognitive empathy is supported by the medial prefrontal cortex (mPFC), inferior frontal gyrus (IFG), anterior mid-cingulate cortex (aMCC), insula (INS), supplementary motor area (SMA), right temporo-parietal junction (TPJ), and precuneus (PREC). In healthy controls, cortical thickness in these regions has been linked to cognitive empathy. As cognitive empathy is impaired in schizophrenia, we examined whether reduced cortical thickness in these regions was associated with poorer cognitive empathy in this population.
Methods: 41 clinically-stable community-dwelling individuals with schizophrenia and 46 healthy controls group-matched on demographic variables completed self-report empathy questionnaires, a cognitive empathy task, and structural magnetic resonance imaging. We examined between-group differences in study variables using *t*-tests and analyses of variance. Next, we used Pearson correlations to evaluate the relationship between cognitive empathy and cortical thickness in the mPFC, IFG, aMCC, INS, SMA, TPJ, and PREC in both groups.
Results: Individuals with schizophrenia demonstrated cortical thinning in the IFG, INS, SMA, TPJ, and PREC (all $p < 0.05$) and impaired cognitive empathy across all measures (all $p < 0.01$) relative to controls. While cortical thickness in the mPFC, IFC, aMCC, and INS (all $p < 0.05$) was related to cognitive empathy in controls, we did not observe these relationships in individuals with schizophrenia (all $p > 0.10$).
Conclusions: Individuals with schizophrenia have reduced cortical thickness in empathy-related neural regions and significant impairments in cognitive empathy. Interestingly, cortical thickness was related to cognitive empathy in controls but not in the schizophrenia group. We discuss other mechanisms that may account for cognitive empathy impairment in schizophrenia.

1. Introduction

Empathy encompasses the ability to understand the emotional perspective of others through mentalizing (i.e., cognitive empathy), and the capacity to share the same emotional state as others (i.e., affective empathy) (Shamay-Tsoory, 2011; Zaki and Ochsner, 2011). Cognitive empathy is impaired among individuals with schizophrenia based on self-report (Achim et al., 2011; Smith et al., 2012; Sparks et al., 2010), behavioral task performance (Derntl et al., 2009; Smith et al., 2014), and functional neuroimaging (Benedetti et al., 2009; Derntl et al., 2012; Lee et al., 2010; Smith et al., 2015). Furthermore, cognitive empathy impairments have been associated with deficits in social functioning among individuals with schizophrenia (Smith et al., 2014; Smith et al., 2012; Smith et al., 2015). Meanwhile, the literature is mixed regarding whether affective empathy is impaired in schizophrenia. Thus, we may gain a deeper understanding of how to develop targeted treatments aimed at enhancing social functioning by evaluating deficits in cognitive empathy.

Most studies suggest that cognitive empathy is supported by the medial prefrontal cortex (mPFC) (Meyer et al., 2012; Rameson et al., 2012; Schnell et al., 2011), right temporo-parietal junction (TPJ) (Hooker et al., 2008; Schulte-Ruther et al., 2007; Vollm et al., 2006), precuneus (PREC) (Farrow et al., 2001; Meyer et al., 2012; Nummenmaa et al., 2008) and supplemental motor area (SMA) (Keysers and Gazzola, 2009; Lamm et al., 2007). Together, these regions are thought to support self-referential representations, transient mental inference of others, and

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mentalizing (Shamay-Tsoory, 2011). Additionally, research suggests that cognitive empathy is supported by regions of the brain that process emotion, such as the inferior frontal gyrus (IFG), anterior midcingulate cortex (aMCC), and anterior insula (INS) (Gonzalez-Liencres et al., 2013). Collectively, these neural substrates support cognitive empathy.

There is also a link between anatomical differences in regions supporting mentalizing and social information processing. Studies in healthy individuals have shown that gray matter volume (Banissy et al., 2012; Sassa et al., 2012; Takeuchi et al., 2014) and density (Mutschler et al., 2013) in neural regions supporting empathy are associated with measures of cognitive empathy. Other studies suggest individuals with neurodevelopmental disorders (e.g., autism spectrum disorder) have reduced cortical thickness in the mentalizing network that correlated with greater social impairment (Hadjikhani et al., 2006; Richter et al., 2015). Similarly, studies of individuals with schizophrenia have revealed reduced cortical thickness in most, if not all, of the neural regions supporting empathy (Goldman et al., 2009; Kuperberg et al., 2003; Nesvag et al., 2008). However, the field has not yet evaluated whether reduced cortical thickness in these regions have been associated with impaired cognitive empathy.

In this study, we examined the relationship between cortical thickness in regions thought to subserve cognitive empathy and both self-reported and performance-based measures of cognitive empathy. We examined this relationship in individuals with schizophrenia and healthy controls. Based on our review of the literature, we had three primary hypotheses. First, we expected that individuals with schizophrenia would have reduced cortical thickness in frontal, temporal, and parietal substrates of empathy relative to controls. Second, we hypothesized that individuals with schizophrenia would demonstrate deficits in performance-based and self-reported measures of cognitive empathy relative to controls. Third, we hypothesized that cortical thickness would correlate with both performance-based and self-reported measures of cognitive empathy in both individuals with schizophrenia and controls.

2. Materials and methods

2.1. Sample

Individuals with schizophrenia ($n = 41$) and healthy controls ($n = 46$) were group-matched for age (18–50 years), gender, ethnicity, parental socioeconomic status and handedness (Table 1). Individuals with schizophrenia were recruited using advertisements placed in outpatient clinics at an academic medical center, community mental health clinics in local and surrounding neighborhoods, and on local National Alliance for Mental Illness websites. Controls were recruited from the same geographic areas as the individuals with schizophrenia using paper and online advertisements. Participants were excluded if they: 1) met DSM-IV criteria for substance abuse or dependence within the past six months; 2) had a severe medical condition; or 3) sustained a head injury with neurological sequelae. Controls were further excluded if they had a lifetime history of any DSM-IV Axis I disorder or a first-degree biological relative with a psychotic disorder. Written informed consent procedures were conducted with all participants. The Institutional Review Board at Northwestern University approved all study procedures.

2.2. Measures

2.2.1. Demographic and clinical measures

Demographic and clinical measures were collected using the Structured Clinical Interview for DSM-IV (SCID-IV) (First et al., 2002), which was administered by trained Masters- and PhD-level research staff. A diagnosis of schizophrenia was validated via consensus between a semi-structured psychiatrist interview and SCID ratings. Recent alcohol and cigarette consumption were assessed using a semi-structured interview adapted from the Lifetime Alcohol Consumption Assessment Procedure (Skinner, 1982). Antipsychotic medication dosages were converted into chlorpromazine equivalents using a standardized method (Andreasen et al., 2010). Psychopathology was assessed in individuals with schizophrenia using the global ratings from the Scale for the

Table 1
Participant characteristics.

	Healthy controls ($n = 46$)	Individuals with schizophrenia ($n = 41$)	Test statistic
	Mean (SD) or %		t or $\chi 2$
Demographics			
Age	31.79 (8.56)	32.91 (6.59)	0.69
Gender (% male)	52.20	65.90	1.67
Non-Hispanic Caucasian (%)	45.70	39.00	1.44
African American (%)	39.10	51.20	
Other ethnicity (%)	15.20	9.80	
Parental socioeconomic status[a]	28.18 (9.78)	25.10 (9.40)	−1.47
Alcohol and tobacco use			
Mean (SD) alcohol use in grams, past year[b]	1248.93 (2147.34)	688.72 (1735.64)	−1.30
Mean (SD) cigarette consumption, past year[b]	281.47 (873.00)	1794.54 (2808.63)	3.23***
Clinical measures			
Duration of illness in years	–	12.87 (7.58)	
Years 1st generation antipsychotic treatment	–	0.38 (1.51)	
Years 2nd generation antipsychotic treatment	–	4.61 (3.70)	
Dosage of current antipsychotic medication (converted to milligrams of chlorpromazine)	–	510.79 (431.10)	
Hallucinations	–	2.90 (2.00)	
Delusion	–	3.10 (1.88)	
Bizarre behavior	–	1.56 (1.87)	
Positive formal thought disorder	–	2.24 (1.56)	
Affective flattening	–	3.29 (1.50)	
Alogia	–	2.49 (1.70)	
Avolition	–	3.43 (1.45)	
Anhedonia	–	3.21 (1.39)	
Attention	–	2.22 (1.85)	

[a] Completed by N = 44 CON and N = 40 SCZ.
[b] Completed by N = 45 CON and N = 39 SCZ.
*** $p < 0.001$.