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Schizophrenia symptom and functional correlates of anterior cingulate cortex activation to emotion stimuli: An fMRI investigation

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ABSTRACT

Schizophrenia is a chronic mental illness characterized by distinct positive and negative symptoms and functional impairment. The anterior cingulate cortex (ACC) is a region of the brain's limbic system that is hypoactive during emotion processing in schizophrenia. Recent evidence suggests the hypoactive ACC in schizophrenia is due to negative (and not positive) symptoms. However, this finding has not been replicated and the *functional* significance of this relationship remains unclear. The present study examined the association between positive and negative symptoms, ACC activation to emotional images, and functional outcome in schizophrenia. Specifically, 16 schizophrenia/schizoaffective disorder (SZ/SZAF) and 15 control (CON) participants underwent an fMRI scan while completing an emotional picture-rating task. SZ/SZAF participants also completed clinician-rated measures of positive and negative symptoms and functional abilities. SZ/SZAF participants with high negative symptoms had reduced ACC activation to pleasant images relative to those with low negative symptoms and CON, who did not differ. Furthermore, amongst all SZ/SZAF participants poorer social functioning was associated with decreased ACC activation to pleasant images. Finally, ACC activation partially mediated the relationship between negative symptoms and social dysfunction. These results provide evidence of the functional significance of the relationship between negative symptoms and ACC dysfunction in schizophrenia.

1. Introduction

Schizophrenia is a chronic mental illness characterized by the presence of distinct positive (e.g., delusions, hallucinations) and negative (e.g., anhedonia, avolition) symptoms (Andreasen and Olsen, 1982; Kirkpatrick et al., 2006) and significant functional disability (Bowie et al., 2006; Fulford et al., 2013; Herbener and Harrow, 2004; Milev et al., 2005). There is substantial evidence implicating emotional dysfunction as a core mechanism of schizophrenia (Kring and Elis, 2013). Indeed, schizophrenia has been associated with deficits in emotional expression (Berenbaum and Oltmanns, 1992; Kring and Neale, 1996), recognition (Mandal et al., 1999; Schneider et al., 1995), and regulation (Strauss et al., 2013; Van der Meer et al., 2009), and emotional dysfunction has been shown to contribute to persistent functional disability (Herbener et al., 2008; Kohler et al., 2010; Kring and Elis, 2013).

There has been a growing interest in identifying the neural correlates of emotional dysfunction in schizophrenia. The processing of motivationally-salient information involves a number of different cortical and subcortical regions (e.g., amygdala, prefrontal cortex, striatum; Phan et al., 2002). The anterior cingulate cortex (ACC) is a key region of the brain's limbic system that is responsible for attention and signaling salience for affective and cognitive processes (Allman et al., 2001; Bush et al., 2000). Schizophrenia has been associated with atypical functioning of the salience network, including reduced activity to salient stimuli, failure to selectively activate and suppress activity in the salience network, and reduced connectivity to brain regions responsible for processing emotional stimuli (Gradin et al., 2013; Orliac et al., 2013; White et al., 2010). Impairments in salience network functioning are also consistent with several functions subserved by the ACC, including emotional appraisal, regulation, and response generation (Etkin et al., 2011).

A number of studies have reported a hypoactive ACC during emotion processing in schizophrenia (e.g., Fallgatter et al., 2003; Reske et al., 2009; see Taylor et al., 2012 for a meta-analysis). Furthermore, a separate investigation found that greater negative (but not positive) symptom severity was associated with decreased ACC activation during an emotion processing task (Dichter

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et al., 2010). However, no other studies have examined the specificity of the relationship between schizophrenia symptoms and ACC activation to emotional stimuli.

To date, neuroimaging research has predominately focused on the association between symptoms (or syndromes) and brain activation. However, the relationship between brain activation and *functional* impairment (e.g., interpersonal or occupational difficulties) remains under-investigated. A significant exception is work by Pinkham et al. (2008), which demonstrated a positive association between frontal (e.g., mPFC, VLPFC) brain activation during a social cognition task and clinician-rated social functioning in people with schizophrenia. This kind of work is essential as it identifies potential mechanisms through which schizophrenia symptoms may contribute to functional impairment.

In the present study, we examined whether ACC activation to emotional stimuli was associated with schizophrenia symptom severity and functional impairment. Specifically, 16 individuals with schizophrenia or schizoaffective disorder (SZ/SZAF) and 15 healthy controls (CON) completed a neutral, pleasant, and unpleasant picture-rating task, and functional magnetic resonance imaging (fMRI) was used to measure ACC activation to the emotional stimuli. A previous investigation documented particular engagement of the ACC in a task, much like ours, in which participants were asked to report on their current emotional experience (Terasawa et al., 2013). SZ/SZAF participants also completed clinician-rated measures of negative and positive symptom severity and current occupational and social functioning. This study was particularly focused on the association between schizophrenia negative symptoms and ACC activation to emotional stimuli; however, we also examined positive symptoms to determine the specificity of this relationship.

The present study had four aims. First, we compared SZ/SZAF and CON participants on their ACC activation while viewing the emotional stimuli. Consistent with previous studies (Fallgatter et al., 2003; Reske et al., 2009), we hypothesized that SZ/SZAF, relative to CON, participants would demonstrate reduced ACC activation to pleasant and unpleasant stimuli. Second, in SZ/SZAF participants we examined whether individual differences in negative and positive symptom severity was associated with ACC activation to emotional stimuli. Similar to prior research (Dichter et al., 2010), we hypothesized that greater negative (but not positive) symptom severity would be associated with decreased ACC activation to pleasant and unpleasant stimuli. Third, in SZ/SZAF participants we also examined whether ACC activation to emotional stimuli was associated with clinician-rated functioning. We hypothesized that greater reductions in ACC activation would be associated with poorer functioning. Finally, in SZ/SZAF participants we tested whether ACC activation to emotional stimuli mediated the relationship between schizophrenia symptom severity and functional outcome.

2. Methods

2.1. Participants

Participants included 16 individuals who met Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV; American Psychiatric Association, 1994) criteria for schizophrenia ($n=10$) or schizoaffective disorder ($n=6$) and 15 healthy controls. Diagnoses were determined using the Structured Clinical Interview for the DSM-IV (SCID; First et al., 1997). SCID interviews were conducted by experienced doctoral-level clinicians trained to a kappa-reliability of.90. SZ/SZAF participants had been on a stable medication regimen for at least 4 weeks. CON participants had no lifetime history of any Axis I disorder or family history of schizophrenia or schizoaffective disorder in first-degree relatives. Exclusionary criteria were a history of head trauma with loss of consciousness longer than 15 minutes, substance abuse or dependence within the past 6 months, contraindication for MRI scanning, or serious medical conditions that could influence brain activity or blood flow (e.g., epilepsy). Intellectual abilities were estimated using the Wide Range Achievement Test-3rd edition (Wilkinson, 1993) and Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). SZ/SZAF participants were outpatients recruited through community advertisements, internet postings, and physician referral, and controls were recruited via community advertisements. All participants were financially compensated for their time.

2.2. Measures

2.2.1. Positive and negative syndrome scale (PANSS)

Positive and negative symptom severity in SZ/SZAF participants was measured using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The PANSS is a semi-structured clinical interview of multiple schizophrenia symptom domains, with higher scores reflecting greater severity. The present study focused on the positive symptom scale, a composite score reflecting the presence of delusions, conceptual disorganization, hallucinations, hyperactivity, grandiosity, suspiciousness/persecution, and hostility; and the negative symptom scale, a composite score encompassing blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. PANSS ratings were completed by experienced doctoral-level clinicians.

2.2.2. Quality of life scale (QLS)

Functioning in SZ/SZAF participants was measured using the Heinrichs-Carpenter Quality of Life Scale (QLS; Heinrichs et al., 1984).[1] The QLS is a semi-structured interview yielding composite scores in several domains, with higher scores reflecting a better quality of life (i.e., greater functioning). The present study assessed interpersonal relations (i.e., social functioning), a composite score reflecting frequency of social contact as well as capacity for intimacy, active versus passive social participation, and avoidance or withdrawal tendencies; and instrumental role (i.e., occupational functioning), a score measuring the extent of functioning as a worker, student, or housekeeper/parent as well as level of accomplishment, degree of underemployment, and satisfaction with the current role.

2.3. Procedure

Data were taken from a larger project examining the neural correlates of emotional memory in schizophrenia. The present study focused on data collected during the initial encoding phase and differed from a previous investigation that examined SZ/SZAF neural response to specific image content (Bjorkquist and Herbener, 2013). All participants completed an emotional picture-rating task using neutral, pleasant, and unpleasant images selected from the International Affective Picture System (IAPS; Lang et al., 2008).[2] Mutilation and erotica images were excluded to reduce the

[1] Only SZ/SZAF participants completed the QLS because controls were expected to produce minimal variance

[2] Pleasant and unpleasant images from the IAPS library were matched on arousal level based on normative ratings. The following IAPS images were used for the neutral, pleasant, and unpleasant categories: neutral (1230, 1303, 1310, 2210, 2215, 2230, 2280, 2381, 2410, 2480, 2485, 2495, 2516, 2518, 2575, 2850, 2870, 2880, 2890, 4534, 4571, 4605, 5534, 5535, 5731, 7185, 7187, 7205, 7283, 7491, 7590, 7830,