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Schizophrenia Symptom and Functional Correlates of Anterior Cingulate Cortex Activation to Emotion Stimuli: An fMRI Investigation

Brady D. Nelson^{a,*}, Olivia A. Bjorkquist^b, Emily K. Olsen^b, and Ellen S. Herbener^{b,c}

^aDepartment of Psychology, Stony Brook University, Stony Brook, NY, USA

^bDepartment of Psychology, University of Illinois-Chicago, Chicago, IL, USA

^cDepartment of Psychiatry, University of Illinois-Chicago, Chicago, IL, USA

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.

Keywords

anterior cingulate; emotion; fMRI; functioning; negative symptoms; schizophrenia

Correspondence concerning this article should be addressed to Brady D. Nelson, Department of Psychology, Stony Brook University, Stony Brook, NY, 11794. Phone: 631-632-7697; Fax: 631-632-7876; brady.nelson@stonybrook.edu.

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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 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; APA, 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 chance that participants would be disturbed from the images and to increase ecological validity of the stimuli. Images were presented for 4 s each in blocks of 12, and each block contained images of just one valence. The task consisted of 3 blocks of each valence, for a total of 36 neutral, 36 pleasant, and 36 unpleasant images. During the presentation of each image, participants rated the intensity of their emotional

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

²Pleasant 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, 8010, 8311, 9070, 9411), pleasant (1340, 1463, 1540, 1590, 1811, 1340, 1463, 1540, 1590, 2040, 2070, 2165, 2208, 2340, 2345, 2530, 2540, 2650, 4614, 4640, 4641, 5270, 5480, 5594, 5629, 5700, 5982, 7230, 7330, 7502, 7580, 8034, 8120, 8185, 8210, 8370, 8400, 8420, 8496, 8540), and unpleasant (2205, 2700, 2800, 3300, 3301, 5971, 6020, 6200, 6213, 6242, 6360, 6370, 6571, 6821, 6830, 6838, 7380, 9001, 9040, 9050, 9090, 9160, 9290, 9330, 9340, 9373, 9390, 9415, 9417, 9421, 9430, 9520, 9530, 9560, 9622, 9911).

experience, low (none to low) or high (moderate to strong), via button press. In-between blocks a 10-s fixation cross was presented to allow brain activity to return to baseline.

Structural and functional scans were acquired on a 3 Tesla scanner (Signa, General Electric Medical System, Milwaukee, Wisconsin) at the University of Illinois Medical Center. The functional scan was acquired using a gradient-echo echo-planar imaging (EPI) series with a 2000 ms TR, 25 ms TE, 90° flip angle, 200 mm, field of view, 64 X 64 mm matrix, 3 mm slice thickness, 1 mm gap, for 33 axial slices. Data were processed using Analysis of Functional Neuroimages (AFNI) software. 3D volume registration program was used to correct for motion across individual participants' time series. Individual data were spatially smoothed using a 5-mm full-width half-maximum Gaussian filter and then deconvolved to obtain per-voxel fit coefficients corresponding to blood-oxygenation-level dependent response for each condition. Images were normalized to stereotaxic space (Talairach and Tournoux, 1988) to correct for individual neuroanatomical variation.

To examine ACC activation, we used an anatomically-derived ROI mask that was obtained from researchers with extensive experience creating masks over this region (see Figure 1; Pavuluri et al., 2012, 2009). The ROI mask was created in Talairach space using AFNI software, and separate masks were used for the left (8678 voxels) and right (8092 voxels) ACC (further details regarding ROI creation and boundaries are available upon request). To quantify ACC activation, we calculated peak intensity using AFNI's 3dROIstats program and used two separate contrasts – pleasant vs. neutral and unpleasant vs. neutral. Peak intensity was calculated separately for the left and right ACC masks, and the values were averaged together to create a bilateral measure of peak ACC activation.

2.4. Data Analysis

Two SZ/SZAF participants were excluded from all analyses due to missing QLS data ($n = 1$) or outlier ACC activation values (> 3 standard deviations above the mean; $n = 1$). In addition to ACC activation, we also examined behavioral ratings (i.e., intensity of emotional ratings) during the picture-rating task. Intensity of emotional ratings ranged from 1 (none to low) to 2 (moderate to strong) for neutral, pleasant, and unpleasant images, and, similar to the fMRI contrasts, difference scores (i.e., pleasant – neutral, unpleasant – neutral) were used to examine the increase in response due to the emotional content of the image. One SZ/SZAF participant was excluded from behavioral analyses due to difficulty using the button box.

Diagnostic (SZ/SZAF vs. CON) group differences in demographics were examined using a χ^2 test for categorical variables and a one-way analysis of variance (ANOVA) for continuous variables. Group differences in ACC activation and behavioral ratings were also examined using a one-way ANOVA and separate analyses were conducted for pleasant vs. neutral and unpleasant vs. neutral contrasts. Within SZ/SZAF participants, Pearson's correlations were conducted to examine the association between the PANSS and QLS measures and ACC activation and behavioral ratings to emotional stimuli. All analyses were conducted in IBM SPSS Statistics, Version 22.0 (Armonk, NY, USA).

3. Results

3.1. Diagnostic Group Differences

3.1.1. Demographics and clinical characteristics—Table 1 presents demographics for SZ/SZAF and CON participants, who were matched on age, sex, race, education, and estimated intellectual abilities. Within the SZ/SZAF group, schizophrenia participants had lower education ($M = 12.20$, $SD = 2.66$), WRAT-3 Word Reading ($M = 95.60$, $SD = 14.59$), and WASI scores ($M = 99.10$, $SD = 12.64$) relative to schizoaffective disorder participants ($M = 16.67$, $SD = 2.66$), $F(1, 14) = 10.18$, $p < .01$, $\eta_p^2 = .42$; ($M = 110.50$, $SD = 4.46$), $F(1, 14) = 5.78$, $p < .05$, $\eta_p^2 = .29$; ($M = 114.50$, $SD = 5.36$), $F(1, 14) = 7.87$, $p < .05$, $\eta_p^2 = .36$, respectively. The schizophrenia and schizoaffective participants did not differ in any other demographic, PANSS symptoms, or QLS scores ($ps > .18$).

3.1.2. ACC activation—A one-sample t-test of the pleasant vs. neutral, $t(28) = 14.48$, $p < .001$, and unpleasant vs. neutral, $t(28) = 9.10$, $p < .001$, contrasts indicated they significantly differed from 0, suggesting ACC activation was greater during pleasant and unpleasant relative to neutral images. There were no diagnostic group differences in ACC activation for either pleasant, $F(1, 27) = 0.11$, ns , $\eta_p^2 < .01$, or unpleasant images, $F(1, 27) = 0.10$, ns , $\eta_p^2 < .01$. There were also no group differences when separate analyses were conducted for the left and right ACC ($ps > .64$).

3.1.3. Behavioral ratings—A one-sample t-test of the pleasant vs. neutral, $t(27) = 6.51$, $p < .001$, and unpleasant vs. neutral, $t(27) = 9.97$, $p < .001$, difference scores indicated they significantly differed from 0, suggesting participants reported greater emotional intensity for pleasant and unpleasant relative to neutral images. In addition, across all participants greater emotional intensity to the pleasant images was associated with increased ACC activation to pleasant images, $r(28) = .51$, $p < .01$; however, there was no association between emotional intensity and ACC activation to unpleasant images, $r(28) = -.16$, ns .

SZ/SZAF participants ($M = 0.31$, $SD = 0.17$) had decreased emotional intensity ratings relative to CON participants ($M = 0.48$, $SD = 0.22$) for unpleasant images, $F(1, 26) = 5.17$, $p < .05$, $\eta_p^2 = .17$; however, there were no group differences for pleasant images, $F(1, 26) = 0.72$, ns , $\eta_p^2 = .03$.

3.2. Correlations within SZ/SZAF Participants

3.2.1. ACC activation—Table 2 displays correlation coefficients for the association between the PANSS, QLS, ACC activation, and behavioral ratings to emotional stimuli in SZ/SZAF participants. As expected, greater PANSS positive symptoms were associated with poorer QLS instrumental role and greater PANSS negative symptoms were associated with poorer QLS instrumental role and interpersonal relationships. In addition, greater PANSS negative symptoms were associated with decreased ACC activation to pleasant images (see top of Figure 2), and decreased ACC activation to pleasant images was associated with poorer QLS interpersonal relationships (see bottom of Figure 2). There were no associations between PANSS positive symptoms or QLS instrumental role and ACC activation to pleasant or unpleasant images ($ps > .35$).³

Given the association between PANSS negative symptoms and ACC activation to pleasant images, we examined whether CON participants differed from SZ/SZAF participants with high (but not low) negative symptoms. To this end, we conducted a median split (median = 19) and dichotomized schizophrenia participants into those with low ($n = 7$; $M = 13.43$, $SD = 4.08$) vs. high ($n = 7$; $M = 22.57$, $SD = 2.07$) negative symptoms. While there are inherent statistical weaknesses associated with artificially dichotomizing a continuous variable (MacCallum et al., 2002), these analyses were conducted to re-examine potential group differences in ACC activation. SZ/SZAF participants in the high and low negative symptom groups were comparable on all demographics ($ps > .40$). As shown in Figure 3, a one-way ANOVA with diagnosis (SZ/SZAF with high negative symptoms, SZ/SZAF with low negative symptoms, and CON) as the between-subjects factor indicated that these three groups differed in ACC activation to pleasant images, $F(2, 26) = 4.57$, $p < .05$, $\eta_p^2 = .26$, such that SZ/SZAF participants with high negative symptoms had reduced brain activation relative to CON and SZ/SZAF participants with low negative symptoms ($ps < .05$), who did not differ ($p = .16$).

3.2.2. Behavioral ratings—As shown in Table 2, there were no associations between the emotional intensity ratings and either PANSS or QLS measures ($ps > .22$).

3.3. Mediation Analyses

To test whether ACC activation to pleasant images mediated the relationship between PANSS negative symptoms and QLS interpersonal relationships in SZ/SZAF participants, we followed MacKinnon and colleagues (2004) recommendations and used a nonparametric bootstrapping method. Mediation models were tested using the SPSS macro PROCESS provided by Hayes (2013), which provides a bootstrap estimate of the indirect effect between the independent variable and dependent variable and 95% confidence intervals (CIs) for the population value of the indirect effect. CIs for the indirect effect that do not include zero are significant at $p < .05$. Direct and indirect effects were tested using 5,000 bootstrap samples. All variables were z-transformed to produce standardized β weights.

Results indicated that the mediation model (see Figure 4) accounted for significant variance in QLS interpersonal relationships, $R^2 = .89$, $F = 20.49$, $p < .001$. Greater PANSS negative symptoms were associated with decreased ACC activation to pleasant images, and decreased ACC activation was in turn associated with poorer QLS interpersonal relationships. Greater PANSS negative symptoms were also directly associated with poorer QLS interpersonal relationships. Most importantly, analyses indicated that there was a significant indirect association between PANSS negative symptoms and QLS interpersonal relationships, mediated through ACC activation to pleasant images (95% CIs: -0.75 to -0.05), and the

³We also examined the association between ACC activation to pleasant images and PANSS negative symptoms and QLS interpersonal relationships separately for the left and right hemisphere. Results indicated that PANSS negative symptoms were negatively associated with right ACC activation, $r(14) = -.62$, $p < .05$, and left ACC activation at a trend level, $r(14) = -.45$, $p = .11$, and QLS interpersonal relationships were positively associated with right ACC activation, $r(14) = .82$, $p < .001$, and left ACC activation, $r(14) = .53$, $p = .05$. Importantly, a Fisher r-to-z transformation indicated the association between PANSS negative symptoms and left and right ACC activation, $z = -0.56$, $p = .58$, and QLS interpersonal relationships and left and right ACC activation, $z = 1.33$, $p = .18$, did not differ. Therefore, we used the average of the left and right peak ACC activation for all subsequent analyses.

indirect effect remained significant even after controlling for PANSS positive symptoms (95% CIs: -1.16 to -0.01).

4. Discussion

The present study examined whether ACC activation to emotional stimuli was associated with schizophrenia symptom severity and functional impairment. Results indicated that 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. In SZ/SZAF participants, greater negative (but not positive) symptoms were associated with decreased ACC activation to pleasant (but not unpleasant) stimuli. Moreover, decreased ACC activation to pleasant stimuli was also associated with poorer social functioning. Finally, we found a significant mediational effect in SZ/SZAF participants, such that ACC activation to pleasant stimuli partially mediated the relationship between negative symptoms and social functioning.

These results add to a growing literature indicating reduced ACC activation during emotional processing in schizophrenia (Fallgatter et al., 2003; Reske et al., 2009). Furthermore, these findings replicate a previous study that found more severe avolition and anhedonia (i.e., negative symptoms) were associated with decreased ACC activation to pleasant (but not unpleasant) stimuli in schizophrenia participants while engaged in an emotional processing task (Dichter et al., 2010). Notably, in the present study there were no associations between negative symptoms and ACC activation to negative images. This is consistent with a previous investigation that reported a significant relationship between anhedonia (a component of negative symptoms) and decreased activity in the striatum and amygdala regions typically involved in indicating stimulus salience - in response to positive relative to negative stimuli in individuals with schizophrenia (Dowd and Barch, 2010). It is possible that other features (e.g., thought disorder) or comorbid conditions (e.g., depression) may contribute to abnormalities in the processing of negative emotional information. Future studies are needed to better understand the potential differential role the ACC plays during the processing of valenced stimuli in schizophrenia.

As part of the midline 'default mode network', the ACC in particular has been shown to be active in internally directed mental activities, such as retrieving autobiographical memories, self-referential thinking, and monitoring one's own emotional state (Amodio and Frith, 2006; Ochsner et al., 2004). Indeed, previous research using a similar experimental task in which participants were asked to report on their current emotional experience found engagement of the ACC (Terasawa et al., 2013). The present study is consistent with the notion that higher levels of negative symptoms are associated with greater difficulty engaging in internally-directed mental processes, including the assessment of positive emotional experience, and in utilizing such information to optimize their behavioral response in the pursuit of social functioning. Specifically, individuals with high negative symptoms may under appraise the motivational-salience of positive information or have difficulty generating an adaptive response, which in turn may impact social interactions and the development of meaningful relationships. Together, this evidence supports the ACC as a potential brain-based target for psychological or pharmacological treatments that attempt to

ameliorate the highly resistant negative symptoms (Buchanan, 2007; Leucht et al., 2009; Levine and Leucht, 2013).

The present study had several limitations that warrant consideration. First, both the schizophrenia ($n = 16$) and control ($n = 15$) samples were relatively small and may have limited our ability to identify overall group differences in ACC activation. We also used an *a priori*, theoretically-driven ROI approach, and it is likely that other brain regions outside the scope of this study may be associated with negative symptoms and functional outcomes in schizophrenia. Second, all measures were collected cross-sectionally and prospective studies are needed to determine the causal relationship between these variables. Third, in an effort to maximize ecological validity, we excluded extreme, high arousal stimuli (e.g., mutilated bodies, erotic images) from our picture-rating task. Many emotion studies using IAPS stimuli include such images, and this decreases the comparability of our results with studies using more arousing stimuli. Inclusion of extreme stimuli would likely elicit increased limbic brain response and perhaps lead to different results. Finally, a majority of the SZ/SZAF participants were taking antipsychotic medication and were heterogeneous in medication usage. Therefore, medication effects may have influenced results for both between group and within schizophrenia analyses. However, most schizophrenia patients under psychiatric care are treated with antipsychotic medication, so our results provide information about the relationship between negative symptoms, ACC activation to emotional stimuli, and functional outcome under typical life circumstances.

In conclusion, the present study adds to a growing literature addressing relationships between clinical presentation, brain response, and functional performance in people with schizophrenia. Our results suggest that decreased neural processing of positive stimuli in the ACC may be one potential mechanism through which negative symptoms influence greater functional impairment. Future studies are needed to better understand how schizophrenia symptoms relate to other limbic and regulatory neural circuits, how those brain-behavior relationships contribute to persistent functional disability, and whether targeting disrupted neural circuits as opposed to clinical symptoms improves treatment efforts (Lewis and Sweet, 2009).

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References

- Allman JM, Hakeem A, Erwin JM, Nimchinsky E, Hof P. The anterior cingulate cortex. The evolution of an interface between emotion and cognition. *Ann N Y Acad Sci.* 2001; 935:107–117.10.1111/j.1749-6632.2001.tb03476.x [PubMed: 11411161]
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4. 1994.
- Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci.* 2006; 7:268–277.10.1038/nrn1884 [PubMed: 16552413]
- Andreasen NC, Olsen S. Negative v positive schizophrenia. Definition and validation. *Arch Gen Psychiatry.* 1982; 39:789–794.10.1001/archpsyc.1982.04290070025006 [PubMed: 7165478]

- Berenbaum H, Oltmanns TF. Emotional experience and expression in schizophrenia and depression. *J Abnorm Psychol.* 1992; 101:37–44.10.1037/0021-843X.101.1.37 [PubMed: 1537971]
- Bjorkquist, Oa; Herbener, ES. Social perception in schizophrenia: Evidence of temporo-occipital and prefrontal dysfunction. *Psychiatry Res - Neuroimaging.* 2013; 212:175–182.10.1016/j.psychres.2012.12.002
- Bowie CR, Reichenberg A, Patterson TL, Heaton RK, Harvey PD. Determinants of real-world functional performance in schizophrenia subjects: Correlations with cognition, functional capacity, and symptoms. *Am J Psychiatry.* 2006; 163:418–425.10.1176/appi.ajp.163.3.418 [PubMed: 16513862]
- Buchanan RW. Persistent negative symptoms in schizophrenia: An overview. *Schizophr Bull.* 2007; 33:1013–1022.10.1093/schbul/sbl057 [PubMed: 17099070]
- Bush G, Luu P, Posner M. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci.* 2000; 4:215–222.10.1016/S1364-6613(00)01483-2 [PubMed: 10827444]
- Dichter GS, Bellion C, Casp M, Belger A. Impaired modulation of attention and emotion in schizophrenia. *Schizophr Bull.* 2010; 36:595–606.10.1093/schbul/sbn118 [PubMed: 18843096]
- Dowd EC, Barch DM. Anhedonia and Emotional Experience in Schizophrenia: Neural and Behavioral Indicators. *Biol Psychiatry.* 2010; 67:902–911.10.1016/j.biopsych.2009.10.020 [PubMed: 20004364]
- Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci.* 2011; 15:85–93.10.1016/j.tics.2010.11.004 [PubMed: 21167765]
- Fallgatter AJ, Bartsch AJ, Zielasek J, Herrmann MJ. Brain electrical dysfunction of the anterior cingulate in schizophrenic patients. *Psychiatry Res - Neuroimaging.* 2003; 124:37–48.10.1016/S0925-4927(03)00072-6
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). 1997.
- Fulford D, Niendam TA, Floyd EG, Carter CS, Mathalon DH, Vinogradov S, Stuart BK, Loewy RL. Symptom dimensions and functional impairment in early psychosis: More to the story than just negative symptoms. *Schizophr Res.* 2013; 147:125–131.10.1016/j.schres.2013.03.024 [PubMed: 23587696]
- Gradin VB, Waiter G, O'Connor A, Romaniuk L, Stickle C, Matthews K, Hall J, Douglas Steele J. Salience network-midbrain dysconnectivity and blunted reward signals in schizophrenia. *Psychiatry Res - Neuroimaging.* 2013; 211:104–111.10.1016/j.psychres.2012.06.003
- Hayes, A. Introduction to mediation, moderation, and conditional process analysis. New York, NY: Guilford; 2013. 978-1-60918-230-4
- Heinrichs DW, Hanlon TE, Carpenter WT. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull.* 1984; 10:388–398.10.1093/schbul/10.3.388 [PubMed: 6474101]
- Herbener ES, Harrow M. Are negative symptoms associated with functioning deficits in both schizophrenia and nonschizophrenia patients? A 10-year longitudinal analysis. *Schizophr Bull.* 2004; 30:813–825. [PubMed: 15957198]
- Herbener ES, Song W, Khine TT, Sweeney JA. What aspects of emotional functioning are impaired in schizophrenia? *Schizophr Res.* 2008; 98:239–246.10.1016/j.schres.2007.06.025 [PubMed: 17689054]
- Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987; 13:261–76. [PubMed: 3616518]
- Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The NIMH-MATRICES consensus statement on negative symptoms. *Schizophr Bull.* 2006; 32:214–219.10.1093/schbul/sbj053 [PubMed: 16481659]
- Kohler CG, Walker JB, Martin EA, Healey KM, Moberg PJ. Facial emotion perception in schizophrenia: A meta-analytic review. *Schizophr Bull.* 2010; 36:1009–1019.10.1093/schbul/sbn192 [PubMed: 19329561]
- Kring AM, Elis O. Emotion deficits in people with schizophrenia. *Annu Rev Clin Psychol.* 2013; 9:409–33.10.1146/annurev-clinpsy-050212-185538 [PubMed: 23245340]

- Kring AM, Neale JM. Do schizophrenic patients show a disjunctive relationship among expressive, experiential, and psychophysiological components of emotion? *J Abnorm Psychol.* 1996; 105:249–257.10.1037/0021-843X.105.2.249 [PubMed: 8723006]
- Lang, P.; Bradley, M.; Cuthbert, B. Technical Report A-8. 2008. International affective picture system (IAPS): Affective ratings of pictures and instruction manual.
- Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet.* 2009; 373:31–41.10.1016/S0140-6736(08)61764-X [PubMed: 19058842]
- Levine SZ, Leucht S. Attaining and sustaining remission of predominant negative symptoms. *Schizophr Res.* 2013; 143:60–64.10.1016/j.schres.2012.11.010 [PubMed: 23218563]
- Lewis DA, Sweet RA. Schizophrenia from a neural circuitry perspective: Advancing toward rational pharmacological therapies. *J Clin Invest.* 2009; 119:706–716.10.1172/JCI37335 [PubMed: 19339762]
- MacCallum RC, Zhang S, Preacher KJ, Rucker DD. On the practice of dichotomization of quantitative variables. *Psychol Methods.* 2002; 7:19–40.10.1037/1082-989X.7.1.19 [PubMed: 11928888]
- MacKinnon DP, Lockwood CM, Williams J. Confidence limits for the indirect effect: Distribution of the product and resampling methods. *Multivariate Behav Res.* 2004; 39:99–128.10.1207/s15327906mbr3901_4 [PubMed: 20157642]
- Mandal MK, Jain A, Haque-Nizamie S, Weiss U, Schneider F. Generality and specificity of emotion-recognition deficit in schizophrenic patients with positive and negative symptoms. *Psychiatry Res.* 1999; 87:39–46.10.1016/S0165-1781(99)00047-5 [PubMed: 10512153]
- Milev P, Ho BC, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: A longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry.* 2005; 162:495–506.10.1176/appi.ajp.162.3.495 [PubMed: 15741466]
- Ochsner KN, Knierim K, Ludlow DH, Hanelin J, Ramachandran T, Glover G, Mackey SC. Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. *J Cogn Neurosci.* 2004; 16:1746–1772.10.1162/0898929042947829 [PubMed: 15701226]
- Orliac F, Naveau M, Joliot M, Delcroix N, Razafimandimby A, Brazo P, Dollfus S, Delamillieure P. Links among resting-state default-mode network, salience network, and symptomatology in schizophrenia. *Schizophr Res.* 2013; 148:74–80.10.1016/j.schres.2013.05.007 [PubMed: 23727217]
- Pavuluri MN, Passarotti AM, Fitzgerald JM, Wegbreit E, Sweeney JA. Risperidone and divalproex differentially engage the fronto-striato-temporal circuitry in pediatric mania: A pharmacological functional magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry.* 2012; 51:157–170.10.1016/j.jaac.2011.10.019 [PubMed: 22265362]
- Pavuluri MN, Passarotti AM, Harral EM, Sweeney JA. An fMRI study of the neural correlates of incidental versus directed emotion processing in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2009; 48:308–319. <http://dx.doi.org/10.1097/CHI.0b013e3181948fc7>. [PubMed: 19242292]
- Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage.* 2002; 16:331–348.10.1006/nimg.2002.1087 [PubMed: 12030820]
- Pinkham AE, Hopfinger JB, Ruparel K, Penn DL. An investigation of the relationship between activation of a social cognitive neural network and social functioning. *Schizophr Bull.* 2008; 34:688–697.10.1093/schbul/sbn031 [PubMed: 18477583]
- Reske M, Habel U, Kellermann T, Backes V, Jon Shah N, von Wilmsdorff M, Gaebel W, Zilles K, Schneider F. Differential brain activation during facial emotion discrimination in first-episode schizophrenia. *J Psychiatr Res.* 2009; 43:592–599.10.1016/j.jpsychires.2008.10.012 [PubMed: 19056093]
- Schneider F, Gur RC, Gur RE, Shtasel DL. Emotional processing in schizophrenia: neurobehavioral probes in relation to psychopathology. *Schizophr Res.* 1995; 17:67–75.10.1016/0920-9964(95)00031-G [PubMed: 8541252]
- Strauss GP, Kappenman ES, Culbreth AJ, Catalano LT, Lee BG, Gold JM. Emotion regulation abnormalities in schizophrenia: Cognitive change strategies fail to decrease the neural response to

- unpleasant stimuli. *Schizophr Bull.* 2013; 39:872–883.10.1093/schbul/sbs186 [PubMed: 23314192]
- Talairach, J.; Tournoux, P. *Co-Planar Stereotaxis Atlas of the Human Brain*, Direct. 1988.
- Taylor SF, Kang J, Brege IS, Tso IF, Hosanagar A, Johnson TD. Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. *Biol Psychiatry.* 2012; 71:136–145.10.1016/j.biopsych.2011.09.007 [PubMed: 21993193]
- Terasawa Y, Fukushima H, Umeda S. How does interoceptive awareness interact with the subjective experience of emotion? An fMRI Study *Hum Brain Mapp.* 2013; 34:598–612.10.1002/hbm.21458
- Van der Meer L, van't Wout M, Aleman A. Emotion regulation strategies in patients with schizophrenia. *Psychiatry Res.* 2009; 170:108–113.10.1016/j.psychres.2009.07.010 [PubMed: 19906439]
- Wechsler, D. *Wechsler Abbreviated Scale of Intelligence*. Psychological Corporation; San Antonio, TX: 1999.
- White TP, Joseph V, Francis ST, Liddle PF. Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. *Schizophr Res.* 2010; 123:105–115.10.1016/j.schres.2010.07.020 [PubMed: 20724114]
- Wilkinson, GS. *Wide Range Achievement Test. 3.* Wide Range Inc; Austin, TX: 1993.

- Examined ACC activation, schizophrenia symptoms, and functional impairment
- Negative symptoms associated with decreased ACC activation to pleasant images
- Decreased ACC activation to pleasant images associated with social impairment
- ACC activation mediated negative symptom-social impairment relationship
- Indicates functional significance of negative symptom-ACC dysfunction relationship

Figure 1.
ROI template for the ACC
ACC = anterior cingulate cortex; ROI = region of interest.

Figure 2.

Scatterplots depicting the relationship between peak ACC activation to pleasant images and PANSS negative symptoms (top) and QLS interpersonal relationships (bottom) in SZ/SZAF participants. ACC = anterior cingulate cortex; PANSS = Positive and Negative Syndrome Scale; QLS = Quality of Life Scale; SZ/SZAF = schizophrenia/schizoaffective disorder.

Figure 3.

Diagnostic group differences between controls and SZ/SZAF participants with low vs. high negative symptoms in peak ACC activation to pleasant images. SZ/SZAF participants with high ($n = 7$) vs. low ($n = 7$) negative symptoms were determined using a median split (median = 19) on the PANSS negative symptoms. Error bars represent standard error. ACC = anterior cingulate cortex; PANSS = Positive and Negative Syndrome Scale; SZ/SZAF = schizophrenia/schizoaffective disorder.

Figure 4.

Results of mediation analyses between PANSS negative symptoms, peak ACC activation to pleasant images, and QLS interpersonal relationships in SZ/SZAF participants. Coefficients are standardized regression weights. a = association between X and M ; ab = indirect effect of X on Y ; ACC = anterior cingulate cortex; b = association between M and Y ; c = total effect of X on Y ; c' = direct effect of X on Y ; M = mediator variable; PANSS = Positive and Negative Syndrome Scale; QLS = Quality of Life Scale; SZ/SZAF = schizophrenia/schizoaffective disorder; X = independent variable; Y = dependent variable.

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 1

Demographics of Schizophrenia/Schizoaffective Disorder and Control Participants

	SZ/SZAF (<i>n</i> = 14)	CON (<i>n</i> = 15)	<i>F</i> or χ^2	<i>p</i>
Age (<i>SD</i>)	33.4 (9.3)	31.9 (11.2)	<i>F</i> = 0.15	.70
Sex (% male)	71.4%	60.0%	χ^2 = 0.42	.52
Race			χ^2 = 1.66	.20
Caucasian	35.7%	20.0%		
Black	35.7%	66.7%		
Asian	7.1%	13.3%		
Latino	21.4%	0.0%		
Years of Education (<i>SD</i>)	13.5 (3.4)	13.6 (1.6)	<i>F</i> = 0.01	.92
Estimated Intelligence				
WRAT-3 Word Reading (<i>SD</i>)	99.7 (14.1)	95.4 (10.9)	<i>F</i> = 0.86	.36
WASI (<i>SD</i>)	102.9 (12.5)	100.1 (14.5)	<i>F</i> = 0.31	.59
PANSS Positive	18.1 (4.8)	-	-	-
PANSS Negative	18.0 (5.7)	-	-	-
QLS Interpersonal Relationships	24.1 (8.3)	-	-	-
QLS Instrumental Role	11.9 (6.6)	-	-	-
Medication				
Any medication	78.6%	-	-	-
Typical antipsychotic	21.4%	-	-	-
Atypical antipsychotic	64.3%	-	-	-
Antidepressant	28.6%	-	-	-
Stimulant	0.0%	-	-	-
Mood stabilizer	7.1%	-	-	-
Sedative/hypnotic	14.3%	-	-	-

Note. WRAT-3 and WASI were index standard scores (*M* = 100, *SD* = 15). CON = controls; QLS = Quality of Life Scale; *SD* = standard deviation; SZ/SZAF = schizophrenia/schizoaffective disorder; WASI = Wechsler Abbreviated Scale of Intelligence; WRAT-3 = Wide Range Achievement Test 3rd Edition.

Table 2

Correlation Coefficients between the PANSS, QLS, and ACC Activation and Intensity Ratings to Emotional Stimuli in Schizophrenia/Schizoaffective Disorder Participants

	1	2	3	4	5	6	7	8
1. PANSS Positive	-	.62*	-.45	-.74**	-.27	-.07	.01	-.19
2. PANSS Negative			-	-.83***	-.67**	.15	-.15	-.37
3. QLS Interpersonal Relationships				.39	.75**	.01	.07	.37
4. QLS Instrumental Role				-	.28	-.21	.15	.26
5. ACC Activation to Pleasant					-	.06	.54+	.28
6. ACC Activation to Unpleasant						-	.11	-.38
7. Intensity Rating to Pleasant							-	-.38
8. Intensity Rating to Unpleasant								-

Note. Intensity of emotional ratings ranged from 1 (none to low) to 2 (moderate to strong) for neutral, pleasant, and unpleasant images. ACC activation and intensity ratings to pleasant and unpleasant stimuli were calculated using difference scores that included response to neutral stimuli as the comparison condition (i.e., pleasant – neutral, unpleasant – neutral). ACC = anterior cingulate cortex; *M* = mean; PANSS = Positive and Negative Syndrome Scale; QLS = Quality of Life Scale; *SD* = standard deviation.

+ $p < .10$.

* $p < .05$.

** $p < .01$.

*** $p < .001$.