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Disconnection Between Amygdala and Medial Prefrontal Cortex in Psychotic Disorders

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Distracting emotional information impairs attention more in schizophrenia (SCZ) than in never-psychotic individuals. However, it is unclear whether this impairment and its neural circuitry is indicative generally of psychosis, or specifically of SCZ, and whether it is even more specific to certain SCZ symptoms (eg, deficit syndrome). It is also unclear if this abnormality contributes to impaired behavioral performance and real-world functioning. Functional imaging data were recorded while individuals with SCZ, bipolar disorder with psychosis (BDP) and no history of psychotic disorders (CON) attended to identity of faces while ignoring their emotional expressions. We examined group differences in functional connectivity between amygdala, involved in emotional evaluation, and sub-regions of medial prefrontal cortex (MPFC), involved in emotion regulation and cognitive control. Additionally, we examined correlation of this connectivity with deficit syndrome and real-world functioning. Behaviorally, SCZ showed the worst accuracy when matching the identity of emotional vs neutral faces. Neurally, SCZ showed lower amygdala-MPFC connectivity than BDP and CON. BPD did not differ from CON, neurally or behaviorally. In patients, reduced amygdala-MPFC connectivity during emotional distractors was related to worse emotional vs neutral accuracy, greater deficit syndrome severity, and unemployment. Thus, reduced amygdala-MPFC functional connectivity during emotional distractors reflects a deficit that is specific to SCZ. This reduction in connectivity is associated with worse clinical and real-world functioning. Overall, these findings provide support for the specificity and clinical utility of amygdala-MPFC functional connectivity as a potential neural marker of SCZ.

Key words: emotion/attention/psychosis/schizophrenia/bipolar/fMRI/connectivity

Introduction

Psychotic disorders including schizophrenia (SCZ) and bipolar disorder with psychosis (BDP) are characterized by deficits in cognitive control.[1] When multiple input dimensions compete for processing access, cognitive control biases attention selectively towards the task-relevant dimension.[2–4] Both selective attention to task relevant aspects of stimuli and inhibition of distractor interference are impaired in psychotic disorders.[5–9] Emotionally salient stimuli that signal potential danger or reward constitute a particularly potent class of distractors that can hijack attentional resources and impair task-relevant processing.[10–13] Neural and behavioral evidence from several studies indicates that emotional (vs neutral) stimuli interfere with processing of task relevant stimuli in psychotic disorders,[14–17] more so than in healthy individuals.

While mounting evidence indicates that the interaction of emotion and attention may play an important role in SCZ,[18–20] the specificity and clinical utility of measures of emotion-related attentional impairment and their underlying neural circuitry remains unclear. For example, studies have not compared disorders directly to test whether emotion interference deficits are unique to SCZ or reflect deficits shared by SCZ and BDP. Furthermore, it is not known whether behavioral or neural markers of emotion-cognition interactions relate to specific symptom dimensions or impaired real-world functioning. An examination of these questions will help shed light on the shared vs distinct etiology of SCZ and BDP, and also determine the potential clinical utility of behavioral and neural measures of emotion-cognition interaction. Here, we used functional magnetic resonance imaging (fMRI) to examine neural mechanisms of emotional interference in SCZ, BDP, and a never-psychotic group during a task

that required attention to a task-relevant dimension (face identity) while ignoring the task-irrelevant dimension (emotional expression).

Maintaining attentional control in the presence of distracting emotional information involves a network of brain regions acting in concert. These regions (figure 1) include the amygdala, which is involved in processing saliency of emotional stimuli,[10,21] as well as anterior cingulate cortex (ACC) and medial prefrontal cortex (MPFC), which are involved in emotion appraisal and regulation.[22] More specifically, the dorsal-caudal regions of ACC (dACC) and MPFC (dMPFC) are involved in monitoring difficulty posed due to competition between choices,[4,23–25] including monitoring of emotion-related competition.[25–28] In contrast, the ventral-rostral portions of ACC (rACC) and MPFC (rMPFC) are involved in regulating emotional conflict,[27,29] directing attention away from irrelevant emotional information,[30,31] and modulating emotional response via strategies such as reappraisal.[32–34]

Anatomically, the amygdala is well connected with rostral and dorsal portions of the ACC, particularly the rostral portion.[35–39] However anatomical connections to the adjacent regions of dMPFC and rMPFC are fewer.[36,37,39] Functionally, amygdala shows strong connectivity with the ACC and MPFC during tasks that require appraisal or regulation of emotional stimuli[22] and the degree of this functional coupling is positively correlated with effectiveness of self-reported emotion regulation.[32] Evaluating functional connectivity of amygdala with the dorsal and rostral ACC and MPFC, thus, provides an ideal focus for examining the disruption of task-relevant processing due to distracting emotional information in psychotic disorders.

In the present study, we used psychophysiological interaction (PPI) analysis to investigate whether amygdala functionally couples with the rostral and dorsal ACC and MPFC when participants attend to face identity while ignoring facial expressions. PPI estimates connectivity from a seed region to the whole brain in response to changes in psychological conditions.[40–42] Compared to controls, individuals with SCZ and BDP show greater deficits in attention towards the task-relevant dimension in the presence of the task-irrelevant emotional dimension that is an integral part of the stimulus.[15,43,44] A recent study found no difference between SCZ and controls for interference from emotional pictures while maintaining object information.[18] However, in this prior study the distraction was from a separate stimulus rather than an integral dimension of the target stimulus. Interference effects are much smaller when competing information is separated vs integrated in the same stimulus.[45,46] Hence, we used a task in which one dimension (emotional expression) interferes with attention to another dimension (identity) of the same facial stimulus.[47–51]

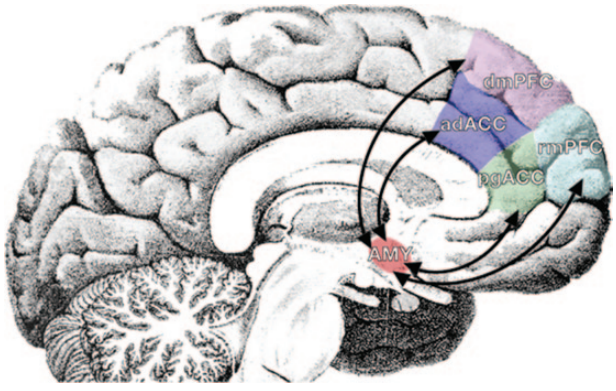

Fig. 1. Hypothetical connectivity model between amygdala and dorsal-caudal regions of the anterior cingulate cortex (dACC) and medial prefrontal cortex (dMPFC), as well as ventral-rostral portions of the ACC (rACC) and MPFC (rMPFC).

Typically, deficits in the ability to manage current goals and execute cognitive control have been reported in both SCZ and BDP, but are more pronounced in the former.[1,52] Thus, one might expect impaired regulation of emotional interference in both disorders, potentially with greater severity in SCZ. Weaker amygdala-prefrontal cortical coupling during distracting emotional information has been noted in SCZ[14,18] however, studies directly comparing neural mechanisms in SCZ to BDP are sparse. A recent study that compared resting state connectivity between the 2 disorders provides evidence of specificity.[53] This study showed altered resting state connectivity of amygdala with the ACC and MPFC in SCZ compared to BDP and healthy controls. Hence, in the present study, we hypothesized that, compared to BDP and CON, SCZ patients will show greater impairment in task-relevant attention due to emotional distraction, along with reduced functional connectivity of amygdala with rostral and dorsal portions of the ACC and MPFC.

Additionally, cognitive and emotional impairments have been related to a range of functional consequences in SCZ.[54–57] However, few studies have examined whether neural measures of emotion-related disruption in task relevant processing are linked to real-world functioning. We hypothesized that emotional interference-related alterations in functional connectivity would be related to social and occupational functioning. Finally, the deficit syndrome is thought to be a particularly severe form of SCZ, characterized by primary and enduring negative symptoms,[58] impaired emotion and social processing,[59] worse functional outcomes and unemployment,[60,61] as well as alterations in anatomical connectivity.[62,63] Thus, we hypothesized that alterations in functional connectivity would also be associated with severity of the deficit syndrome.

Methods

Participants

The participants (SCZ = 26, BDP = 21, CON = 29) were drawn from the Suffolk County Mental Health Project

(SCMHP): a longitudinal investigation of first-admission psychosis.[64,65] Inclusion criteria were first admission for psychosis within the previous 6 months, between ages 15 to 60 years, having IQ > 70, speaking English, and judged as being able to give informed consent.

Since differential diagnosis between psychotic disorders is prone to misclassification,[66] diagnosis was made by longitudinal consensus of study psychiatrists who reviewed 6 assessments spanning 20 years, which included face-to-face assessments by masters-level clinicians using the Structured Clinical Interview for DSM-IV (SCID[67]), interviews with significant others, and review of medical records collected at 5 time points spanning 10 years (first admission, 6-month, 2-year, 4-year, and 10-year). The imaging analysis was performed at 20-year follow-up. The SCZ group included 16 individuals with SCZ and 10 individuals with schizoaffective disorder. These 2 diagnoses were combined based on previous work in our cohort,[68,69] as well as other work[70,71] showing that schizoaffective disorder and SCZ are very similar and characterized by more severe symptoms, worse course, and greater cognitive impairment than other psychotic disorders. People with schizoaffective disorder experience substantial burden of mood symptoms, which overlaps with bipolar disorder to some degree. However, this also is true of many people with SCZ, as substantial majority have comorbid mood disorders although lesser in duration than those seen in schizoaffective disorder.[72,73] With regard to cognitive functioning and long-term outcome, schizoaffective disorder in this cohort is qualitatively different from mood disorder with psychosis but indistinguishable from SCZ.[68,69] CON, the comparison group of age and gender matched individuals with no history of psychosis was selected from the same neighborhoods as the cases.

The present study was approved by Stony Brook University institutional review board. Participants gave informed consent and were screened for MRI contraindications. For behavioral data 8 participants were excluded, 6 due to accuracy less than 60% and 2 due to technical problems in data acquisition resulting in a total of 68 participants for the present study (SCZ = 20, BDP = 21, CON = 27). For fMRI, 10 participants were excluded due to past brain surgery, excessive movement, technical problems, and behavioral accuracy less than 60% resulting in a total of 66 participants for the present study (SCZ = 22, BDP = 15, CON = 29; see supplementary table 1 for details).

Measures

Measures used for assessment of functioning included (1) social functioning (sum of social activity, social initiative, and socio-sexual relations ratings on the Quality of Life Scale),[74] (2) employment status (gainfully employed or not at the time of the scan), (3) severity of the deficit syndrome (rated according to criteria of the Schedule for the Deficit Syndrome),[75] and (4) socioeconomic status (SES) based on primary bread winner's occupation. These assessments were conducted by master-level mental health professionals.

Experimental Tasks

Participants completed a modified version of the emotional face assessment paradigm[76] in which they matched the identity of faces while ignoring their emotional expressions (fear, anger or neutral; figure 2). For details, see supplementary methods.

Image Acquisition and Processing

Functional images were acquired on a 3 Tesla Siemens TIM Trio scanner with an interleaved echo-planar

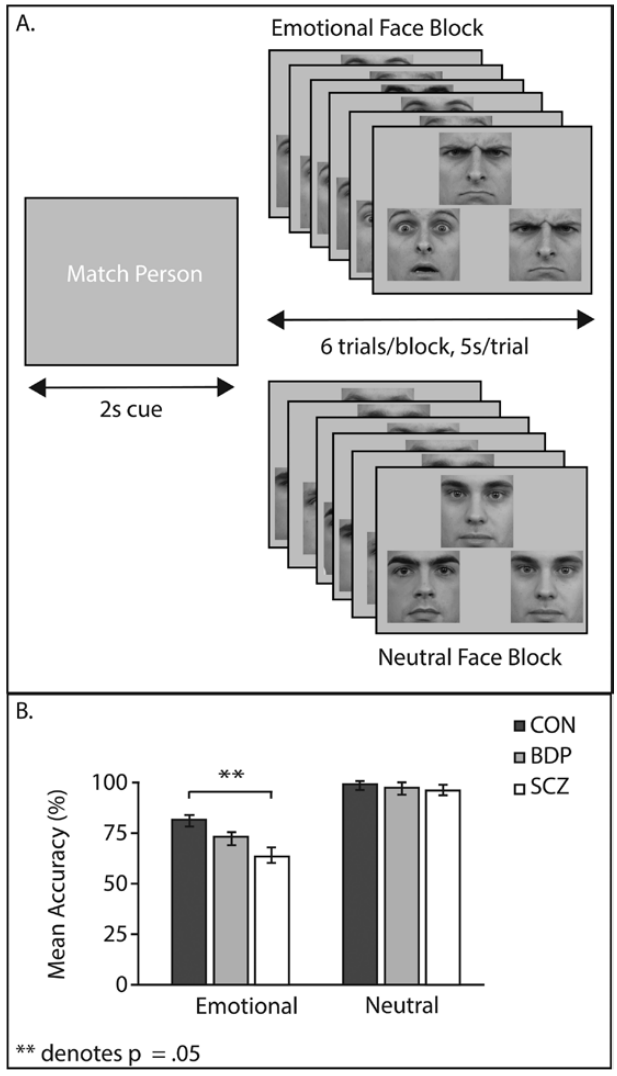

Fig. 2. (A) Modified emotional face assessment task. From the pair of faces at the bottom, participants chose the face whose identity best matched the identity of the face at the top and (B) Mean accuracy while matching identity of emotional and neutral faces for no history of psychotic disorders (CON), bipolar disorder with psychosis (BDP) and schizophrenia (SCZ) groups.

imaging sequence. Thirty-four slices parallel to the anterior and posterior commissures (field of view: 210 mm, slice thickness: 3.5 mm, gap: 0.3 mm [distance factor 10%], in-plane resolution: 3.1 × 3.1 mm, repetition time [TR]: 2 s, echo time [TE]: 30 ms) were collected per volume. Structural images were acquired via a sagittal magnetization prepared rapid gradient echo (MPRAGE) sequence (TR: 1900 ms, TE: 2.53 ms, flip angle: 9°, slice thickness: 1 mm, in-plane resolution: 1 × 1 mm).

Connectivity Analysis

Functional data were slice-time and motion-corrected, and spatially normalized via SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Functional connectivity was estimated by PPI,[40] using the generalized form of context-dependent gPPI (http://brainmap.wisc.edu/PPI).[42,77] Amygdala voxels used for connectivity analyses were selected using a combination of functional and anatomical approaches.[78] Voxels showing the strongest task-related effect across groups were identified using univariate fMRI analyses and results were examined within an amygdala region of interest (ROI) generated using the automated anatomical labeling (AAL) atlas.[79] The seed was defined as a 6 mm sphere around the peak Montreal Neurological Institute (MNI) coordinates thus obtained (−18, −2, −18). For each subject, the PPI term was computed as a product of the task-related regressor and amygdala seed region activity. This interaction term was regressed against activity in the whole brain generating the per-voxel parameter estimate (β) maps representing the magnitude of functional connectivity with the seed region (ie, amygdala) as function of task. To assess how functional connectivity varies between groups, as well as between the emotional and neutral conditions, these β maps were subjected to a 3 (groups: SCZ, BDP, CON) by 2 (conditions: emotional and neutral) flexible factorial ANOVA implemented in SPM8.[80] Since our hypothesis focus on the connectivity of amygdala with rostral and dorsal ACC and MPFC, we examined the ANOVA results using an anatomical ROI mask that included these regions (for details see supplementary methods). Post hoc analyses with pairwise and independent *t* tests were performed within SPM for clusters of voxels showing significant group × condition interaction in the ANOVA. All results were corrected for multiple comparisons using the AlphaSim toolbox.[81] For details see supplementary methods.

Mediation Analysis

Given that amygdala shows relatively poorer anatomical connectivity with dMPFC[82,83] compared to dACC,[84–87] we performed a mediation analyses to examine if dACC mediates the connectivity between amygdala and dMPFC and if this mediation differs in patients. See supplementary methods for details.

Associations With Real-World Outcomes

Next, using voxelwise multiple regression, we investigated whether functional connectivity differences are associated with task accuracy for all participants in our ROI mask. We also examined whether functional connectivity differences are associated with social functioning, employment status, as well as severity of deficit syndrome and positive symptoms across patients, while controlling for SCID diagnosis. For details see supplementary methods.

Replication Analyses

We conducted a replication of the present study using the same sample but with a different task (supplementary material 2). In the present study, the task involved ignoring emotional distractors while attending to task-relevant face identity. In the replication study, the task involved ignoring emotional distractors while maintaining task-relevant information in working memory. As in the present study we used PPI to examine group differences in amygdala connectivity.

Results

Behavior

Group differences in accuracy were examined with a 3 (BPD, SCZ, CON) × 2 (emotional and neutral) repeated measures ANOVA. There was a main effect of group, F (2, 65) = 4.732, P = .012, η^2 = 0.16, condition, F (2, 65) = 126.13, P < .001, η^2 = 0.66; and group × condition interaction, F (2, 65) = 3.69, P = .030, η^2 = 0.10 on accuracy of face identity matching (figure 2). Simple effects tests showed no significant difference between the groups for the neutral condition (P > .05). All 3 groups showed lower accuracy in matching identity of emotional compared to neutral faces. Additionally, the SCZ group demonstrated lower accuracy than CON (d = 0.95, P = .004) while matching identity of emotional faces, indicating that impaired task-relevant processing due to emotional distractors is most pronounced in SCZ. There was no difference between SCZ and BDP (d = 0.40, P = .129) or between BDP and CON (d = 0.42, P = .202; figure 2).

Functional Connectivity

To examine whether greater interference from emotional expressions in psychotic disorders is associated with reduced functional connectivity of amygdala with rostral and dorsal portions of ACC and MPFC, we first confirmed that the amygdala was sensitive to task-related modulation. There was greater amygdala activation for emotional vs neutral distractor condition, and this activation did not differ by group. Next, we examined connectivity of the task-sensitive amygdala ROI to subregions of the MPFC. PPI analyses showed a significant group × condition interaction effect in amygdala connectivity

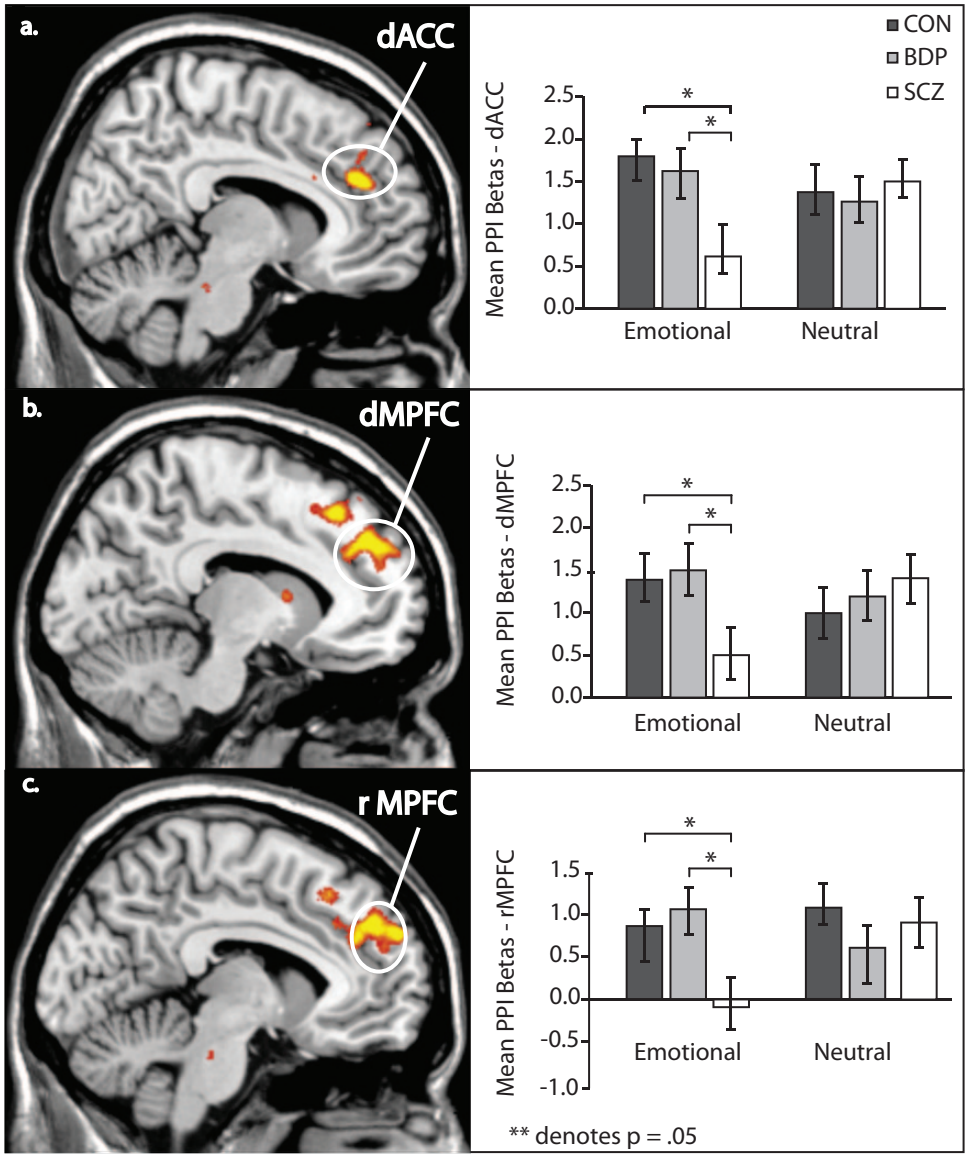

Fig. 3. Amygdala connectivity with (a) dorsal-caudal regions of the anterior cingulate cortex (dACC) (b) dorsal-caudal regions of the medial prefrontal cortex (dMPFC) and (c) ventral-rostral portions of the MPFC (rMPFC) is reduced for schizophrenia (SCZ) compared to bipolar disorder with psychosis (BDP) and no history of psychotic disorders (CON) when matching identity of the emotional compared to neutral faces. Left panel depicts regions showing significant group (CON, BDP, SCZ) × condition (emotional vs neutral face) interaction for amygdala-MPFC connectivity ($P < .05$, corrected for multiple comparisons). Right panel shows corresponding mean parameter estimates of amygdala-MPFC connectivity for the 3 groups for display purposes only. *Indicates group differences that were significant in voxelwise post hoc analyses conducted in SPM8 ($P < .05$, corrected for multiple comparisons).

with dACC (peak coordinates: 8, 38, 26; cluster size 161; peak F 9.81; peak Z 3.71), dMPFC (peak coordinates −11, 48, 32; cluster size 1453; peak F 12.77; peak Z 4.32), and rMPFC (peak coordinates −7, 59, 29; cluster size 192; peak F 10.89; peak Z 3.95), but not rACC (figure 3).

Voxelwise post hoc tests conducted to further investigate these group × condition interactions showed that, while the 3 groups did not differ from each other for the neutral condition, SCZ showed lower amygdala connectivity with dACC, dMPFC, and rMPFC than BDP and CON, when matching identity of emotional faces ($P <$ .05, corrected; figure 3 a–c). Amygdala connectivity for BPD did not differ significantly from CON. Furthermore, only SCZ showed lower amygdala connectivity with dACC, dMPFC, and rMPFC for emotional distractors vs neutral distractors.

To ensure group differences in connectivity are not confounded by task performance, we conducted a post hoc voxelwise ANCOVA with diagnosis (SCZ, BDP and CON) as the between group factor, face type (emotional and neutral) as the within group factor and behavioral accuracy scores as a covariate. Our results showed that the group differences in amygdala connectivity to dACC, dMPFC, and rMPFC remain significant ($P <$

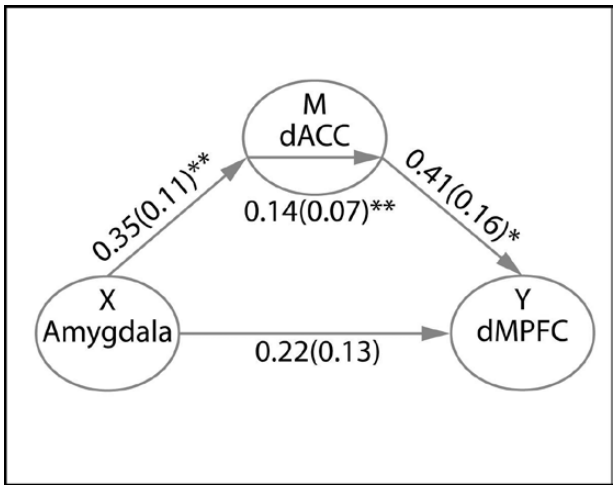

Fig. 4. Mediating variable analyses shows that dorsal-caudal regions of the anterior cingulate cortex (dACC) mediates the relationship between amygdala and dorsal-caudal regions of the medial prefrontal cortex (dMPFC) across all participants.

.05, corrected) even after controlling for differences in behavioral accuracy. Post hoc comparisons between the SCZ and BDP groups also showed that connectivity differences remain significant even after controlling for behavioral accuracy differences. Finally, we simultaneously entered performance in task (accuracy) and connectivity during the task in logistic regression predicting group membership (SZ vs BPD), we found that accuracy did not independently distinguish the groups (P = .84), whereas amygdala-MPFC connectivity did distinguish them (P = .02).

Mediation Analysis

While the amygdala has direct anatomical connections with rMPFC, it has little direct anatomical connectivity to dMPFC.[82,83] Furthermore, there is stronger anatomical connectivity of amygdala to dACC[38] than the adjacent dMPFC. Hence, we investigated whether the dACC mediates the connectivity between amygdala and dMPFC and whether this differs by group. Results showed a significant indirect connectivity between amygdala and dMPFC mediated by dACC (r = .14, P = .006). A significant relationship was found between amygdala and dMPFC (r = .36, P = .009), amygdala and dACC (r = .35, P = .005), as well as between dACC and dMPFC (r = .41, P = .016). Further, once the effect of dACC was factored out, the relationship between dMPFC and amygdala was no longer significant (r = .22, P = .090). This mediation effect did not differ by group (figure 4).

Association of Connectivity With Task Performance and Real-World Functioning

Voxelwise multiple regression across all participants showed that greater accuracy for emotional vs neutral trials was associated with greater amygdala-dACC connectivity (peak coordinates: −6, 20, 32; cluster size 73; peak T 3.61; peak Z 3.29) indicating that worse performance in SCZ may be related to weaker amygdala-dACC connectivity in this group (figure 5a). We also examined the relationship of connectivity differences with symptoms and real-world functioning. Results showed that amygdala-dACC/DMPFC connectivity correlated positively with employment status (peak coordinates: 20, 36, 41; cluster size 66; peak T 2.78; peak Z 2.64; figure 5b), and correlated negatively with deficit syndrome severity, a strong predictor of poor functional outcomes (peak coordinates: 10, 37, 16; cluster size 171; peak T 2.32; peak Z 2.24; figure 5c). No significant correlations of social functioning or positive symptoms with connectivity or behavioral measures were observed.

Replication Study

We found that lower amygdala connectivity with dACC again differentiated the SCZ group from the bipolar with psychoses and the control group. Additionally, we replicated our findings regarding the deficit syndrome such that lower amygdala-dACC connectivity was associated with more severe deficit syndrome symptoms even when controlling for group-related differences (see supplementary material 2 for details).

Discussion

We examined whether psychological and neural mechanisms of emotional interference are specific to SCZ, or whether they are transdiagnostic markers of psychotic disorders. On a task in which participants matched identity of faces, SCZ showed the worst accuracy when the faces were emotional but performed similar to CON when they were neutral. Neurally, compared to BDP and CON, SCZ showed reduced amygdala connectivity to dACC, dMPFC, and rMPFC, indicating that the functional connectivity impairment is specific to SCZ and specific to the emotional condition. BPD did not differ from CON either for accuracy or amygdala connectivity. Additionally, impaired amygdala-dACC functional connectivity during emotional distractors was related to poorer behavioral performance on the task across all participants, as well as worse clinical and real-world functioning in patients.

The task used in the present study involves competition between dimensions of facial identity and facial expression. Emotional expressions tend to interfere with processing of facial identity,[47,48,50,51] an effect we replicated in our study, with all participants showing worse accuracy when matching identity of emotional vs neutral faces. Emotional expressions may make it difficult to identify faces due to facial contortion. However, threatening and happy faces both produce distortions of facial features

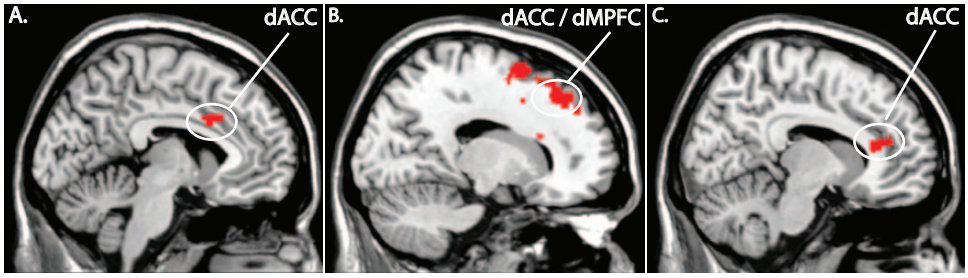

Fig. 5. Regions in dorsal-caudal regions of the medial prefrontal cortex (dMPFC) and anterior cingulate cortex (dACC) significantly correlated with measures of (a) accuracy while matching identity of emotional vs neutral faces, (b) employment, controlling for diagnoses and (c) global deficit symptoms, while controlling for diagnoses.

but have differing effects on identification[88,89] with positive expressions sometimes enhancing recognition and negative impairing recognition. Further, identity processing is impacted even by emotions conveyed by body in which the face is embedded.[90] Thus it is likely that, due to their salience, emotional expressions use up a major portion of the limited capacity attentional system and leave little for task-relevant processing.[91]

While there was no significant difference in accuracy between SCZ, BPD, and CON for matching identity of neutral faces, SCZ performed significantly worse than CON when matching identity of emotional faces and BPD did not differ from CON. These results demonstrate that, in the presence of strongly competing emotional information that requires immediate responses, SCZ show greater impairment in attentional control. Although SCZ is characterized by emotional face processing deficits, these deficits chiefly concern explicit emotion perception measured via recognition, labeling or matching of facial emotional expressions. However, our study involves implicit emotion perception, which is typically intact in SCZ.[92–99] Hence individuals with SCZ can perceive emotional expressions and these emotional expressions can interfere with task-relevant processing as our results indicate.

While ignoring emotional distractors the SCZ group showed reduced connectivity with dACC. The dACC is recruited when there is increased demand for cognitive control, especially in the presence of distraction or strongly competing responses (eg, habitual or emotional) that must be overcome to stay task-focused.[100–103] Specifically, dACC is involved in monitoring conflict arising between competing choices.[23,104,105] Recently, researchers have hypothesized that dACC plays an important role in the evaluation of expected value of control, which involves integration of payoff expected from implementing control, the amount of control required to achieve that payoff, and the cost using cognitive effort.[106] Overall, the role of the dACC is to integrate information to determine whether, where, and how much control to allocate.

While most dACC research is conducted on interference due to relatively nonemotional stimuli, research on emotional interference monitoring also implicates dACC, with subsequent resolution of interference being attributed to rACC inhibiting amygdala activation.[27,107–111] Additionally, dACC itself has been shown to be associated with down-regulation of negative emotions.[112,113] Recent theories of dACC function have proposed that this region connects emotional valence with executive control processes.[91,114,115] The connectivity of dACC with amygdala is considered important for communication of error signals between the 2 regions.[116] In the present study, stronger dACC-amygdala connectivity in controls may be indexing better monitoring of emotion-related interference, whereas reduced connectivity in SCZ may be indicative of worse monitoring of emotional interference. In fact, our results show that worse performance during emotional vs neutral distractors correlates with greater dACC-amygdala connectivity across all groups, suggesting that reduction in this connectivity may be contributing to worse behavioral performance during emotional distractors in SCZ.

Our connectivity findings for dMPFC were similar to those for the adjacent dACC, showing reduced amygdala-dMPFC connectivity specifically in SCZ while matching identity of emotional vs neutral faces. dMPFC has been shown to be involved in similar functions of conflict monitoring and cognitive control as dACC.[22,117] However, while there is dense connectivity between amygdala and dACC,[84–87] there is little direct anatomical connectivity between amygdala and dMPFC.[82,83] Using mediation analyses, we found that dACC mediates the functional relationship between amygdala and dMPFC across all subjects in our study.

Finally, our study showed decreased amygdala-rMPFC connectivity during emotional interference, more so in SCZ than BDP and CON. The anterior portion of the rMPFC enables making choices between competing aspects of stimuli by predicting the expected outcome, or "affective value" of the competing choices[118–121] and, accordingly, modulating attention.[122,123] It has rich connectivity with amygdala and, thus, together they play a role when evaluating of subjective value of threatening stimuli.[122–126] Contrary to what we hypothesized, we did not find connectivity differences between amygdala and the adjacent rACC. The lack of amygdala-rACC

connectivity differences for emotional vs neutral distractors in the present study is inconsistent with previous studies that showed a negative relationship between amygdala and the rACC.[111] While the rACC has been shown to be involved in emotion regulation, its role is very specific in that it helps in resolving emotion-related conflict.[29] Although our stimuli involve attentional competition between emotional (facial emotional expression) vs nonemotional (facial identity) dimensions, they do not involve direct conflict, in that the emotional expression does not have any inherent conflict with the identity of a face. The absence of direct emotion-related conflict may have contributed to the negative findings in our study.

Although our study shows that amygdala-dACC and amygdala-rMPFC connectivity deficits are specific to SCZ, amygdala connectivity with other regions in the PFC has been implicated in many disorders. Amygdala-MPFC connectivity has been found to vary in anxiety but the region of the MPFC implicated lies in pregenual ACC or rACC.[127–129] Similarly, amygdala-PFC connectivity differences may be seen in depression but the regions implicated are typically in ventral and subgenual ACC.[130] The one study that examined task-based amygdala-MPFC connectivity in bipolar disorder showed no deficits in amygdala-ACC connectivity.[131] To our knowledge, no study has compared task-based amygdala-MPFC connectivity deficits directly between BDP and SCZ spectrum disorders. Additionally our findings of specificity compliment findings showing that resting-state amygdala-MPFC connectivity deficits are specific to SCZ compared to bipolar disorder.[53]

We also found a relationship between reduced amygdala-dACC connectivity and greater deficit syndrome severity, across both psychotic groups even after controlling for diagnosis. Deficit symptoms include restricted affect, diminished emotional range, diminished social drive or sense of purpose, and in the present study they were higher for SCZ as compared to BDP group (Cohen's $d = 0.80$). To examine the possibility that our group behavioral and neural brain differences are driven by the deficit syndrome, we conducted an ANCOVA with diagnosis (SCZ, BDP and CON) as the between group factor, face type (emotional and neutral) as the within group factor and deficit syndrome score as a covariate. Our behavioral and neural results showing differences between SCZ and the other groups remained significant, indicating that they cannot be solely attributed to the deficit syndrome. Additionally, the relationship between deficit syndrome and amygdala-dACC connectivity remained significant even after controlling for diagnosis, suggesting that the effect is independent of diagnosis. Finally, we found that reduced amygdala-MPFC connectivity is associated with unemployment, possibly because this circuitry plays an important role in the ability to selectively attend to task-relevant aspects of stimuli while ignoring irrelevant emotional distractors. However, group differences in connectivity remained significant even when controlling for unemployment, establishing that they are independent. Further, this effect was specific relative to social functioning, which did not correlate with amygdala-MPFC connectivity.

A limitation of the present study is that we employed a block design, which does not allow us to separate the different components of processing which could have been achieved with an event-related design. However, given our patient sample a faster block design is better suited than a longer event related design.

Functional imaging offers a window into the neurobiology supporting cognitive and emotional processing, as well its disruption in SCZ, creating the potential for better diagnosis and more targeted treatment development.[132] However, this knowledge has not been effectively translated into diagnostics and treatment development. While increasing data support the validity and reliability of neuroimaging markers of cognitive and emotional processing in SCZ, little is known about the clinical utility of these measures.[55,133] By leveraging an exquisitely characterized cohort and well-defined neural circuitry identified from animal and human research, the present study advances the literature by clarifying the diagnostic and clinical utility of neuroimaging measures of emotion-cognition interactions in SCZ. Our results demonstrating the specificity of neural measures of emotion-cognition interactions to SCZ and their relationship to clinical and real-world functioning are an important step in facilitating the translation of these behavioral and neural measures from basic affective/cognitive neuroscience into brain-based tools for better diagnosis and treatment development. Although larger studies would be required to establish translation of these promising findings into a reliable biomarker of SCZ, our findings provide the first evidence for specificity and utility in SCZ. Further, our results highlight the importance of conducting future longitudinal studies to determine whether observed neural processes contribute to the development of symptoms and impairments.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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