Impaired Modulation of Attention and Emotion in Schizophrenia

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Objective: Fronto-limbic interactions facilitate the generation of task-relevant responses while inhibiting interference from emotionally distracting information. Schizophrenia is associated with deficits in both executive attention and affective regulation. This study aims to elucidate the neural correlates of emotion-attention regulation and shifting in schizophrenia. *Method:* We employed functional magnetic resonance imaging to probe the fronto-limbic regions in 16 adults with schizophrenia and 13 matched adults with no history of psychiatric illness. Subjects performed a forced-choice visual oddball task where they detected infrequent target circles embedded in a series of infrequent nontarget aversive and neutral pictures and frequent squares. *Results:* In control participants, target events activated a dorsal frontoparietal network, whereas these regions were deactivated by aversive stimuli. Conversely, ventral frontolimbic brain regions were activated by aversive stimuli and deactivated by target events. In the patient group, regional hemodynamic timecourses revealed not only reduced activation to target and aversive events in dorsal executive and ventral limbic regions, respectively, but also reduced deactivation to target and aversive stimuli in ventral and dorsal regions, respectively, relative to the control group. Patients further showed reduced spatial extent of activation in the right inferior frontal gyrus during the target and aversive conditions. Activation of the anterior cingulate to aversive images was inversely related to severity of avolition and anhedonia symptoms in the schizophrenia group. *Conclusions:* These results suggest both frontal and limbic dysfunction in schizophrenia as well as aberrant reciprocal inhibitions between these regions during attention-emotion modulation in this disorder.

Key words: schizophrenia/attention/emotion/frontal lobes/limbic system/functional magnetic resonance imaging

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Introduction

Growing evidence from nonclinical samples indicates that reciprocal interactions occur between dorsal "executive" and ventral "affective" processing systems, and limbic output to the prefrontal cortex (PFC) plays an important modulatory role in regulating goal-directed behavior.[1,2] Accordingly, the determination of task-appropriate behaviors is mediated by dorsal prefrontal regions with input from both ventromedial prefrontal[3] and ventral limbic structures such as the amygdala (AMG) and hippocampus.[4–6] As such, response selection includes both cognitive and emotional processing. Recent studies have demonstrated a strong interaction between affective processing and goal-directed response selection in nonclinical samples.[1,2,7] For instance, stimuli that engage frontal executive cognitive control circuits simultaneously induce deactivation or suppression of limbic cortical regions as detected by functional magnetic resonance imaging (fMRI) studies. Moreover, activation of limbic regions by affective stimuli appears to similarly downregulate or suppress activity in prefrontal cognitive control areas.[1,2,7] Recent studies have further suggested that this reciprocal relation between higher order cognitive control decision making regions and limbic affective processing areas subserves a critical function in the regulation of attention and response selection in the presence of emotionally arousing information and vice versa.[8–11] These reciprocal regulation mechanisms constitute a critical property of adaptive systems that facilitates the balance between task-relevant information processing and adaptive gating of emotionally salient but task-irrelevant distracting information.

Both executive attention impairments and affective dysregulation (eg, affective flattening, alogia, and avolition) are core symptoms of schizophrenia,[12] and paradigms requiring task-appropriate stimulus and response selection have identified deficits in attentional control in this disorder.[13,14] Although not always consistent in their direction,[15–17] findings of distributed abnormalities have been reported across a wide range of regions in schizophrenia, including hypoactivation in dorsolateral PFC (DLPFC),[13,18] as well as the medial PFC, including the anterior cingulate cortex,[15,17] during attentional aspects of cognitive and affective processing. These cognitive deficits appear to further deteriorate in

patients with prominent negative symptoms.[16] Although these findings suggest a critical interaction between poor executive attention and affective processing deficits reflected through negative symptoms in schizophrenia, the neural correlates of affective processing in the context of goal-directed responses are poorly understood in schizophrenia.

A breakdown in the reciprocal interactions between the dorsal executive attention and ventral affective processing systems may be present in schizophrenia, and may even precede the onset of psychosis or be present in spectrum individuals, suggesting a possible role for this deficit as a vulnerability indicator. Limbic functional abnormalities have been demonstrated in schizotypy with affective interference paradigms,[19] indicating a fundamental failure in the interaction between emotional and attentional control mechanisms in individuals experiencing spectrum deficits. Neuroimaging studies have also revealed significant, early emerging neuroprogressive functional deficits in ventral limbic regions in schizophrenia,[20–22] further suggesting that emotion dysregulation is present early and further declines with illness progression. Evidence of aberrant interactions between executive attention and affective processes in schizophrenia are suggested by deficits on tasks requiring the selection of responses based on valence and success in achieving rewards.[23] Suppressed AMG-prefrontal interactions have been associated with reductions in incentive motivational signals and decreased prefrontal activity in schizophrenia.[24,25] Thus, whereas limbic output to the PFC plays an important modulatory or gating role in regulating goal-directed behavior in nonclinical contexts, such modulation may be impaired in schizophrenia. Such aberrant interactions between dorsolateral and ventral prefrontal regions in schizophrenia may fail to provide a balance between task-dependent rule-based response selection and motivational or incentive-based response inhibition. The presence of these deficits early in the disorder suggests that understanding the mechanisms of these deficits may provide a glimpse into the core pathophysiological processes that precede the onset of schizophrenia. Moreover, the neuroprogressive nature of these deficits further suggests that early interventions may reduce the severity, progression, or negative impact of these deficits upon functional outcome measures in schizophrenia and may serve as useful treatment outcome measures.

The purpose of the present study was to use fMRI to evaluate whether functional fronto-limbic impairments in schizophrenia are associated with aberrant evaluation of both task-relevant stimuli as well as emotionally salient information processed within the context of such goal-directed behavior. The present study was designed to build upon an existing body of literature documenting unique and overlapping brain regions mediating attentional engagement and processing emotional stimuli

in nonclinical samples and to assess functioning of these processes in schizophrenia. While previous imaging studies with schizophrenia patients explored functioning in either executive or affective processing domain, the current study was specifically designed to simultaneously probe both frontostriate and frontolimbic regions in parallel using an emotional version of a visual oddball task.[14,26] This new task incorporates a target detection task, shown to activate frontostriate task-relevant response selection circuits, and affective pictures from the International Affective Picture System (IAPS),[27] which have been demonstrated to induce reliable activation in ventral-limbic regions in nonclinical samples, as well as reciprocal interactions between dorsal prefrontal and ventral limbic regions. Use of nonemotional pictures depicting neutral scenes provides a balanced control for the perceptual complexity and visual novelty of the affective stimuli. Previous fMRI studies in nonclinical samples employing similar affective paradigms have demonstrated activation of a dorsal brain network in response to target stimuli and a ventral brain network in response to aversive stimuli, as well as deactivation of a dorsal brain network in response to aversive stimuli and a ventral brain network in response to target stimuli.[1,7,28] Because impaired goal-directed behavior and affective dysregulation are core areas of deficit in schizophrenia, this task is particularly well-suited to address functional deficits in this disorder as well as interdomain interactions between emotional and attention processing[1,7,26,28] see, eg, Philips[29] for a review.

We hypothesized that patients with schizophrenia would demonstrate relative hypoactivation in the dorsal processing stream and relatively decreased deactivation in the ventral processing stream in response to the target stimuli. We further hypothesized that the schizophrenia group would be characterized by hypoactivation in ventral regions and relatively decreased deactivation in relevant dorsal regions in response to emotional distractors, although the mixed findings regarding AMG responses to aversive stimuli in schizophrenia (reviewed above) tempered this latter hypothesis. Such a pattern of results would suggest that abnormal cortical and subcortical activity in schizophrenia extends to impaired inhibitory processes linked to shifting between attentional and emotional domains. Finally, in exploratory analyses, we assessed relations between task-dependent brain activation in frontolimbic regions and severity of positive and negative symptoms in the schizophrenia group. Because of evidence of frontal abnormalities in schizophrenia patients with negative symptoms,[30] and evidence that the anterior cingulate is a critical node modulating attention and emotion,[28] we hypothesized that negative symptoms would be associated with decreased anterior cingulate activation in participants with schizophrenia.

Method

Participants

Sixteen individuals who met criteria for schizophrenia or schizoaffective disorder and 13 individuals with no history of psychiatric illness participated in this study. Data from 4 participants in the patient group were discarded due to excessive motion. The final sample included 12 participants with schizophrenia [10 Caucasian, 2 African American; 1 female; age mean (SD) = 29.4 (10.2)] and 13 control participants [11 Caucasian, 2 African American; 1 female; age mean (SD) = 31.6 (10.7)] who were paid $40 for their participation in the imaging portion of this study. All had normal or corrected-to-normal vision, were right-handed, and were screened for neurological illnesses.

Control participants were recruited via local newspaper and Duke University Medical Center Web site advertisements, as well as via flyers posted in campus and medical center locations, and did not meet criteria for current or past Axis-I disorders as assessed by the *Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), (SCID) Axis I Disorders*[31] in an initial clinical assessment session. Patients were recruited through local media and had a diagnosis of schizophrenia or schizoaffective disorder. Patients and controls did not meet *DSM-IV* criteria for past substance dependence or substance abuse within the past month as assessed by the SCID.[31] Both groups also had no current or past history of migraines or major medical illness, including multiple sclerosis, stroke, insulin-dependent diabetes, significant head injury, and epilepsy within 3 years; had no history of treatment with ECT/rTMS within 3 months; were not pregnant at the time of scanning; and did not have a family history of neurologic or neurodegenerative disorder (eg, Parkinson's Disease, Huntington chorea, multiple sclerosis). All procedures were approved by the institutional review boards at the University of North Carolina at Chapel Hill and at Duke University Medical Center, Durham, NC. After complete description of the study to the subjects, written informed consent was obtained. Negative results of urine toxicology were confirmed before study inclusion.

Measures

In addition to the SCID, all participants were administered the North American Adult Reading Test[32] and the Hollingshead Socioeconomic Scale (A. B. Hollingshead, unpublished manuscript, 1975). Participants with schizophrenia were also administered the Scale for the Assessment of Negative Symptoms (SANS)[33] and the Scale for the Assessment of Positive Symptoms (SAPS).[34]

Task Parameters

Stimuli and task parameters were identical to those described in Fichtenholtz et al.[28] The MRI session consisted of 10 task runs each containing 132 stimuli centrally presented every 2000 milliseconds for 500 milliseconds. During the 1500-millisecond interstimulus interval, a fixation cross was presented. There were 4 stimulus categories: squares and circles of various sizes and colors, aversive scenes, and neutral scenes. Squares were the "standard" frequent stimuli and occurred on 84.4% of trials. Circles were the infrequent "target" stimuli and occurred on 8% of trials. Aversive and neutral scenes also occurred on 3.8% of trials each. No stimuli were repeated during the imaging session. Circles, aversive scenes, and neutral scenes were pseudorandomly distributed throughout each task run and separated by 12–21 seconds (mean = 18 s) to allow the full deployment and recovery of the hemodynamic response (HDR) for the planned time-course analysis. Within each session, participants viewed a total of 106 circles, 50 aversive scenes, and 50 neutral scenes.

Participants were instructed to press one button with their right index finger if they detected a circle (ie, targets) and to press another button with their right middle finger for all other stimuli. Thus, in this forced-choice task, motor responses were required of all stimuli to avoid potential motor preparation confounds. Furthermore, the forced-choice paradigm allows for collection of accuracy and reaction time data for all trials. Aversive and neutral pictures were selected from the IAPS.[27] Aversive pictures depicted human violence, mutilation, and disease; neutral pictures depicted everyday activities. Mean luminance was adjusted to fall between 112.5 and 113.5 luminance units with an SD between 62.5 and 63.5. All scenes contained human figures or body parts. Images were selected according to normative ratings for arousal (1 = low, 9 = high) and valence (1 = negative, 9 = positive). Arousal ratings were between 5 and 8 for aversive scenes and between 1 and 3 for neutral scenes. Valence ratings were between 1 and 3 for aversive scenes and between 4 and 6 for neutral scenes. All stimuli were presented using CIGAL presentation software[35] and displayed in the scanner through magnet-compatible XGA goggles (Resonance Technology, Inc, Northridge, CA).

Imaging

Scanning was performed on a General Electric 4T LX NVi MRI scanner system equipped with 41 mT/m gradients (General Electric, Waukesha, WI). A quadrature birdcage radio frequency head coil was used to transmit and receive. The participant's head was immobilized using a vacuum cushion and tape. Sixty-eight high-resolution images were acquired using a 3D fast spoiled gradient recalled pulse sequence (repetition time [TR] = 500 ms, echo time [TE] = 20 ms, Field of View [FOV] = 24 cm, image matrix = 256^2, voxel size = 0.9375 × 0.9375 × 1.9 mm) and used for coregistration with the functional data. These structural images were aligned

in a near-axial plane defined by the anterior and posterior commissures. Whole-brain functional images were acquired using a gradient-recalled inward spiral pulse sequence[36,37] sensitive to blood oxygenation level–dependent (BOLD) contrast (TR = 1500 ms, TE = 35 ms, FOV = 24 cm, image matrix = 64^2, α = 62°, voxel size = 3.75 × 3.75 × 3.8 mm, 34 axial slices). The functional images were coplanar with the structural images. A semiautomated high-order shimming program ensured global field homogeneity. This pulse sequence on this scanner has been shown to provide adequate signal recovery in ventral brain regions.[38]

Imaging Data Analysis

Our data analysis strategy was consistent with prior work from our research group and others[14,28,39,40] and utilized an epochal, rather than general linear model-based, approach. Although both approaches are valid and have methodological strengths and weaknesses, an epochal analysis strategy is well suited to extracting condition-specific hemodynamic timecourses. Our data analysis procedures consisted of 3 components, all described in greater detail below. First, standard preprocessing steps were performed. Second, a whole-brain voxel-based analysis allowed for an exploratory examination of regional activation patterns for each condition as well as random-effects analyses to compute within-group differential activation patterns in response to specific condition contrasts. Third, a region-of-interest analysis was conducted to extract the HDR timecourse in the regions identified through the random-effects contrasts performed in the preceding steps and to conduct between-groups tests on the percent signal change and counts of active voxels (extent of activation) obtained form these regions. This analysis strategy allowed for examinations of within-groups activation patterns as well as between-groups tests of condition-specific timecourse amplitudes and voxel counts.

Image preprocessing was performed with custom programs and SPM modules (Wellcome Department of Cognitive Neurology, London, UK). Functional images were corrected for time of acquisition within a TR and head motion and were coregistered and normalized into a standard stereotaxic space (Montreal Neurological Institute [MNI]) for intersubject comparisons. Head motion was detected by center of mass measurements. No subject had greater than a 3-mm deviation in the center of mass in any plane. A smoothing filter of 8-mm full-width at half-maximum was applied following normalization. These normalized and smoothed data were used in the analysis procedures described below. Only epochs during which participants made a correct button press were included in analyses.

Whole-brain, voxel-based analyses consisted of both group-averaged activation maps in response to individual conditions (eg, targets) as well as random-effects contrast maps (eg, "target > aversive"). Group-averaged activation maps were computed by excising from the continuous time series of volumes the epoch of image volumes beginning 2 images before (−3.0 s) and 9 images after (13.5 s) the onset of each event. Next, the average intensity of the HDR for each condition was derived in the following steps: (1) the single-trial epochs for each participant were averaged separately for each condition, and BOLD-intensity signal values within the averaged epochs were converted to percent signal change; (2) the waveforms for each voxel were correlated with an empirically derived hemodynamic function,[41,42] and *t* statistics were calculated for these correlation coefficients, providing whole-brain *t* maps in MNI space; and (3) the *t* maps were used to calculate an average *t* map across participants that was then thresholded using a false discovery rate (FDR)[43] of $P < .001$.

Random-effects contrast analyses were performed to assess the significance of differences across participants. Random-effects contrasts were restricted to (ie, were masked by) voxels where a significant, FDR-corrected HDR was evoked by either condition composing the contrast. In other words, the differences in HDR amplitudes between conditions were only evaluated for those voxels in which at least one condition evoked a significant HDR. The threshold for significance in the HDR peak was set at $P < .01$ (2 tailed) and a minimal spatial extent of 8 uninterpolated voxels (we note that our primary analyses contrasted conditions compromised of different numbers of events [ie, target-aversive contrasts include responses to up to 106 circle stimuli but up to 50 aversive scenes]. Contrasting responses to the target events with a condition created by pooling events from the aversive and novel conditions yields a contrast with more balanced numbers of events and yields highly similar results. Additionally, we note that the imaging task employed has been demonstrated to recruit dorsal and ventral regions in response to target and aversive events, respectively, in previous nonclinical studies[27,28]).

A region-of-interest analysis was performed to derive the HDR timecourses by averaging BOLD activations from voxels identified to be active by the random-effects analysis described above. We performed group × condition repeated-measures analyses of variance (ANOVAs) with percent BOLD signal change and percentages of active voxels within functionally defined regions of interest as dependent measures. The percent signal change values were derived by averaging activation values at the peak of the HDR (defined as average responses 4.5–6.0 s after stimulus onset) for voxels identified to have greater activation in random-effects contrast analyses in response to target relative to aversive trials in dorsal stream regions and in voxels identified to have greater activation in response to aversive relative

to target trials in ventral stream region. For contrasts revealing no significant effects in the schizophrenia group, voxels showing a significant contrast effect in the control group were queried in the schizophrenia group to generate average HDRs because data were warped to the same normalized space. The percentages of active voxels within functionally defined regions of interest (ie, the random-effects contrast maps) were evaluated with group × category repeated-measures ANOVAs to assess between-condition and between-group differences in the spatial extent of regional brain activation.

Results

Participant Characteristics

Table 1 illustrates that groups did not differ on age or estimated intelligence (P's > .05), but control participants reported higher socioeconomic status (A. B. Hollingshead Ph.D., unpublished manuscript, 1975) ($P < .001$). SANS and SAPS scores indicate mild-to-moderate levels of negative and positive symptoms, respectively.

Behavioral Performance

Accuracy means for the fMRI task are as follows: controls had a higher accuracy on aversives [control mean (SE) = 0.94 (0.012), schizophrenia mean (SE) = 0.88 (0.027)], circles [control mean (SE) = 0.76 (0.037), schizophrenia mean (SE) = 0.68 (0.059)], neutrals [control mean (SE) = 0.94 (0.019), schizophrenia mean (SE) = 0.90 (0.025)], but not on standards [control mean (SE) = 0.82 (0.031), schizophrenia mean (SE) = 0.85 (0.037)]. Schizophrenia patients had slower reaction times for all stimuli: aversives [control mean (SE) = 538.90 (30.79), schizophrenia mean (SE) = 674.54 (62.08)], circles [control mean (SE) = 538.75 (31.10), schizophrenia mean (SE) = 605.57 (21.56)], neutrals [control mean (SE) = 516.39 (30.36), schizophrenia mean (SE) = 614.71 (37.60)], and standards [control mean (SE) = 431.38 (31.03), schizophrenia mean (SE) = 481.62 (22.43)]. A 2 (group: control, schizophrenia) × 4 (condition: aversive, circle, neutral, standard) repeated-measures multivariate ANOVA conducted on response latency revealed a main effect of condition (multivariate $F_{3,21} = 39.47$, $P < .0001$) and a trend toward a main effect of group, ($F_{1,23} = 4.01$, $P < .06$), reflecting that participants with schizophrenia had slower response times across all categories, but no group × condition interaction, $P > .40$. Despite a lack of significant interactions, for completeness we report results of paired comparisons: paired within-subjects comparisons between condition levels across groups indicated that responses to standard stimuli were quicker than to each of the other three categories, P's < .0001 and that responses to neutral stimuli were quicker than those to aversive stimuli, $P < .01$. Paired between-groups comparisons within each condition revealed trends toward slower responses by individuals with schizophrenia to aversive, neutral, and target stimuli, P's < .09, but not standard stimuli, $P > .20$.

Analyses of accuracy data indicated a main effect of condition (multivariate $F_{3,21} = 18.07$, $P < .0001$) but not a main effect of group or group × condition interaction, P's > .20. With the exception of aversive vs neutral responses ($P > .50$), all other paired within-subjects comparisons between condition levels across diagnostic

Table 1. Participant Characteristics (Top) and Medication Status of the 12 Schizophrenia Participants Included in Functional Magnetic Resonance Imaging Analyses (Bottom)

	Scz ($n = 12$), mean (SD)	Ctr ($n = 13$), mean (SD)	t_{23}
Age	29.4 (10.2)	31.6 (10.7)	0.39
Full-scale IQ	110.3 (8.0)	115.9 (3.4)	1.9
Performance IQ	109.7 (4.7)	113.0 (7.3)	1.9
Verbal IQ	108.1 (10.1)	115.1 (8.1)	1.9
Socioeconomic status	38.3 (7.7)	17.6 (5.3)	7.18[*]
SANS global ratings			
Affective flattening or blunting	2.33 (1.67)		
Alogia	1.42 (1.56)		
Avolition-apathy	3.00 (1.41)		
Anhedonia-asociality	2.17 (1.80)		
Attention	1.01 (1.60)		
SAPS global ratings			
Hallucinations	1.2 (1.2)		
Delusions	2.08 (1.62)		
Bizarre behavior	0.25 (0.87)		
Positive formal thought disorder	0.25 (0.62)		

Note: Scz: Schizophrenia; Ctr: control; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; IQ scores are estimated from the National Adult Reading Test[30]; socioeconomic status was derived from the 4-factor index of social status.[31]
[*]$P < .0001$.

Subject Number	Medications
1	Wellbutrin XL 300 mg/d, Zyprexa 15 mg/d
2	Risperdal 1 mg/d
3	Unmedicated
4	Depakote 1250 mg/d, Risperdal 1 mg/d, Lexapro 10 mg/d
5	Abilify 15 mg/d
6	Abilify 15 mg/d
7	Risperdal 2 mg/d
8	Seroquel 200 mg/d, Trazadone 100 mg/d, Lithium 800 mg/d
9	Geodon 160 mg/d
10	Risperdal 1 mg/d
11	Abilify 20 mg/d, Zoloft 100 mg/d
12	Risperdal 4 mg/d, Depakote 2500 mg/d

groups were significant, P's $< .002$. Paired between-groups comparisons within each stimulus condition revealed that participants with schizophrenia were less accurate to aversive stimuli relative to control participants, $P < .05$, but that diagnostic groups did not differ with respect to accuracy to the other 3 stimulus conditions (P's $> .15$). Behavioral performance was also assessed via d' (calculated as $|Z_{hit} - Z_{false\,alarms}|$), a measure of target discrimination abilities relative to the other stimulus conditions. Groups did not differ on d' values, $t_{23} = 1.08$, $P > .29$ [control mean (SE) = 3.56 (0.61), schizophrenia mean (SE) = 3.20 (1.00)].

fMRI Results

Figure 1 depicts whole-brain group-averaged activation maps in response to target, aversive, and neutral conditions (P's $< .001$) in both groups. The coronal view highlights activation in the midfrontal and anterior cingulate cortices in response to target events and inferior and orbital frontal cortex in response to aversive events in the control group (top). Conversely, whereas the schizophrenia group demonstrated ventral frontal activations in response to aversive images, the schizophrenia group did not demonstrate midfrontal gyrus (MFG) activation to target events (bottom). Interestingly, the schizophrenia group demonstrated anterior cingulate gyrus (ACG) activation in response both aversive and target stimuli, and this latter activation appears to be more dorsal than in the control group. Activations in response to neutral
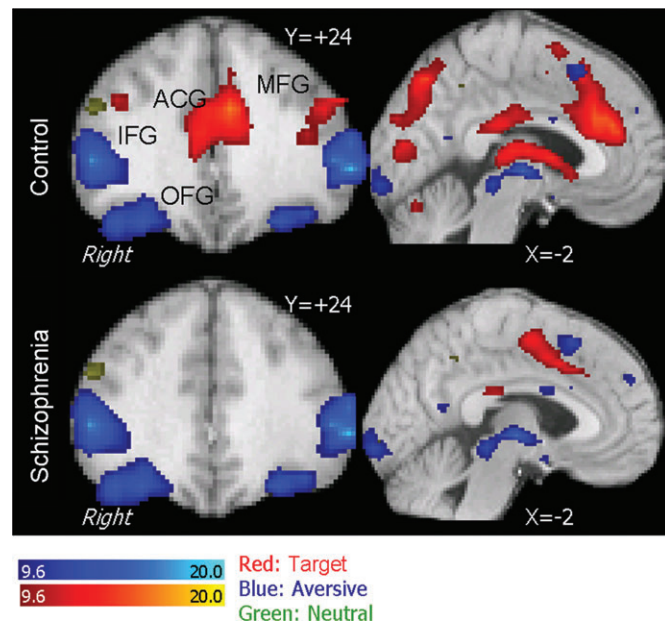

Fig. 1. Group Average Activation Maps Depicting Responses To Target Events in Red, Aversive Events in Blue, and Neutral Events in Green for Control (Top) and Schizophrenia (Bottom) Participants. Contrasts are thresholded at $P<.001$. Activation maps are depicted overlaid on within-groups average structural images.

events were constrained to mainly the occipital lobe in both groups (not shown).

Because the focus of the present investigation was to investigate fronto-limbic functioning in schizophrenia in response to task-relevant (ie, target events) and emotionally distracting, task-irrelevant (ie, aversive) stimuli, we restricted our contrasts to the target and aversive conditions. The top left side of figure 2 depicts random-effects contrast maps of responses to target minus aversive events (in red) and aversive minus target events (in blue) for control (top) and schizophrenia (bottom) participants. The figures reveal that, in control participants, target vs aversive stimuli activated the left MFG, including the DLPFC, as well as the ACG. Also visible is right inferior frontal gyrus (IFG) activation in response to aversive vs target events. The schizophrenia group demonstrated bilateral inferior frontal activation to aversive vs target stimuli but no significant activation in MFG or ACG in response to target vs aversive stimuli. Tables 2 and 3 indicate regions with significant Target > Aversive and Aversive > Target contrasts, respectively, for both diagnostic groups.

The top right side of figure 2 illustrates average hemodynamic activity within functionally derived regions of interest. The schizophrenia group demonstrated significantly less activation to target events in the left MFG from 3.0–7.5 seconds, inclusive, after stimulus onset, and demonstrated a trend toward less deactivation to aversive events 10.5 seconds after stimulus onset. This latter trend effects reflects a faster return to baseline after deactivation to target events in the control group. The ACG demonstrated significantly less activation to target events 4.5 and 6.0 seconds after stimulus onset and trends toward deactivation differences to aversive events 7.5 and 9.0 seconds after stimulus onset in the schizophrenia group, once again reflecting a faster return to baseline after deactivation to target events in the control group. The right IFG, on the other hand, showed greater activation in the control group in response to aversive images relative to the schizophrenia group from 4.5–7.5 seconds, inclusive, after stimulus onset and trends toward deactivation differences to target events 12.0 and 13.5 seconds after stimulus onset, reflecting a slower return to baseline after deactivation to target events in the control group. Although not explicitly tested, visual inspection of the timecourses revealed that overall, deactivations elicited by the aversive stimuli peaked later than activations for both groups, particularly in the left MFG.

The bottom left side of figure 2 illustrates the same contrasts at slices highlighting bilateral AMG activation in the control group to the aversive relative to target stimuli. In participants with schizophrenia, however, only right AMG activation was observed. Notably, as illustrated on the bottom right side of figure 2, groups did not differ with respect to right AMG activation to aversive events, although patients showed greater right AMG activation
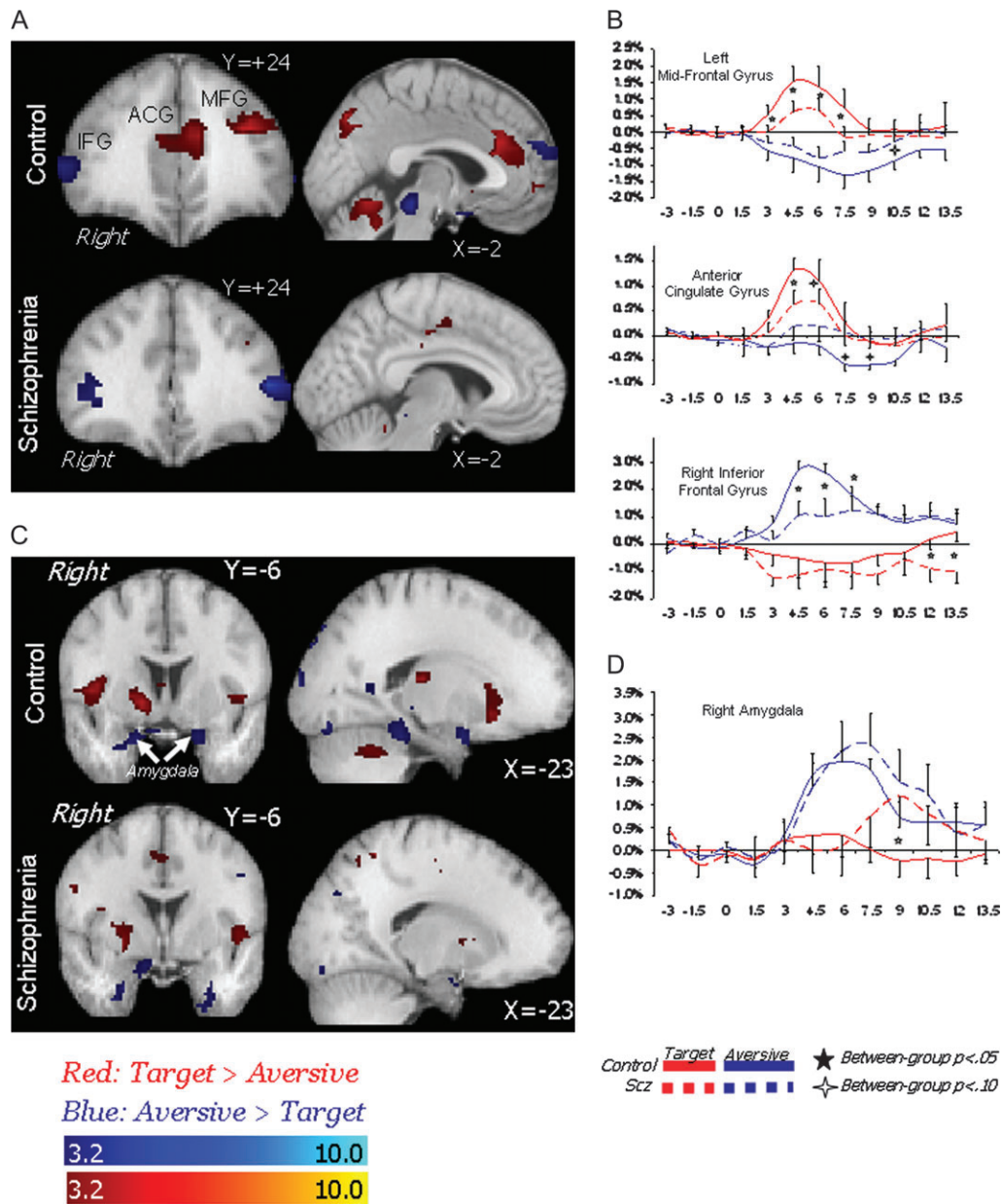
Fig. 2. Top Left: Random-Effects Contrasts Maps Depicting Areas With Greater Activation To Target Relative To Aversive Stimuli (Red) and Aversive Relative To Target Stimuli (Blue) for Control (Top) and Schizophrenia (Bottom) Participants. Contrasts are thresholded at $P < .01$. Activation maps are depicted overlaid on within-groups average structural images. Top right: hemodynamic responses from active voxels in the left midfrontal gyrus (top), anterior cingulate gyrus (middle), and right inferior frontal gyrus (bottom) for the control (blue) and schizophrenia (red) participants in response to target (solid lines) and aversive (dashed lines) stimuli. The y-axes are percent signal change, and the x-axes are seconds. Bottom left: random-effects contrasts maps depicting areas with great activation to target relative to aversive stimuli (red) and aversive relative to target stimuli (blue) for control (top) and schizophrenia (bottom) participants. Contrasts are thresholded at $P < .01$. Activation maps are depicted overlaid on within-groups average structural images. Bottom right: hemodynamic responses from active voxels in the right amygdala for the control (blue) and schizophrenia (red) participants in response to target (solid lines) and aversive (dashed lines) stimuli. The y-axes are percent signal change, and the x-axes are seconds.

to target events 9 seconds after stimulus presentation, although the anomalous shape of the HDR response of the schizophrenia group to aversive stimuli suggests that this may not be a meaningful difference.

Figure 3 depicts the percentages of active voxels on a subject-by-subject basis within functionally defined regions of interest for both diagnostic groups. Group ×

category repeated-measures ANOVAs revealed a significant interaction in the right IFG, multivariate $F_{1,23} = 4.58$, $P < .05$) but not in any other region analyzed. Within-subjects comparisons revealed main effects of category for all regions analyzed (P's < .05).

Finally, to assess for associations between severity of symptoms and functional brain imaging data, relations

Table 2. Summary of Observed Regions of Target > Aversive Activations

X	Y	Z	MaxT	NumVox	Side	Region
Control group						
−1	−58	−14	7.20	388	L	Declive
39	54	−12	4.10	13	R	Middle frontal gyrus
16	6	14	8.49	1306	R	Extranuclear white matter
49	48	−8	4.20	8	R	Middle frontal gyrus
38	48	23	7.43	311	R	Superior frontal gyrus
9	35	26	6.23	608	R	Cingulate gyrus
−50	−17	22	7.54	888	L	Postcentral gyrus
34	−16	3	3.22	9	R	Extranuclear white matter
7	49	3	4.58	29	R	Medial frontal gyrus
56	−40	43	8.50	756	R	Inferior parietal lobule
−27	49	19	5.41	120	L	Middle frontal gyrus
−62	10	21	3.98	14	L	Inferior frontal gyrus
8	−73	43	7.29	244	R	Precuneus
Schizophrenia group						
−14	−56	−22	4.45	40	L	Dentate
10	−55	−12	4.61	172	R	Declive
35	−48	−25	3.87	9	R	Culmen
49	−34	58	7.1	802	L	Inferior parietal lobule
−1	−14	−18	4.39	10	L	Brain stem
10	−25	40	9.05	2076	R	Cingulate gyrus
45	55	13	3.57	22	R	Middle frontal gyrus
27	52	24	4.07	9	R	Superior frontal gyrus
31	37	44	3.70	11	R	Middle frontal gyrus

Note: X, Y, and Z refer to the stereotaxic coordinates of the center of the region-of-interest activation. NumVox: number of voxels; L: left; R: right.

between both the magnitude and the extent of stimulus-dependent BOLD activation in functionally defined regions of interest, presented above, and SANS and SAPS scores were assessed in an exploratory fashion. Significant relations were found between activation of the ACG to aversive stimuli and SANS measures of avolition and anhedonia, P's $< .002$, uncorrected (see figure 4). No other fMRI-symptom relations were significant, and relations between behavioral performance on the task (ie, reaction time and accuracy to target and aversive events) and SANS and SAPS scores were not significant as well (P's $> .05$).

Discussion

The findings from this study suggest that abnormal cortical and subcortical activity in schizophrenia extends to impaired inhibitory processes linked to shifting between attentional and emotional domains, indicating that individuals with schizophrenia may fail to generate and maintain a balance between task-dependent rule-based response selection and motivational or incentive-based response inhibition.

When confronted with a task requiring task-relevant response selection and simultaneous selective inhibition of responses to task-irrelevant emotionally salient stimuli, control subjects activated a frontostriate circuitry while activity in limbic regions was suppressed, including the amygdala and orbitofrontal cortex. Between-condition analyses further revealed that control participants activated a dorsal brain network in response to target vs aversive stimuli and a ventral brain network in response to aversive vs target stimuli. This pattern of activity indicates that control subjects engaged executive attentional processes to respond to task-relevant targets while inhibiting responses to task-irrelevant salient emotional stimuli.

In contrast, patients with schizophrenia showed not only aberrant regional activations to targets and emotional stimuli but also reduced activation in executive regions to aversive stimuli, such as inferior frontal and reduced midfrontal activation to target events, while simultaneously showing abnormally increased dorsal activation of the ACG in response to aversive events. The schizophrenia group further showed no significant dorsal activation in response to target vs aversive stimuli but evidence of ventral brain network activation in response to aversive vs target stimuli (with the exception of the left AMG).

Between-group analyses of hemodynamic timecourses revealed that, as predicted, the schizophrenia group demonstrated statistically less activation to target events in the MFG and ACG compared with controls. Interestingly, they also showed trends toward less MFG and ACG deactivation to aversive events as compared with controls. Both these findings appeared to be more

Table 3. Summary of Observed Regions of Aversive > Target Activations

X	Y	Z	MaxT	NumVox	Side	Region
Control group						
−33	−67	10	7.81	1493	L	Subgyral white matter
38	−66	6	10.32	1093	R	Middle occipital gyrus
−18	12	−18	3.6	8	L	Inferior frontal gyrus
23	−4	−12	3.42	11	R	Amygdala
−19	−2	−13	3.12	13	L	Amygdala
−43	29	8	5.92	379	L	Inferior frontal gyrus
57	30	13	4.6	64	R	Inferior frontal gyrus
2	−54	23	4.4	198	R	Posterior cingulated
28	−48	45	4.65	17	R	Precuneus
−25	−55	53	4.95	12	L	Subgyral white matter
Schizophrenia group						
−23	8	−27	7.48	43	L	Uncus
39	−2	−26	4.43	19	R	Subgyral white matter
39	−70	7	13.84	989	R	Middle occipital gyrus
−31	−73	8	8.12	868	L	Middle occipital gyrus
25	−10	−10	3.97	12	R	Amygdala
−24	37	−10	3.60	8	L	Middle frontal gyrus
−47	35	7	9.12	280	L	Inferior frontal gyrus
37	37	−6	5.84	14	R	Middle frontal gyrus
−59	−56	7	3.97	17	L	Middle temporal gyrus
−11	−46	12	3.95	23	L	Posterior cingulated
53	18	25	7.17	226	R	Inferior frontal gyrus
−8	57	13	4.49	50	L	Medial frontal gyrus
−36	10	32	4.26	43	L	Middle frontal gyrus
31	−61	47	3.21	9	R	Superior parietal lobule

Note: X, Y, and Z refer to the stereotaxic coordinates of the center of the region-of-interest activation. NumVox: number of voxels; L: left; R: right.

prominent in the left rather than right hemisphere. The results also indicated that the control group demonstrated longer deactivation latencies before responses returned to baseline. These trends suggest that perhaps control individuals engage in longer frontal inhibitory processes in response to emotionally aversive information. Individuals with schizophrenia, however, may engage such inhibitory processes for shorter durations, resulting in poor frontal control when confronted with
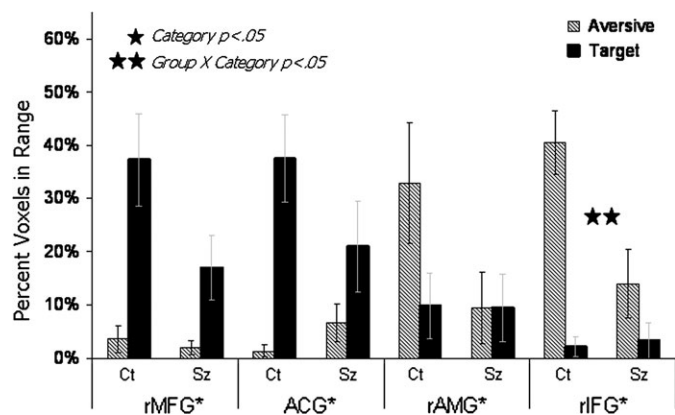
aversive stimuli. This conclusion is tentative, however, given that these effects were trends. Conversely, the schizophrenia group demonstrated less activation to aversive events in the right IFG and trends toward less right IFG deactivation differences to target events in
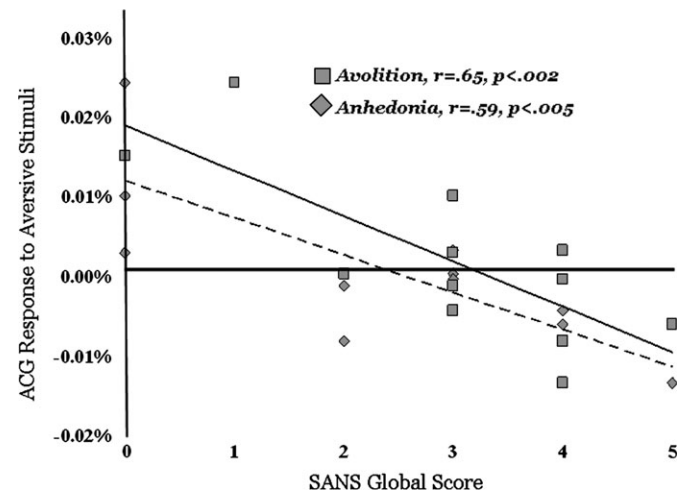

Fig. 3. Percentages of Active Voxels Within Functionally Defined Regions of Interest Subdivided by Diagnostic Group and Region.

Fig. 4. Scatterplot of the Magnitude of Blood Oxygenation Level–Dependent Activation in the Anterior Cingulate in Response To Aversive Events and Scale for the Assessment of Negative Symptoms Global Scores.

this region, although the shapes of these HDR curves suggests that these results may be spurious and warrant replication.

Notably, groups did not differ with respect to right AMG activation to aversive vs target events. Intact AMG response to aversive stimuli, in conjunction with reduced deactivation of frontal regions in response to aversive events, suggests that schizophrenia may be characterized not by blunted responses to emotionally salient events but rather by poor inhibition of responses to such events in the context of goal-directed behavior. Additionally, diagnostic groups differed in the spatial extent of IFG activation to target and aversive events, lending further support to the notion that the schizophrenia group was characterized by abnormal ventral modulation in response to emotionally salient stimuli.

Finally, we assessed relations between regional brain activation intensities and symptom severity. We found significant inverse correlations between ACG activation to aversive stimuli and SANS global scores of avolition and anhedonia. These findings suggest that anterior cingulate hypoactivation in response to aversive events may represent a core aspect of the abnormal regulation of attention and emotion circuits in schizophrenia or for affective dysregulation in this disorder. This proposition is consistent with recent evidence of differential functional disconnects between frontal and limbic areas based on paranoia subtype[44] and indicate that tasks that assess patterns of frontolimbic activity in schizophrenia may be particularly sensitive to specific schizophrenia symptom profiles.

One notable finding of the present study was that target-related activation in the anterior cingulate in the schizophrenia group was considerably more dorsal than in the control group (Talairach coordinates of centroids: control: +9, +35, +26; schizophrenia +10, −25, +40; see table 2). Additionally, the schizophrenia group showed midcingulate activation in response to aversive events. This pattern is interesting in light of findings in nonclinical samples using the same task indicating that the cingulate shows activation in response to aversive events when participants are instructed to respond to aversive events as targets.[26] Thus, the schizophrenia group responded to the aversive events in much the same way as control participants did when instructed to attend to these events, suggesting an inability to suppress attentional orienting and cognitive processing of emotionally salient but task-irrelevant information.

It is also interesting to note that both control and schizophrenia subjects appeared to demonstrate later regional deactivations relative to activations, particularly in the left MFG. Though this observation is qualitative in nature, it may suggest that processing one set of stimuli is protected by projections from active regions that serve to deactivate other regions (eg, target events activate the MFG, which in turn may have projections that serve

to deactivate ventral brain regions). In other words, rather than occurring in parallel, deactivations may be a downstream consequence of regional activations.

With regard to the forced-choice oddball design employed in the present study, unlike other tasks designed to evaluate responses to goal-directed behaviors (eg, go-nogo or nogo-go tasks), a forced-choice oddball design elicits a response to every event. This paradigm results in an "active baseline," ie, baseline activation that does not reflect a resting state but rather active responses that include perceptual and decision-making components. Some have suggested that schizophrenia may be characterized by an elevated resting state characterized by "neural noise,"[47] and the "active" baseline created by this task does not allow for an evaluation of the potential effects of elevated "neural noise" in schizophrenia. We note, however, that the present task was selected not for its ability to provide a baseline devoid of active decision-making components but rather because it has been shown to activate critical regions of interest in schizophrenia, namely the frontal cortex, cingulate, and AMG. Additionally, a forced-choice task allows for an examination of behavioral responses to all stimuli, a design feature not shared by other tasks that do not require responses to all stimuli.

Behavioral performance revealed a trend toward slower responding in the schizophrenia group to all 3 infrequently presented categories. This pattern is consistent with psychomotor retardation that is characteristic of the disorder.[12] However, significant accuracy differences were only evident in response to aversive images (although accuracy differences to the target and neutral stimuli were in the same direction). While this result may reflect that arousing, emotionally salient stimuli prompt "target" responses in the patient group, or alternatively, these findings may indicate an interruption of or a reduced inhibitory mechanisms that typically serves to gate orienting to task-irrelevant salient stimuli. This pattern is also consistent with poor response inhibition that has been observed in schizophrenia in other paradigms.[48,49] Most relevant in the present context, there were no group interactions with stimulus category, suggesting that diagnostic groups did not differentially moderate responses to the stimulus categories. Additionally, relations were not evident between behavioral performance and brain imaging data, indicating that imaging results likely did not reflect deficits in task performance but rather differential recruitment of brain regions employed to perform the task.

We note that future studies should address a number of issues. First, participant ratings of the aversive images were not collected; such data would permit examinations of possible relations between subjective responses to aversive images and regional brain activation to parse the relative contributions of the high arousal and negative valence of the images employed to brain activation

patterns. We also note that larger sample sizes would afford increased power to detect other relations between symptom severity and BOLD responses to experimental conditions. Additionally, accuracy rates for both groups were generally lower in the present study than in previously reported studies using the same paradigm (ie, Fichtenholtz et al[28] reported 93%–94% accuracy for target events). Although the source of this discrepancy is unclear, we note that in the present study only epochs corresponding to correct behavioral responses were included in analyses. Furthermore, in light of recent evidence of relations between attentional efficiency and diffusion tensor imaging measures of cingulum bundle fractional anisotropy in schizophrenia[45] as well as evidence of smaller gray matter cingulate gyrus volumes in individuals with schizophrenia,[46] the cingulum would appear to be a brain region warranting further study in studies of attentional impairments in schizophrenia. Finally, the fact that all but one participant with schizophrenia were taking antipsychotic medications at the time of fMRI assessment may have attenuated our between-groups findings, and future studies with unmedicated patients may be more sensitive to diagnostic group differences in this context.

In summary, the present study investigated functional frontolimbic modulation in schizophrenia and revealed that individuals with schizophrenia showed attenuated activation in a dorsal executive attention network and attenuated deactivation in response to target vs aversive events in a ventral emotional processing network. These results are consistent with a model of abnormal cortical and subcortical activity in schizophrenia that extends to impaired inhibitory processes linked to shifting between attentional and emotional domains, indicating that individuals with schizophrenia may fail to generate and maintain a balance between task-dependent rule-based response selection and motivational or incentive-based response inhibition.

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