

Neural Mechanisms of Affective Interference in Schizotypy

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Negatively valenced stimuli foster cognitive impairment in schizotypy and schizophrenia. To identify relevant brain mechanisms, the authors had 16 positive-schizotypy and 16 control participants perform an emotional Stroop task, judging the ink color of negative and neutral words during functional magnetic resonance imaging (fMRI) of regional brain activity. Schizotypy individuals showed increased right and decreased left activity in dorsolateral prefrontal cortex, indicating a deficit in maintenance of attentional set in the presence of negative emotional distractors. They also showed abnormal activity in ventral limbic areas, including decreased activity in nucleus accumbens and increased activity in hippocampus and amygdala, a circuit involved in the integration of cognitive and affective processes. These results indicate that aspects of emotion–cognition processes and the brain mechanisms that implement them are similar in schizotypy and schizophrenia.

Conceptualizations of schizophrenia often focus on cognitive disturbances such as delusions and disorganized speech and on the role that cognitive mechanisms play in the development of these symptoms. However, extensive evidence indicates that affective factors play an important role in the development, clinical picture, prognosis, and treatment of schizophrenia. Several lines of investigation, including life event, family environment, clinical, and laboratory studies, provide evidence of symptom exacerbations in response to negative affect in schizophrenia (for review, see Docherty, 1996; Malla & Norman, 1992; Slade, 1972), particularly for positive symptoms (Docherty, Evans, Sledge, Seibyl, &

Krystal, 1994; Docherty & Hebert, 1997; Schwartz & Myers, 1977). To better understand the role of affective disturbance in the formation and exacerbation of positive symptoms, it is important to examine the role affective disturbance plays in the disruption of basic cognitive processes such as attention, perception, judgment, and language that may ultimately manifest as psychotic symptoms, as well as the brain mechanisms involved in this disruption.

Researchers have hypothesized that the interplay of cognitive and affective processes leads to the formation and maintenance of positive symptoms including delusions and hallucinations (e.g., Freeman, Garety, Kuipers, Fowler, & Bebbington, 2002; Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001). For example, negative affect compromises basic areas of cognition in schizophrenia, including language (Burbridge & Barch, 2002; Docherty, 1996; Grosh, Docherty, & Wexler, 1995), semantic processing (Kerns & Berenbaum, 2000), and size estimation (Asarnow, Cromwell, & Rennick, 1978). Although there is extensive research demonstrating selective attention deficits in schizophrenia and schizotypy (e.g., Braver, Barch, & Cohen, 1999; Lubow & Gervitz, 1995), there is little research examining the impact of emotion on attentional processing in individuals with schizophrenia or schizotypy. Patients with predominantly positive symptoms show more interference for threat-related words on an emotional Stroop task than do patients without active psychotic symptoms (Epstein, Stern, & Silbersweig, 1999). Similarly, perceptual aberration and magical ideation as measures of positive schizotypy are associated with increased behavioral interference on an emotional Stroop task, whereas negative schizotypy (social and physical anhedonia) shows no relationship (Mohanty et al., 2001). These findings are in line with earlier research demonstrating that individuals with predominantly positive symptoms appear to be more responsive to stressors (e.g., Schwartz & Myers, 1977) and show increased affective reactivity of cognitive disturbance than do

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individuals with negative symptoms (Docherty et al., 1994), a finding that has been replicated with positive schizotypy as well (Fernandes & Miller, 1995; Kerns & Berenbaum, 2000). It is unclear what brain mechanisms are involved in this association of cognitive disturbance and negative affect in positive-symptom schizotypy and schizophrenia. The present study used an emotional Stroop paradigm and fMRI to examine brain regions involved in the adverse impact of emotion on attentional processing seen in positive schizotypy.

Schizotypy involves characteristics that predispose individuals to schizophrenia (Edell, 1995; Fernandes & Miller, 1995). Self-report measures of schizotypal features are associated with elevated risk for symptoms of psychosis (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Erlenmeyer-Kimling et al., 1993; Fernandes & Miller, 1995; Freedman, Rock, Roberts, Cornblatt, & Erlenmeyer-Kimling, 1998). High-schizotypy nonpatients exhibit some of the psychological and biological abnormalities reported in individuals with schizophrenia yet generally lack a history of psychotropic medication, hospitalization, and other complications common in studies of schizophrenia (Dickey et al., 2000; Fernandes & Miller, 1995). Schizotypy factor dimensions parallel symptom domains observed in patients with schizophrenia, suggesting that schizotypal traits and schizophrenic symptoms can be viewed on a continuum (e.g., Vollema & Hoijsink, 2000). In summary, some but not all aspects of clinical schizophrenia are present in schizotypy, providing a relatively pure context for studying selected symptoms and identifying associated brain mechanisms.

According to Braver, Barch, and Cohen (1999), the most consistently reported attentional impairments in schizophrenia involve the exertion of attention in a selective and controlled manner to facilitate processing of task-relevant information, to inhibit the processing of task-irrelevant information, or both. This impairment is likely due to a failure in the maintenance of contextual information in the presence of salient distractors. The color-word Stroop task, referred to as the “gold standard” for the measurement of selective attention (MacLeod, 1992), has been used to demonstrate this impairment in schizophrenia (e.g., Barch, Carter, et al., 2001). Given that cognitive impairment in schizophrenia is exacerbated by negative affect, it is likely that attentional functioning will tend to deteriorate in the presence of aversive stimuli. The present investigation used a variant of the color-word Stroop task called the emotional Stroop task, which involves the simultaneous presentation of task-relevant (color of letters) and task-irrelevant (emotional meaning) attributes. The task was to identify the ink color of a word as quickly as possible while ignoring the word’s meaning. Performance depends on selective attention to task-relevant versus task-irrelevant stimulus features and maintenance of contextual information (J. D. Cohen & Servan-Schreiber, 1992; Servan-Schreiber, Cohen, & Steingard, 1996). On the basis of prior literature (reviewed later), we proposed the involvement of a constellation of brain regions, including dorsolateral prefrontal cortex (DLPFC), ventral and dorsal striatum, and limbic regions, to account for the increased interference for negative versus neutral words in positive schizotypy.

DLPFC appears to play an important role in active maintenance of contextual information (e.g., Banich et al., 2000, 2001; Barch et al., 1996; Braver et al., 1999), particularly in the face of interference (Miller, Erickson, & Desimone, 1996). It has been proposed

that the deficit in the ability to maintain contextual information in patients with schizophrenia involves a disturbance in DLPFC (e.g., Barch, Braver, et al., 2001). Studies integrating neuropsychological performance with neuroimaging data show that individuals with schizophrenia or those at risk for schizophrenia do not activate DLPFC normally when performing a task that places demands on DLPFC processing resources (e.g., Andreasen et al., 1992; Barch, Braver, et al., 2001; Gold, Goldberg, & Weinberger, 1992; MacDonald, Johnson, Becker, & Carter, 2003; Weinberger, Berman, & Zec, 1986). This finding has contributed to the concept of “hypofrontality” in schizophrenia. However, there is increasing evidence that the traditional concept of hypofrontality in schizophrenia is incomplete (Ramsey et al., 2002; Weiss et al., 2003). For example, recent studies provide evidence for increased task-related activity in either right (Callicott et al., 2000, 2003; Weiss et al., 2003) or left (Manoach et al., 1999, 2000; Weiss et al., 2003) DLPFC in individuals with schizophrenia or those at risk for developing schizophrenia. These apparent inconsistencies might be attributed to many factors, including experimental design and behavioral task complexity (e.g., Callicott et al., 1999), presence of reward (Manoach et al., 2000), and data analytic techniques such as examining group-averaged data (which underestimates DLPFC activation because of heterogeneity of location within DLPFC) versus single-participant data (Manoach et al., 2000). Evidence for the role of these factors in the inconsistencies is inconclusive. Although DLPFC dysfunction has been observed in relatives of individuals with schizophrenia (Callicott et al., 2003; MacDonald et al., 2003), it remains to be studied in at-risk individuals who are elevated on measures of schizotypy. The primary hypothesis in the present study was that DLPFC dysfunction would be evident even in nonpatient individuals with elevated positive schizotypy scores when asked to perform a task requiring maintenance of context in the presence of distracting, aversive information.

Despite considerable evidence demonstrating DLPFC dysfunction in schizophrenia, it remains uncertain whether this dysfunction arises from neural abnormalities primarily in DLPFC or as a result of dysregulation of DLPFC by other structures (Callicott et al., 2000; Manoach et al., 2000). An important circuit that has frequently been implicated in cognitive and affective dysfunction in schizophrenia is the “ventral limbic cortical–basal ganglia circuit” (Grace & Moore, 1998). The ventral circuit includes the prefrontal cortex (PFC), limbic, and ventral striatal regions as well as connections among them. As the main striatal link in the ventral circuit, the nucleus accumbens receives inputs from hippocampus, amygdala, and PFC and can influence higher cognitive processing through efferents to a thalamocortical network that modulates PFC (Grace & Moore, 1998; Groenewegen et al., 1991; O’Donnell, Greene, Pabello, Lewis, & Grace, 1999). For example, single-cell studies have shown that both hippocampal and amygdalar inputs to the nucleus accumbens modulate or gate neurons in PFC (Grace, 2000a). The firing of neurons in PFC results in the transmission of action potentials via the striatum only when there is concurrent input to the striatum from the hippocampus (Grace, Moore, & O’Donnell, 1998). Besides this gating role, the hippocampus plays a very important role in contextual learning (N. J. Cohen & Eichenbaum, 1993; Rudy & Sutherland, 1995; Salzmann, Vidyasagar, & Creutzfeldt, 1993) and recognition of context for an event (Chun & Phelps, 1999). Together with the evidence that hippocampus can modulate activity in PFC, the latter findings

suggest a cardinal role that hippocampus may play in the development of positive symptoms (Liddle, Lane, & Ngan, 2000). In fact, there is considerable evidence implicating hippocampus and parahippocampal gyrus in positive symptoms of schizophrenia (Bogerts, 1997). More recent functional imaging studies have also reported that overactivity of hippocampus and parahippocampal gyrus is associated with positive symptoms (Epstein et al., 1999; Liddle et al., 1992; Silbersweig et al., 1995).

The amygdala, another important component of the ventral circuit, is crucial in the evaluation of internal and external stimuli in terms of their motivational and emotional significance (e.g., Cahill, Roozendaal, & McGaugh, 1997; Davidson & Irwin, 1999; LeDoux, 1995). The amygdala provides a different kind of neuromodulation or gating: Stimulation of amygdala will facilitate prefrontal spiking only if it precedes PFC stimulation by less than 40 ms (Grace & Moore, 1998). As a result, the amygdala provides a more event-related gating, rather than the more general, context-dependent gating from the hippocampus, a means by which salient emotional stimuli can override an otherwise context-limited response system. Studies examining the role of amygdala in emotional processing in schizophrenia have yielded mixed results, including reports of decreased (e.g., Schneider et al., 1998) and increased (Epstein et al., 1999) amygdalar activity in response to emotional stimuli. An important factor that might account for varied results is that most studies did not determine whether the schizophrenia sample included individuals with predominantly positive or negative symptoms. This is particularly important because positive symptoms tend to be more reactive to negative affect than are negative symptoms (Docherty et al., 1994). Although one study reported that positive-schizophrenia individuals show less amygdala activity than control participants (M. L. Phillips et al., 1999), two others found a positive association between positive symptoms and amygdala activity (Epstein et al., 1999; Taylor, Liberzon, Decker, & Koeppe, 2002). Clearly, there is a need for more studies that delineate distinct symptom dimensions and examine their differential relationship with amygdala activity. Furthermore, it is also possible that the amygdala findings in the schizophrenia literature are confounded with medication status because ventral brain regions including amygdala are sites of action for antipsychotic medication (Taylor et al., 2002). The present study avoided these confounds by recruiting at-risk individuals who were unmedicated and who scored high only on measures of positive schizotypy.

In summary, based on the architecture of the ventral circuit and the roles its components play in cognitive and affective processing, it is plausible that abnormalities within any of the components of the ventral circuit are associated with positive symptoms in schizotypy and schizophrenia. Despite evidence implicating the role of different components of this ventral circuit in cognitive and affective dysfunction in schizophrenia, very few studies have examined the role that these components play in similar deficits among at-risk populations such as those individuals who score high on measures of schizotypy. In the present study, it was hypothesized that positive-schizotypy individuals would show abnormal activation in the network of regions involved in the ventral circuit including nucleus accumbens, hippocampus, amygdala, and PFC while performing the task for the negatively valenced words.

Another region that is functionally and anatomically well connected with the PFC is the dorsal striatum (basal ganglia, including

caudate and putamen; Middleton & Strick, 2000). Researchers have hypothesized that the basal ganglia plays an important role in working memory by providing a gating mechanism that modulates a prefrontal active maintenance system (Frank, Loughry, & O'Reilly, 2001). It is possible that working memory deficits in schizophrenia are related to a dysfunction in the dorsal frontostriatal circuitry that implements this gating mechanism. Dysfunction in frontostriatal circuitry in schizophrenia has been demonstrated using a variety of techniques (Buchsbaum et al., 1992; Manoach et al., 2000; Rubin et al., 1991; Siegel et al., 1993). For example, Rubin et al. (1991) showed that abnormal prefrontal activity in schizophrenia is associated with a failure to suppress blood flow to the striatum during working memory performance. Severity of formal thought disorder in schizophrenia is positively correlated with activity in right caudate nucleus (Kircher et al., 2001). Furthermore, dorsal striatal dopamine receptor abnormalities are implicated in thought and movement abnormalities as well as in abnormal sensitivity to stress in schizophrenia (Walker, Neumann, Baum, & Davis, 1996).

Thus, another goal of the present study was to investigate whether individuals who score high on a positive schizotypy measure, like patients with schizophrenia, show abnormal activity in the basal ganglia while performing the Stroop task for negative-emotion stimuli. Use of a nonpatient sample to test these hypotheses regarding the emotional factors affecting the neural circuits involved in cognitive impairment allowed a relatively uncompromised evaluation, especially with respect to alterations in dopaminergic systems targeted by antipsychotic medication.

Method

Participants

Two groups of right-handed, native English speakers were recruited from the university community, 17 scoring high on a measure of positive-schizotypy (12 men and 5 women; mean age = 19.1, $SD = 1.9$) and 17 control participants (7 men and 10 women; mean age = 20.5, $SD = 3.9$). Participants were screened for a history of neurologic damage, color blindness, claustrophobia, or contraindications for fMRI participation and gave informed consent prior to participation. Positive-schizotypy individuals were selected from large groups of introductory psychology students tested with a battery of questionnaires including the Chapman scales for psychosis proneness. Individuals with a score at least 1.5 standard deviations above the mean on either the Perceptual Aberration Scale (Chapman, Chapman, & Raulin, 1978) or the Magical Ideation Scale (Eckblad & Chapman, 1983) were included in the positive-schizotypy group. Control participants scored 0.5 standard deviation below the mean on both the Magical Ideation and the Perceptual Aberration Scales. The t tests confirmed that the positive-schizotypy group scored higher than the comparison group on the Perceptual Aberration and Magical Ideation Scales ($p < .01$). Anxiety measures were obtained using the Penn State Worry Questionnaire (Meyer, Miller, Metzger, & Borkovec, 1990) from 15 of the positive-schizotypy and 12 for the control participants.

Stimuli and Experimental Design

Stimulus presentation and collection of response times (RTs) were accomplished with MEL v2.0 PC software (Psychology Software Tools, Pittsburgh, PA). Each participant was involved in a single fMRI session consisting of blocks of positive- or negative-emotion words alternating with blocks of neutral words. Four positive, four negative, and eight neutral blocks were presented in a session. Stimuli were blocked on emotional

valence for several reasons. Behavioral studies have demonstrated that the emotional quality of words is harder to ignore when they are blocked rather than intermixed with neutral words (Holle, Neely, & Heimberg, 1997; see also Compton, Heller, Banich, Palmieri, & Miller, 2000; Dalgleish, 1995). The valence of real-world emotional information does not typically alternate rapidly. Finally, several behavioral pilot studies for this project demonstrated an interference effect with emotional words for blocked but not intermixed designs.

Each block consisted of 16 trials with 1 trial occurring every 2,000 ms. A trial began with the presentation of a word for 1,700 ms, followed by a fixation cross for 300 ms. Each trial consisted of one word presented in one of four ink colors (red, green, yellow, or blue), with each color occurring equally often with each word type (positive, neutral, or negative). The first and third blocks were neutral words, and the second or fourth blocks were positive or negative words, with this pattern repeated for the total of 16 blocks. The valence order was counterbalanced across participants to minimize order effects. Negative words were chosen based on available norms of arousal and valence ratings (Bradley & Lang, 1998). Each neutral word list was matched closely to one of the emotion word lists on concreteness, imageability, familiarity, and word length based on published norms (Toglia & Battig, 1983). Neutral words were chosen to be semantically related within a list, just as the emotion words were semantically related within list. Thus, one neutral word list consisted of time-related words (e.g., *decade*, *minute*), and the other of math-related words (e.g., *add*, *subtract*).

Procedure

Before the fMRI session, participants were thoroughly informed about the nature of the study and the magnetic resonance environment; consent was obtained. The experiment lasted approximately 45 min. Visual stimuli were presented using a goggle system (Resonance Technology, Northridge, CA). Participants were instructed to identify the ink color of each word (red, yellow, green, or blue) while ignoring the word's meaning. They were asked to indicate their response by pressing one of four buttons corresponding to the ink colors. To reduce motion artifact, a manual response was used, consistent with previous studies in our laboratory and others' indicating successful elicitation of Stroop effects (e.g., Compton et al., 2003; Herrington et al., 2004). A short practice session was conducted outside the magnet in order to familiarize the participants with the stimuli and to help them learn the button order on the response pad.

Echo-planar (EPI) images were acquired in a 1.5 Tesla GE Signa scanner (Milwaukee, WI). Head position was stabilized using a bite bar molded to each participant's dentition. For each participant, 445 EPI images were acquired (time for repetition = 1,517 ms, echo time = 40 ms, and flip angle = 90°). Each image consisted of 15 contiguous slices (thickness = 7 mm; no gap, in-plane voxel size = 3.75 × 3.75 mm) parallel to the horizontal plane containing the anterior and posterior commissures. High-resolution, three-dimensional (3D) anatomical images (T1-weighted 3D gradient echo images) of the whole brain were collected for each participant for landmark selection purposes. T1-weighted anatomical images of the 15 functional acquisition slices were also collected for image registration purposes.

Image Processing

Image processing and analyses was carried out using the Oxford Center for functional magnetic resonance of the brain (FMRIB) FEAT (FMRIB's easy analysis toolVersion 5.00), part of FSL (FMRIB's software library; www.fmriv.ox.ac.uk/fsl). The first six volumes from each participant were discarded to allow the signal to reach steady state. Prior to analysis, functional data for each participant were motion corrected through the use of motion correction using FMRIB's linear image registration tool (MCFLIRT; Jenkinson & Smith, 2001), intensity normalized, temporally

filtered with a nonlinear high-pass filter, and spatially smoothed using a 3D Gaussian kernel (full width half maximum = 7 mm). MCFLIRT effectively adjusts for motion up to 2 mm (Jenkinson, Bannister, Brady, & Smith, 2002), so individuals showing head motion more than 2 mm were excluded (e.g., Schaefer et al., 2002). One participant in each group exceeded this criterion for a final number of 16 per group.

Regression Analyses

Regression analyses were performed on the processed functional time series of each participant using FMRIB's improved linear model (FILM). Four regressors, one each for the positive, negative, and two neutral conditions, were included in the regression model. For each regressor, the vector of assigned weights corresponding to word type was convolved with a gamma function to better approximate the temporal course of the blood-oxygen-dependent hemodynamic response. Each regressor yielded a per-voxel effect-size parameter (beta) estimate map representing the magnitude of activity associated with that regressor. Because present hypotheses focused specifically on the effect of negative stimuli on attentional processing, subsequent steps in the data analysis involved only the RT and fMRI measures derived from the negative and matched neutral word condition.

Thus, the beta values for the negative word condition were contrasted with the neutral word condition, resulting in per-voxel contrast parameter (beta) estimate maps. These functional activation maps, as well as the corresponding structural MRI maps, were morphed into a common stereotaxic space (Talairach & Tournoux, 1988) using FMRIB's linear image registration tool (FLIRT).

Prior to group comparisons, regions that were significantly more active for negative than for neutral word conditions were identified within each group via voxelwise, one-sample *t* tests on contrast beta maps. Probability values from the *t* tests were then converted to *z* scores. The *z* maps were thresholded for significance using a cluster-size algorithm (Forman et al., 1995) that reduces false positives in the context of multiple comparisons by taking into account the spatial extent of the activation. Regions were considered active if they contained at least 30 contiguous voxels, each voxel active above an alpha threshold of .05. That cluster-size threshold provides a corrected per-voxel, false-positive rate of .0005 (Forman et al., 1995). To minimize experiment-wise Type I error, group comparisons were confined to voxels with significant activation for negative versus neutral words in at least one group. Voxelwise, two-tailed *t* tests compared the effect sizes (contrast betas) for the two groups. Once again, a cluster-size threshold of at least 30 contiguous voxels with each voxel above an alpha of .05 (providing a corrected per-voxel, false-positive rate of .0005) was chosen to identify regions that differentiated the groups. Requiring conjunction of orthogonal within-group and between-groups tests yielded a corrected per-voxel error rate of $p < .00000025$ (.0005 × .0005; Barch, Braver, et al., 2002; Barch, Carter, et al., 2001; Braver, et al., 2001).

Mohanty et al. (2001) showed that anxiety and depression are strongly correlated with positive schizotypy. Thus, for the present independent data set, a mediating variable analysis (Baron & Kenny, 1986) examined whether anxiety mediated the relationship between positive schizotypy and brain activity in the regions identified in the cluster-threshold analyses.

RT data were not available for 2 schizotypy individuals because of technical difficulties. Although the present article evaluates responses to negative emotional words, parallel analyses of positive versus neutral words found no regionally overlapping group differences.

Results

Behavioral Data

Every participant showed choice-RT performance accuracy of at least 80%. RTs for incorrect trials were excluded from behavioral

data analyses. Emotional Stroop interference was calculated as the difference in RT for negative and neutral words. The group RT interference effect was in the expected direction of greater interference in the schizotypy group (5.7 ms, $SD = 38.2$) than in the control group (1.7 ms, $SD = 43.6$), but RT interference and error-rate differences as a function of group did not approach significance. Results from a behavioral study using a very similar paradigm and a larger sample found a significant relationship between composite schizotypy score and interference (Mohanty et al., 2001), supporting the effectiveness of the present experimental manipulation.

fMRI Data

Table 1 reports regions showing greater activity for negative words than neutral words, within each group. For both groups this included DLPFC (Brodmann Area [BA] 9 and BA 46), inferior frontal gyrus (BA 46 and BA 47), and anterior cingulate (BA 32; see also Figure 1, lower right panel). Each group showed effects in several additional brain regions listed in Table 1.

Table 2 lists all brain regions showing group differences in negative-minus-neutral-condition activation. Figure 1 focuses on differences in regions that are part of the brain circuits hypothe-

sized to differentiate individuals with schizotypy. As predicted, the two groups differed in a network of regions believed to be involved in the implementation of attentional control, in maintenance of contextual information, and in emotional processing, including prefrontal, striatal, limbic, and cerebellar regions.

The schizotypy group showed greater activation in right middle frontal gyrus within DLPFC (BA 9) and inferior frontal gyrus (BA 46). The schizotypy group also showed differential activity in a network of regions constituting the ventral limbic cortical–basal ganglia circuit. Specifically, the schizotypy group showed more activation in the right parahippocampal gyrus and in a region around and extending into the amygdala (a cluster for which the peak was in the putamen per Table 1). Parallel analyses of deactivations showed that schizotypy individuals showed more deactivation in nucleus accumbens than did control participants. Outside of these components of the ventral circuit, the schizotypy group showed greater activation in dorsal striatal regions including caudate and putamen as well as left cerebellum. The control group showed greater activation in a number of areas, including the left middle frontal gyrus (BA 46), left superior temporal gyrus (BA 22), right inferior temporal gyrus (BA 21), and right middle occipital gyrus (BA 18 and BA 19).

Table 1
Brain Regions Showing More Activity for Negative Words Than for Neutral Words for Each Group

Region	Cluster size	Mean Z	Location		
			X	Y	Z
Control					
Left fusiform gyrus (BA 20)	33	2.16	−52	−34	−22
Right inferior temporal gyrus (BA 21)	193	2.52	62	−8	−18
Left and right inferior frontal gyrus (BA 47)	75	2.18	56	32	−4
	63	2.08	−52	36	−4
Anterior cingulate (BA 32)	79	2.24	0	36	−2
Right middle occipital gyrus (BA 18 and BA 19)	155	2.28	30	−96	2
	59	2.32	40	−82	12
Left superior temporal gyrus (BA 22)	106	2.21	−56	−40	16
Left and right middle frontal gyrus (BA 46)	180	2.26	58	34	22
	34	2.18	−32	22	22
Positive schizotypy					
Left cerebellum	615	2.38	−40	−40	−22
Right hippocampus	204	2.28	30	−20	−18
Left putamen	132	2.26	−20	4	−10
Anterior cingulate (BA 32)	119	2.14	6	44	−2
Left middle temporal gyrus (BA 22 and BA 21)	49	2.16	−62	−38	4
	56	2.13	−64	−56	10
Left and right inferior frontal gyrus (BA 46)	77	2.16	−54	48	4
	137	2.52	40	42	6
Right middle frontal gyrus (BA 9)	75	2.33	50	24	28
Posterior cingulate (BA 23)	37	2.17	−12	−34	24
Left inferior parietal lobule (BA 40)	339	2.27	−54	−58	40

Note. Activation was defined as significantly greater activity for negative than for neutral words within a group. Regions having at least 30 contiguous voxels each active above $z = 1.96$ ($p = .05$, two-tailed) are listed. The first column lists the names (Talairach & Tournoux, 1988) and Brodmann areas (BA) of brain regions that showed significant activation. The second and third columns provide the number of contiguously active voxels in the cluster and mean z (effect size in standard deviation units) for the voxels in the cluster, respectively. The location columns provide the cluster location in Talairach coordinates.

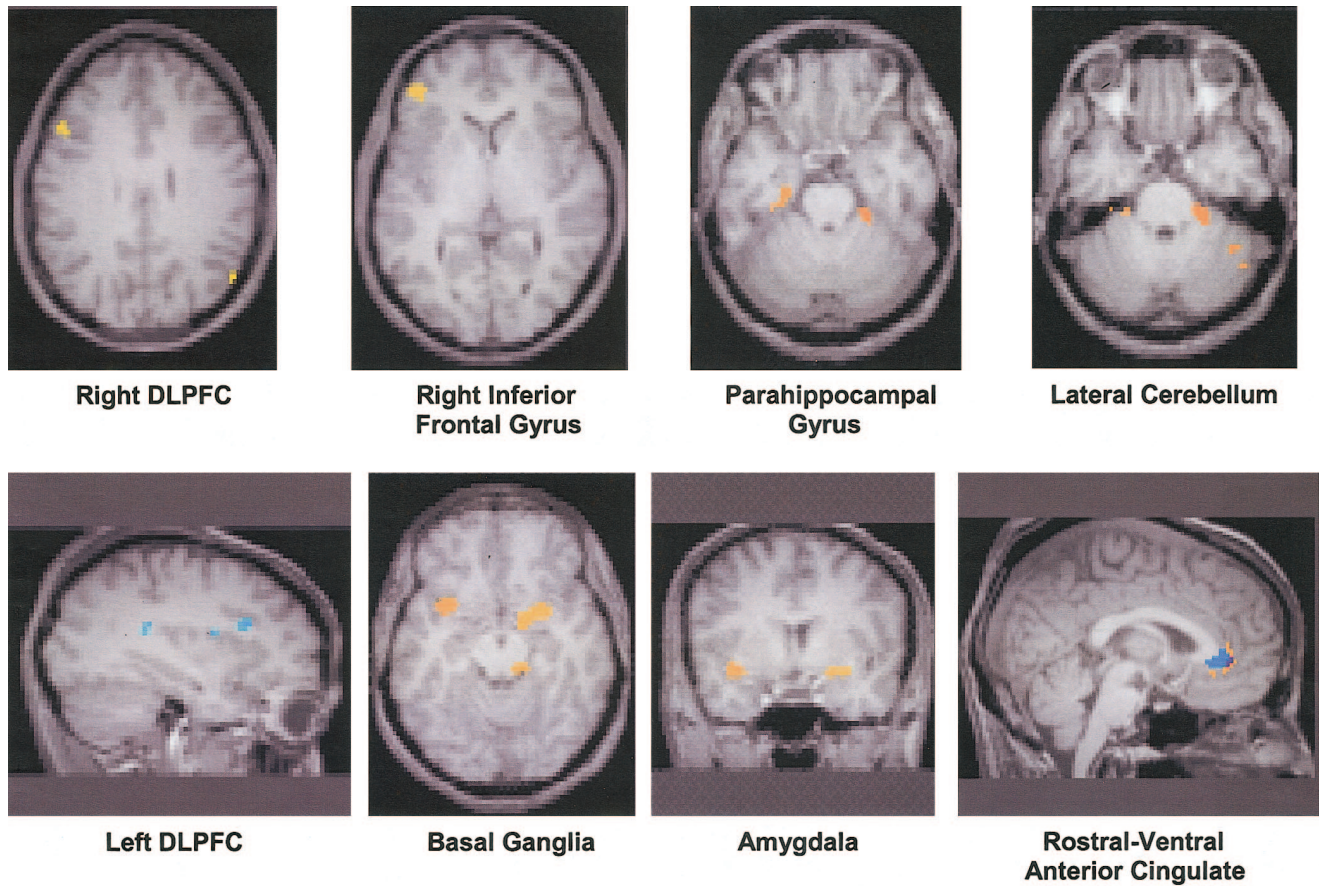


Figure 1. The lower right panel illustrates greater activity in rostral–ventral anterior cingulate for negative than for neutral words for schizotypy (in orange) and control (in blue) groups. Dark pixels between orange and blue regions were significant in both groups. The remaining panels show hypothesized regions with significant group differences in activation, with activation defined as greater activity for negative words than for neutral words. Orange depicts more activation for schizotypy participants than for control participants, and blue depicts more activation for control participants than for schizotypy participants. Following radiological convention, the right side of the brain is on the left side in axial and coronal slices. For all panels, highlighted voxels are those with z scores >1.96 ($p < .05$, two-tailed) meeting cluster-size threshold (see the Method section in text). Tables 1 and 2 present Talairach coordinates of highlighted regions.

Finally, as predicted from an earlier behavioral study (Mohanty et al., 2001), the positive schizotypy group had higher anxious apprehension scores than the control group. However, a mediating variable analysis (Baron & Kenny, 1986) indicated that anxious apprehension did not fully mediate the relationship between positive schizotypy and brain activity in regions identified as more active in schizotypy individuals. Only the group difference in right inferior frontal gyrus (BA 46) was mediated by the variance shared between positive schizotypy and anxious apprehension.

Discussion

In light of the evidence indicating that negative affect fosters cognitive disturbance in individuals with positive symptoms of schizotypy and schizophrenia, it was hypothesized that positive schizotypy would be associated with an abnormal pattern of brain activity in DLPFC and ventral–limbic–striatal regions when challenged with negative emotion words in a selective attention task.

Results supported this hypothesis. The schizotypy group showed reduced left DLPFC and elevated right DLPFC activation. They also produced larger changes in nucleus accumbens, hippocampus, amygdala, and basal ganglia activity. Although there is evidence indicating that nonpatients who score high on measures of schizotypy and individuals with schizophrenia show similar cognitive abnormalities, this appears to be the first hemodynamic neuroimaging study providing direct evidence that positive-schizotypy individuals' task-related brain activation patterns resemble those of patients with schizophrenia.

Studies investigating DLPFC function in schizophrenia have yielded mixed results, with both hypoactivity and hyperactivity reported. DLPFC is involved in sustaining selective attention in the presence of emotionally aversive and nonemotional distractors and is also sensitive to manipulations of intensity within each of these categories (Compton et al., 2003). Furthermore, DLPFC activity related to working memory can be influenced by affective vari-

Table 2
Brain Regions Showing Group Differences in Negative-Minus, Neutral-Word Activation

Region	Cluster size	Mean Z	Location		
			X	Y	Z
Positive schizotypy > control					
Right middle frontal gyrus (BA 9)	36	2.14	52	22	28
Right inferior frontal gyrus (BA 46)	47	2.17	44	42	6
Right hippocampus including parahippocampal gyrus	102	2.32	28	-18	-18
Left putamen	104	2.53	-20	4	-10
Left cerebellum	95	2.54	-22	-28	-22
	58	2.20	-46	-50	-26
Control > positive schizotypy					
Left middle frontal gyrus (BA 46)	31	2.25	-32	22	22
Right inferior temporal gyrus (BA 21)	100	2.36	62	-8	-18
Right middle occipital gyrus (BA 18 and BA 19)	77	2.44	30	-94	2
	50	2.51	40	-82	12
Left superior temporal gyrus (BA 22)	81	2.56	-56	-40	18

Note. Activation was defined as significantly greater activity for negative than for neutral words. A voxel showed a significant group difference in activation if it exceeded a z threshold of 1.96 ($p = .05$, two-tailed) and was part of a cluster of at least 30 contiguous active voxels. The first column lists the names (Talairach & Tournoux, 1988) and Brodmann areas of brain regions that showed significant differential activation for the two groups. The second and third columns characterize the number of contiguously active voxels in the cluster and the group difference in terms of mean z (effect size in standard deviation units), respectively. The location columns provide three-dimensional Talairach coordinates of these brain regions.

ables (Gray, Braver, & Raichle, 2002; Perlstein, Elbert, & Stenger, 2002), and there is considerable literature documenting hemispheric differences in PFC activity as a function of emotional valence (e.g., Davidson, 1992; Heller, 1993). In the present study, participants selectively attended to task-relevant aspects in the presence of distractors that were emotionally aversive or nonemotional in nature. The schizotypy group showed less left and more right DLPFC activation for negative words. Present lateralized DLPFC results provide some of the first fMRI support for the association of valence with frontal lateralization previously documented with electroencephalogram studies and indicate that emotional aspects of tasks need to be considered when designing and interpreting studies intended to investigate cognitive dysfunction in psychopathology.

Evidence from fMRI and positron-emission tomography studies indicates that during verbal working memory tasks, prefrontal activity tends to be lateralized toward the left hemisphere (Cabeza & Nyberg, 2000). In particular, left inferior brain activity reflects processing more specific to the Stroop task (Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997). Similarly, negative emotional Stroop stimuli activate left DLPFC (Compton et al., 2003). In light of these findings, decreased left DLPFC activity in schizotypy participants may be interpretable as a failure to fully engage optimal executive processes leading to increased interference from emotional stimuli on the task, as indicated by the performance data from a behavioral study with a large number of participants (Mohanty et al., 2001). Right PFC has been implicated in vigilance and response to threat (for reviews, see Nitschke & Heller, 2002; Nitschke & Heller, in press; Nitschke, Heller, & Miller, 2000). Thus, increased right DLPFC activity in schizotypy participants suggests exaggerated attention to negative stimuli even though

they are task irrelevant. Indeed, there is evidence that individuals with schizophrenia (Blackwood, Howard, Bentall, & Murray, 2001) or those at risk for schizophrenia (Green, Williams, & Davidson, 2001) preferentially attend to threat-related stimuli. Thus, present lateralized DLPFC findings sensitive to group and emotional valence suggest that uncontrolled task differences in emotion processing demands could account for a portion of the heterogeneity in findings about DLPFC patterns in schizophrenia. These results again underscore the importance of considering the emotional aspects of tasks when designing and interpreting studies that investigate cognitive dysfunction in psychopathology.

The schizotypy sample also showed more activation in right inferior frontal gyrus. Inferior frontal cortex tends to be involved in situations requiring resolution of interference among conflicting task attributes (Nelson, Reuter-Lorenz, Sylvester, Jonides, & Smith, 2003). A number of studies have shown that the ability to inhibit processing of irrelevant or interfering stimuli is associated with right inferior frontal gyrus (e.g., Garavan, Ross, Murphy, Roche, & Stein, 2002; Garavan, Ross, & Stein, 1999; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998). In present results, increased right inferior frontal gyrus activity in schizotypy individuals may indicate a greater effort to inhibit strongly interfering emotional stimuli in order to achieve normal behavioral performance. Researchers have hypothesized that anxiety, particularly anxious apprehension, and positive symptoms have many thematic similarities (e.g., a bias toward threat-related stimuli) and that anxiety makes a direct contribution to positive symptom development (Freeman et al., 2002). In light of that literature, the finding in the present study that right inferior frontal gyrus activation (BA 46) is mediated by the variance shared between posi-

tive schizotypy and anxious apprehension suggests a brain mechanism common to both.

Additional interesting findings emerged for regions constituting the ventral limbic cortical–basal ganglia circuit, which is believed to play a crucial role in the interaction and integration of cognitive and affective processes. Dysfunction in any component of this circuit could contribute to symptoms in schizophrenia (Grace & Moore, 1998). Because the nucleus accumbens, a major component of this circuit, receives inputs from hippocampus, amygdala, and PFC, it may play a particularly important role in their modulation or integration. Thus, decreased activity in this region in schizotypy suggests a mechanism for dysregulation of inputs from important brain regions in the face of aversive stimuli.

Greater activation in hippocampus and amygdala in the schizotypy group is consistent with reports indicating that positive symptoms in schizophrenia are associated with increased activity in hippocampal and amygdalar regions during performance on an emotional Stroop task (Epstein et al., 1999; Taylor et al., 2002) and other tasks (Blackwood et al., 2001). The amygdala is believed to be central to the emotional evaluation of fear and threat-related sensory stimuli (LeDoux, 1995; see Zald, 2003, for review), and the hippocampus is believed to mediate contextual aspects of emotional evaluation (Grace & Moore, 1998; Kim & Fanselow, 1992; R. G. Phillips & LeDoux, 1992). Abnormal inputs from these limbic structures to the ventral striatum are believed to play an important role in psychotic symptoms (e.g., Bogerts, 1997; Weinberger & Lipska, 1995). For example, there is evidence that hippocampal and amygdalar inputs to the nucleus accumbens modulate activity in prefrontal brain regions in distinct ways (Grace & Moore, 1998). The hippocampus provides general, context-dependent modulation, whereas the amygdala provides a more discrete, event-related input, such that salient emotional stimuli can override an otherwise context-dependent system. Accordingly, if hippocampal neurons were to show abnormal firing patterns that were due to a pathological condition, the result could be the reinforcement of a pattern of cerebral activity representing a contextually uncorroborated mental event—a mechanism potentially involved in delusions, hallucinations, magical ideation, and perceptual aberration (Liddle et al., 2000). Thus, abnormal activity in limbic and striatal regions prompted by negative stimuli suggests a mechanism through which negative affect is associated with an exacerbation of DLPFC-related cognitive disturbance in schizotypy and schizophrenia. That this disrupted mechanism is evident in a nonpatient sample merely reporting elevations in selected positive symptoms indicates that the mechanism and its disruption can be in place prior to the onset of the diagnosed disorder.

In addition to support for the two major a priori hypotheses about DLPFC and ventral limbic areas, the present study obtained other findings consistent with the schizophrenia literature. Schizotypal individuals showed more activation in basal ganglia and cerebellum than did control participants. Some of these regions may contribute to the DLPFC and ventral limbic relationships on which the study focused. The findings of increased activity in basal ganglia are similar to those in schizophrenia, in which positive symptoms are associated with increased task-related activity in the dorsal striatum (e.g., Kircher et al., 2001). Furthermore, decreased suppression of striatal activity during working memory performance is associated with abnormal PFC activity in schizophrenia

(Rubin et al., 1991), indicating that a frontostriatal circuitry dysfunction may be involved in cognitive deficits in schizophrenia (Manoach et al., 2000).

The finding of increased cerebellar activation in the schizotypy group is in line with considerable clinical and neuroimaging evidence supporting cerebellar involvement in schizophrenia. The cerebellum and its connections to PFC have been implicated in thought abnormalities in schizophrenia (Andreasen et al., 1996, 1999; Andreasen, Paradiso, & O'Leary, 1998). More specifically, the fluid coordination of motor activity and thought may involve rapid feedback between cerebral cortex and cerebellum mediated through thalamus, and its disruption has been proposed as a fundamental deficit in schizophrenia called “cognitive dysmetria” (Andreasen et al., 1996, 1998, 1999). Evidence from neuroimaging studies using a variety of tasks, including recall of complex narratives, episodic memory, memory for word lists, and random episodic silent thought, indicates abnormal activity in various elements of a cortico–cerebellar–thalamic–cortical circuit in schizophrenia. Present findings in the lateral cerebellum suggest that negative affect, or the distraction it can provide from task-relevant cognitive activity, is another means to foster cognitive dysmetria. This may contribute to the exacerbation of cognitive disturbance associated with negative affect in schizophrenia and schizotypy.

Another interesting finding in the present study involved the anterior cingulate, a region that plays an important role in cognitive and emotional processing. Both schizotypy and control groups showed more activity in rostral–ventral anterior cingulate for negative than for neutral words. This finding is consistent with literature showing that rostral–ventral anterior cingulate is activated by affect-related tasks, including the emotional Stroop task, for normal control participants and psychiatric patients (e.g., Shin et al., 2001; Whalen et al., 1998; for review, see Bush, Luu, & Posner, 2000). The rostral–ventral division of the anterior cingulate differs from the dorsal division in terms of its anatomical connectivity and the functions it implements (Bush et al., 2000). The dorsal subdivision has been shown to play an important role in a variety of cognitive functions, including response selection, competition monitoring, error detection, and working memory. In contrast, the rostral–ventral subdivision (referred to as the “affective subdivision” by Bush et al., 2000) is involved in assessment of the salience of emotional information and regulation of emotional responses. The rostral–ventral subdivision is connected to amygdala, nucleus accumbens, hypothalamus, hippocampus, and orbitofrontal cortex (Devinsky, Morrell, & Vogt, 1995). Researchers have hypothesized that rostral–ventral cingulate regulates or inhibits other brain regions involved in response to threat such as amygdala (e.g., Shin et al., 2001). In present data, both groups activated rostral–ventral cingulate when processing emotionally negative stimuli, indicating a regulatory process. However, compared with the control group, the schizotypal group also activated amygdala and hippocampus and deactivated nucleus accumbens (all connected to rostral–ventral anterior cingulate), suggesting a failure to fully engage optimal regulatory processes, a possible mechanism by which emotional stimuli disrupt cognitive functioning.

There is little research examining the impact of emotion on attentional processing in individuals with schizotypy or schizophrenia. The present investigation is the first hemodynamic neu-

roimaging study examining such processing in an at-risk population, and the replication of some findings from the schizophrenia literature is noteworthy (Barch, Carter, et al., 2001; Callicott et al., 2000; Epstein et al., 1999; Kircher et al., 2001; Liddle, Friston, Frith, & Frackowiack, 1992; Rubin et al., 1991; Silbersweig et al., 1995; Taylor et al., 2002; Weinberger & Lipska, 1995). Apparently, at least some of the functional brain phenomena noted in schizophrenia are observable in a relatively well-functioning non-patient sample, suggesting that they reflect predisposing mechanisms in schizophrenia rather than the sequelae of the disease or its treatment. That the present sample is unmedicated avoids serious confounds that are often present in studies of individuals with schizophrenia. This is particularly important because limbic regions of the forebrain and the amygdala are sites of action of antipsychotic mediation. Chronic schizophrenia, but not schizotypy, is associated with illness-related epiphenomena driven by antipsychotic medication and hospitalization. Moreover, the cognitive performance of individuals with schizotypy is less likely to be confounded with or compromised by the often-substantial deficits in motivation, task comprehension, and task performance associated with the disease process, antipsychotic medication, and hospitalization.

Although there were more similarities than differences in regional brain activation observed for positive-symptom schizotypal individuals and control participants, most of the observed regional differences were supportive of (a) continuity between this nonpatient sample and some of the schizophrenia literature, (b) neural circuitry proposed to play a central role in schizophrenia, and (c) emotional factors in putatively cognitive tasks substantially affecting regional brain patterns. Mechanisms contributing to this modulation of cognitive dysfunction by emotional processing may prove central to understanding schizophrenia.

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