

Neural Response to Emotional Salience in Schizophrenia

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Neuroimaging probes of brain regions implicated in emotion represent an important research strategy for understanding emotional dysfunction in schizophrenia. Anterior limbic structures, such as the ventral striatum and the amygdala, have been implicated in the pathophysiology of schizophrenia and the generation of emotional responses, although few studies to date have used emotion probes to target these areas in schizophrenia. With this goal in mind, emotionally salient visual images were used in a simple, nondemanding task. In all, 13 medicated, schizophrenic patients, five unmedicated patients, and 10 healthy volunteers viewed complex visual pictures and a nonsalient, blank screen while regional cerebral blood flow was measured with the [O–15] water technique. Pictures consisted of real world scenes with aversive, positive, and nonaversive content. Eye movements were recorded simultaneous with scan acquisition. Positron emission tomography images were analyzed for baseline, tonic activity, in addition to phasic changes ('activation') to salient stimuli. Lateral eye movement measures and on-line ratings showed good behavioral compliance with the task. Patients with schizophrenia showed impaired neural responses to salient stimuli in the right ventral striatum (VS), and they exhibited elevated tonic activity levels in the right VS and bilateral amygdala, inversely correlated with overall symptom severity. The patients also showed reduced modulation of visual cortex by salient stimuli. The results show that patients with schizophrenia exhibit impaired neural responses to emotionally salient stimuli in the VS, supporting a role for this structure in the pathophysiology of the illness. Reduced modulation of visual cortex by emotionally salient stimuli also suggests a failure to organize cerebral activity at a global level.

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INTRODUCTION

Schizophrenia clearly impairs emotional functioning in patients, who show both reduced emotional expression, in the form of negative symptoms (Andreasen, 1982; Carpenter *et al*, 1988), as well as excessive emotions, such as those associated with persecutory delusions. The mechanisms of emotional disturbance in schizophrenia remain poorly understood, but an emerging functional anatomy of emotion suggests experimental leverage that might reveal some of the large-scale circuitry behind the symptoms. Several regions of the brain appear to mediate responses to salient stimuli that lead to appetitive and aversive behaviors, areas implicated in emotion. Anterior, limbic/paralimbic regions, including the amygdala (Davis, 1992; Ledoux, 1992; Adolphs *et al*, 1995), ventral striatum (Nauta and Domesick, 1982; Haber and McFarland, 1999), anterior

cingulate cortex (Devinsky *et al*, 1995), insula (Augustine, 1985), and orbitofrontal cortex (Rolls, 1996) play central roles in emotional behavior, in addition to receiving extensive mesocortical and mesolimbic dopaminergic innervation (Joyce *et al*, 1991; Haber and Fudge, 1997; Meador-Woodruff *et al*, 1997). Given the role of dopamine in the pathophysiology of schizophrenia (Seeman, 1987; Davis *et al*, 1991; Grace *et al*, 1998), probes directed at these limbic/paralimbic regions are particularly relevant. Emotionally salient stimuli are also processed in regions outside limbic/paralimbic brain, such as the medial prefrontal cortex, thought to be critical for mediating interactions between cognition and emotion (Gusnard *et al*, 2001; Ochsner *et al*, 2002; Taylor *et al*, 2003). Neuroimaging work has also demonstrated that emotionally salient stimuli lead to increased activity in visual cortex (Phan *et al*, 2002), which may reflect top-down processing to enhance processing of salient stimuli (Pessoa *et al*, 2002). Taken together, this emerging neuroanatomy presents a reasonable framework in which to interpret emotional dysfunction in schizophrenia.

Several recent studies have used emotionally salient stimuli to probe emotions and relevant circuitry in schizophrenia. Using an odor challenge, Crespo-Facorro *et al* (2001) found that unmedicated schizophrenic patients

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failed to activate limbic and paralimbic cortex (insular cortex, nucleus accumbens, and parahippocampal gyrus). In medicated schizophrenic patients, the left amygdala and bilateral hippocampus failed to activate while passively viewing faces (Gur *et al*, 2002), both amygdalae failed to respond during sadness induction while viewing mood-congruent faces (Schneider *et al*, 1998), and the right amygdala failed to activate to nonaversive, salient visual content (Taylor *et al*, 2002; Takahashi *et al*, 2004). Both medicated (Phillips *et al*, 1999) and unmedicated schizophrenic patients (Paradiso *et al*, 2003) have demonstrated a failure to organize regional cerebral blood flow while viewing emotional pictures (Paradiso *et al*, 2003) or emotional faces (Phillips *et al*, 1999; Williams *et al*, 2004). More specifically, patients did not exhibit the normal modulation of visual cortical processing to emotionally salient stimuli (Taylor *et al*, 2002; Paradiso *et al*, 2003; Takahashi *et al*, 2004; Williams *et al*, 2004).

Work to date suggests that patients with schizophrenia do not activate regions important for the determination of emotional salience, but several different mechanisms might account for impaired activation. Neural responses to a behavioral challenge—that is, ‘phasic’ activity—say nothing about sustained, baseline activity, that is, ‘tonic’ activity. For example, we found less *phasic* change to salient stimuli in schizophrenic patients, relative to healthy controls, whereas we noted nonsignificantly greater *tonic* activity in the amygdala while viewing salient and nonsalient stimuli, raising the possibility that patients had tonic elevation of amygdaloid activity (Taylor *et al*, 2002). Elevated tonic activity could represent nonspecific activation of threat-related neural circuitry (Davis, 1992; Ledoux, 1992; Adolphs *et al*, 1995) and a consequent failure to respond to an emotional challenge. Studies that have probed amygdala function in schizophrenia have measured changes in blood oxygenation level (Schneider *et al*, 1998; Phillips *et al*, 1999; Gur *et al*, 2002; Takahashi *et al*, 2004) or only reported changes in cerebral perfusion with a task (Crespo-Facorro *et al*, 2001; Paradiso *et al*, 2003). These studies have either not reported or not measured tonic activity.

The current study employed a neurobehavioral probe with emotional and nonemotional stimuli to assess both tonic and phasic neural activity with positron emission tomography (PET). The PET technique, with [O-15] water as a radiotracer, permitted the measurement of relative cerebral blood flow during each condition (tonic activity) and changing with the salience of stimuli containing aversive and positive emotional content (phasic activity). The use of positive stimuli was an important addition over our prior study (Taylor *et al*, 2002), since patients with schizophrenia tend to report equal intensity of negative experience as controls, but reduced intensity of positive experience (Myin-Germeys *et al*, 2000). The prediction was tested that schizophrenic patients would exhibit less phasic activity (activation to salient stimuli) and greater tonic activity in the amygdala and ventral striatum (VS). Although emotional tasks typically put minimal demands on subjects, it is possible that some of the findings, such as reduced modulation of visual cortex (Taylor *et al*, 2002; Paradiso *et al*, 2003; Takahashi *et al*, 2004; Williams *et al*, 2004), might reflect reduced eye movements while viewing the salient stimuli. In an attempt to rule out this possibility,

we also measured eye movements while our subjects viewed the salient visual stimuli.

METHODS

Subjects

From a university-staffed community mental health center, 15 stable, medicated outpatients entered the study. Five, recently hospitalized, unmedicated patients were also recruited (two naïve to antipsychotic therapy, three off antipsychotic treatment >6 months). All patients were free of significant medical or neurological illness. A diagnosis of schizophrenia according to DSM-IV criteria (American Psychiatric Association, 1994) was established by a Structured Clinical Interview for Diagnosis (First *et al*, 1996). One of the unmedicated patients only met criteria for psychosis NOS at the time of the scan; however, 6-month follow-up revealed the persistence of psychosis, hence her diagnosis was changed to schizophrenia.

A total of 10 healthy control subjects were recruited from community advertisements, selected from the same age range as the patients. They were not taking medication, without any Axis I psychiatric disorders (Structured Clinical Interview for Diagnosis, non-patient version (First *et al*, 1996)) and without any psychosis in first-degree relatives.

The purpose and risks of the study were explained to all subjects, who gave written, informed consent to participate, as approved by the local institutional review board. The results from the healthy controls have been previously reported (Liberzon *et al*, 2003).

Task Design

The task consisted of viewing pictures with salient emotional content, obtained from the International Affective Picture System (IAPS; Lang and Greenwald, 1988).

Three sets of 18 images each were selected from the IAPS, plus supplements (approximately 10% of all images), consisting of positive (POS) pictures (animals, children, food), aversive (AV) pictures (mutilation, dead bodies), and nonaversive (NA) pictures (faces with neutral expressions, benign scenes). A fourth condition (blank condition—BL) consisted of a white fixation cross on a gray background (five different shades). The sets (POS, AV, NA) were transformed into black and white, luminance was balanced across the four sets (Photoshop 4.0, Adobe Systems), and they were matched with respect to faces and human figures.

Eye Movement Recording

Eye movement data were recorded using an MP-100 psychophysiological monitoring system (BioPac Systems, Santa Barbara, CA) to record horizontal electro-oculograms (EOG). The percentage of time lateral gaze fell outside the bounds of the monitor screen was calculated. Total scanning of the image was expressed as the standard deviation of eye position, which was log transformed for analysis in a mixed-model, two-way ANOVA, with task condition as a within-subjects factor and subject type as the between-subjects factor.

PET Image Acquisition

During the scanning sessions, subjects viewed nine blocks of images. Images were displayed consecutively (5 s each) on a computer monitor suspended 40 cm from the subject, using SuperLab (Cedrus, Inc.). The first block consisted of neutral stimuli without acquisition of PET data, allowing subjects to adjust to the scanner environment. After this initial block, scan acquisition began. Eight scans were acquired, in two identically ordered sets of four blocks from each of the four conditions (BL, NA, AV, POS), with order counterbalanced in a partial Latin square. Subjects were instructed to focus on feelings that they experienced while watching the pictures. During stimulus presentation, subjects rated images according to a 5-point scale (from 1, 'very pleasant' to 5, 'very unpleasant'). For each blank screen, the subjects said '3'. Subjects practiced the task prior to scanning to ensure their comprehension and performance.

A Siemens CTI 931-08/12 PET scanner (CTI Inc, Knoxville, TN) acquired 15 axial slices over an axial length of 10 cm, capturing inferior, limbic structures and excluding the superior parietal lobe. A transmission scan measured by external $^{68}\text{Ge}/^{68}\text{Ga}$ ring sources preceded emission scanning. A small dose (8 mCi) of radiotracer, injected prior to actual data acquisition but while the subjects viewed the initial block of neutral pictures, revealed the bolus transit time to the brain, in order to time stimulus presentation. For each emission scan, an i.v. bolus injection of 50 mCi of [^{15}O]H $_2$ O was administered, and data collection began 5 s after arrival of radioactivity in the brain, continuing for 60 s. Eight PET scans, each separated by 10 min, were acquired for each subject. Stimuli presentation began 15 s prior to image acquisition, and continued for the first 30 s of each scan (uptake phase of the tracer), so as to maximize changes in the PET signals associated with the task of interest (Cherry *et al*, 1993). The second 30 s of each scan always contained blank stimuli with the fixation cross, exactly as in the 'blank' condition.

PET Data Analysis

Analysis of the PET data first employed a standardization process for each image which enabled averaging of image data both within and across subjects. Two sets of analyses occurred: an *a priori* volume of interest (VOI) analysis, which enabled the analysis of tonic activity, and a voxel-by-voxel, whole brain analysis, which enabled a more sensitive assay of phasic changes.

For the VOI analysis, a high-resolution normalization routine, developed in our laboratory, was applied to the data. Images were proportionally normalized, aligned within subjects, warped by a nonlinear transformation to standardize individual anatomy (Minoshima *et al*, 1993, 1994), and resliced into isotropic 2.25 mm voxels. From atlas coordinates (ICBM152 of the Montreal Neurological Institute), spherical volumes (15.75 mm diameter) of interest were placed over the right and left amygdala ($x = \pm 24$ mm; $y = -3$ mm; $z = -19$ mm). A VS VOI was constructed from two, contiguous, spherical volumes (13.5 mm diameter; $x, y, z = \pm 10, 9, -8; \pm 15, -1, -8$), including both the VS and the associated SLEA (Alheid and Heimer 1988). Activity was extracted from the anatomically

standardized, individual images and analyzed in a mixed-model, three-way ANOVA, with task *condition* (BL, NA, AV, POS) and *side* as within-subject factors and *subject type* (medicated patient, unmedicated patient, comparison subjects) as the between-subjects factor (Systat, Inc, Evanston, IL). Main effects of *side* and *subject type* constituted the analysis of tonic CBF, whereas the main effect of task *condition* represented phasic effects. Only subjects with a complete data set, that is, at least one observation for each condition, were entered into this analysis.

The whole brain, voxel-by-voxel analysis utilized Statistical Parametric Mapping (SPM99, Wellcome Institute of Cognitive Neurology) to assess phasic changes occurring between the task conditions. Reconstructed images were realigned to the first volume acquired for each subject, anatomically normalized, resliced into $2 \times 2 \times 2$ mm voxels, adjusted for global values (ANCOVA by subject) and smoothed (12 mm FWHM in three dimensions). A single, general linear model, modeling subject by condition effects, fitted each group. Subject-specific effects for each condition were then entered into a second-level, random effects analysis for three contrasts of interest: NA-BL; AV-NA; POS-NA. Voxel-by-voxel maps of phasic differences were obtained and thresholded for Z-scores at an uncorrected probability of $p < 0.01$, which yielded '*k*,' the size in voxels of a contiguous cluster of activation. Activation foci were examined when the peak magnitude of activation exceeded a Z-score with an uncorrected probability of $p < 0.001$. Group differences were examined with voxel-by-voxel, paired *t*-tests for all positive activation foci from each contrast.

RESULTS

Behavioral Results

All subjects tolerated exposure to the images without significant difficulty. In debriefing interviews, no patients reported any exacerbation of symptoms while viewing the pictures. One medicated, schizophrenic subject had excessive (> 1 cm), gross head movement, and a technical failure corrupted the scan data of another medicated schizophrenic patient. Both of these subjects were excluded from analysis. Of the remaining subjects, two scans for two medicated patients and one scan for one control subject were not obtained due to technical failures. One unmedicated, schizophrenic subject requested a bathroom break, leaving two BL, one NA, and one AV scans for analysis. Thus, for the final analysis, we had 13 medicated schizophrenic patients, five unmedicated schizophrenic patients (one patient with an incomplete data set), and 10 control subjects (Table 1). Image data was not available for two control subjects at the level of the amygdala, and one subject at the level of VS, where the brain fell outside the field of view of the scanner.

On-line ratings of stimuli showed clear effects of the intended manipulation of valence (Table 2). Comparisons between groups showed that the patients rated the POS stimuli as less positive than the control subjects. There were no significant differences between groups for the NA or the AV stimuli. There were no significant differences between the medicated and unmedicated patients in their ratings of the salient pictures.

Table 1 Demographic and Clinical Characteristics of Subjects

Mean \pm SD	Medicated schizophrenic patients (n = 13)	Unmedicated schizophrenic patients (n = 5)	Healthy control subjects (n = 10)
Age, years	35.2 \pm 11.9	25.4 \pm 8.0	27.5 \pm 8.6
(range)	20–54	18–38	20–46
Males	9	2	6
Socioeconomic status ^a	2.9 \pm 0.5	3.2 \pm 0.8	2.6 \pm 0.5
Duration ill, years	16.3 \pm 11.0	5.6 \pm 7.6	—
(range)	1–34	1–19	—
Age of onset, years	18.9 \pm 3.8	19.8 \pm 3.3	—
(range)	10–24	17–25	—
Medications			
Clozapine	8		
Mean dose	375 \pm 128 mg		
Other atypicals	5		
Mean dose (risperidone equivalent)	5.6 \pm 2.6 mg		
Symptom ratings			
BPRS ^b total	33.6 \pm 8.7	45.4 \pm 5.4	
BPRS positive	9.9 \pm 4.1	15.0 \pm 1.6	
BPRS negative	8.1 \pm 3.5	7.0 \pm 2.9	
SANS ^c global sum	8.4 \pm 4.7	6.4 \pm 3.1	

^aAssessed by Hollingshead–Redlich Scale (Hollingshead and Redlich, 1958).

^bBrief Psychiatric Rating Scale (Overall and Gorham, 1962).

^cSchedule for the Assessment of Negative Symptoms (Andreasen, 1983).

Table 2 Ratings of Visual Stimuli

Condition ^a	Schizophrenic patients	Healthy control subjects	t-value	p
Positive pictures (POS)	1.75 \pm 0.27	1.46 \pm 0.28	2.69	0.01
Nonaversive pictures (NA)	2.57 \pm 0.24	2.67 \pm 0.22	0.54	0.59
Aversive pictures (AV)	4.64 \pm 0.12	4.69 \pm 0.06	0.42	0.68

^aRatings on a 5-point scale, from 1 (pleasant) to 5 (unpleasant), \pm SD.

Effect of condition: $F[2, 52] = 443$, $p < 0.0001$.

NA > POS, $t[27] = 9.3$, $p < 0.0001$.

AV > NA, $t[27] = 17.5$, $p < 0.0001$.

AV > POS, $t[27] = 32.1$, $p < 0.0001$.

Eye Movements

The EOG data revealed that all analyzed subjects looked at the images and maintained lateral eye position within the bounds of the display screen for 100% of the scans for the control subjects, and 96% of the scans for the patients. Four patients showed eye positions away from the display screen in the following amounts: one medicated patient (POS—0.5%), one unmedicated patient (NA—0.4%; POS—3%), one unmedicated patient (POS—0.5%), one unmedicated

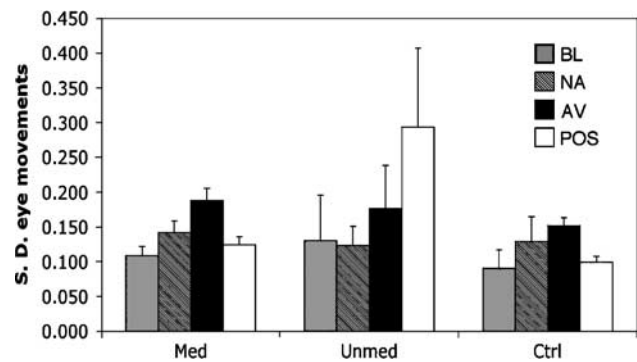


Figure 1 Lateral eye movements for medicated (Med) schizophrenic patients, unmedicated schizophrenic patients (Unmed), and control subjects (Ctrl) while viewing pictures. BL: blank condition; NA: nonaversive condition; AV: aversive condition; POS: positive condition. Units are in standard deviation (SD) of lateral eye movements.

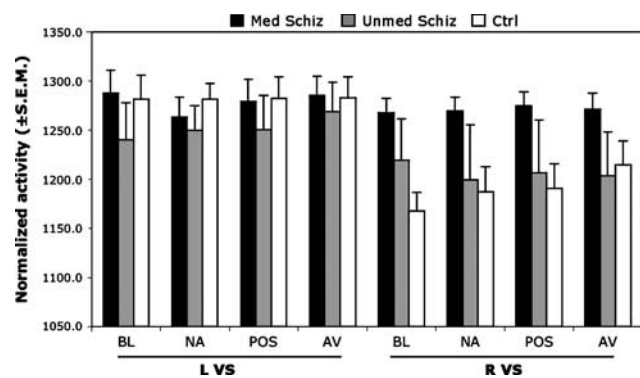


Figure 2 Normalized, tonic activity (arbitrary units) in the *a priori* regions placed on the right and left ventral striatum (VS). There was a significant side-by-subject type interaction (see text for statistical details). Abbreviations as in Figure 1.

patient (BL—3.6%; AV—4.3%). ANOVA of the log-transformed eye movements showed a significant main effect of condition ($F[3,72] = 13.3$, $p < 0.0001$). Figure 1 demonstrates an identical pattern of viewing across the conditions for the medicated patients and the control subjects, in the following order: AV > NA > POS > BL. There were no significant effects of group ($F[2, 24] = 0.6$, $p = 0.56$), but a trend towards a significant condition-by-group interaction was noted ($F[6,72] = 1.85$, $p = 0.11$), which appeared as slightly greater eye movements in the POS condition for the unmedicated patients.

Volume of Interest Analysis in the VS and Amygdala

Overall, CBF in the VS exhibited greater tonic activity on the left side (See Figure 2; effect of side: $F[2, 23] = 17.16$, $p = 0.000$), and there was a significant interaction between subject type and side ($F[2, 23] = 6.72$, $p = 0.005$). As Figure 2 shows, the medicated patients had greater tonic activity in the right VS than the control subjects, and little sign of left-laterality. The overall effect of subject type was not significant for tonic activity ($F[2, 23] = 1.59$, $p = 0.22$). There were no other significant main effects or interactions ($p > 0.20$).

In the amygdala, the patients showed a trend towards greater tonic activity on both sides (effect of subject type $F[2,22] = 3.13$, $p = 0.06$; Figure 3). As in the VS, tonic activity on the left was greater than the right ($F[1,22] = 4.36$, $p = 0.05$), but unlike the VS, all three groups exhibited left-laterality in the amygdala. For phasic changes to condition, the polynomial test of order was calculated, with conditions arranged in the following sequence: BL, NA, POS, AV. This order reflected the fact that activation of the amygdala occurs with positive stimuli, but is more likely to occur with aversive stimuli (Phan *et al*, 2002). We found a significant linear effect for condition ($F[1,22] = 10.05$, $p = 0.004$). *Post hoc* tests revealed significant pairwise comparisons in the left amygdala for $AV > BL$ ($t[24] = 2.13$, $p = 0.04$) and in the right amygdala for $AV > BL$ ($t[24] = 2.28$, $p = 0.03$), $AV > NA$ ($t[24] = 2.73$, $p = 0.01$), and $AV > POS$ ($t[24] = 2.47$, $p = 0.02$). There were no significant interactions with subject type for any of these main effects or first-order linear effects ($p > 0.4$).

Direct comparison of the unmedicated and medicated patients revealed no significant group differences for this VOI analysis in the VS and amygdala ($p > 0.20$), although the small number of unmedicated subjects limits the power of this analysis. Combining the two patient groups yielded essentially the same results, except that the trend for greater tonic activity in the amygdala among the patients became significant (main effect of subject type, $F[1,23] = 6.45$, $p = 0.02$).

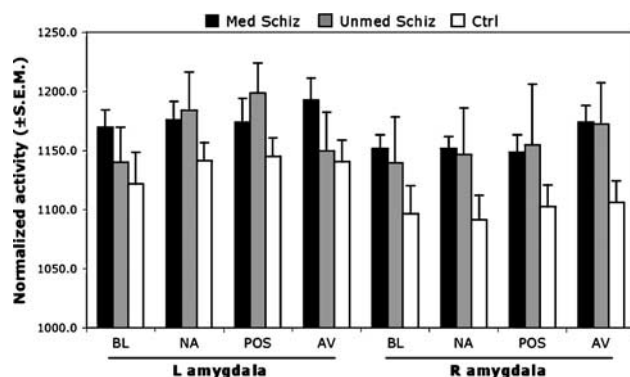


Figure 3 Normalized, tonic activity (arbitrary units) in the *a priori* regions placed on the right and left amygdala. There was a significant effect of side, and a trend effect for subject type (see text for statistical details). Abbreviations as in Figure 2.

Table 3 Correlations between Tonic Activity in *a Priori* Volumes of Interest and Symptoms

Symptoms	L VS	R VS	L amygdala	R amygdala
SANS	-0.52*	-0.12	-0.51*	-0.06
BPRS positive symptoms	-0.47*	-0.49*	-0.34	-0.24
BPRS total symptoms	-0.55**	-0.57**	-0.53*	-0.31

* $p < 0.05$.

** $p < 0.02$.

Volume of Interest Analysis: Correlation with Symptoms

Calculation of the Pearson correlation coefficients revealed that greater symptom severity (positive, negative, and total BPRS ratings) correlated with less tonic activity in the bilateral VS and the left amygdala, averaged over all four conditions (see Table 3). This pattern was essentially unchanged when we looked at the correlation of each condition with symptoms, separately. Examination of scattergrams for the bivariate correlations did not show any pattern attributable to medicated/unmedicated status or particular medication, for example, clozapine vs other atypical antipsychotics. We also looked for correlations between tonic and phasic activity, and found none significant.

Voxel-by-Voxel Analysis of Phasic Activity in the VS and Amygdala

In the voxel-by-voxel analysis, the controls activated the right VS for POS-NA, and this activation was significantly greater compared with the patients (10, 20, -2, $Z = 3.54$, $k = 173$). In the contrast of AV-NA, control subjects activated the right VS (at a trend level, $Z = 3.07$). In the group comparison, the control subjects exhibited more VS phasic activity than the patients (14, 14, -4, $Z = 3.14$, $k = 240$).

For the control subjects, a cluster of activation for the NA-BL contrast occurred in the left medial temporal region, which included the amygdala (Table 4). However, the group comparison did not reveal significant differential activation (controls > patients). There were no other activations in the amygdala for the other contrasts, for either group.

Voxel-by-Voxel Analysis of Phasic Activity in Visual Cortex

Activation for NA relative to BL gave abundant CBF changes in the posterior cortex, including visual processing regions of the occipital cortex, and downstream areas such as the fusiform gyrus. The patients exhibited nominally higher magnitude and extent of activation in the visual cortex (12% more voxels activated). However, in the direct comparison of the groups, controls exhibited higher activity in the right lingual gyrus (10, -44, -2, $Z = 3.29$, $k = 180$; 26, -70, 2, $Z = 3.19$, $k = 118$). There were no foci in the visual cortex where phasic activity was greater for patients.

SPM analysis showed robust phasic modulation of visual cortical regions for AV-NA in both groups (see Table 5 and Figure 4a). Controls exhibited greater magnitude and extent of activation than patients, and this was significantly greater in the left lingual gyrus (-18, -52, 10, $Z = 4.32$, $k = 347$), and the left lateral occipital gyrus (-26, -72, 16, $Z = 3.29$, $k = 207$). For the POS-NA contrast, significant phasic modulation of visual cortical regions was also observed, for both groups (Table 6 and Figure 4b). As with AV-NA, the controls modulated visual cortex in response to the salient positive stimuli with greater magnitude and greater extent, significantly greater in the right superior occipital cortex (24, -80, 28, $Z = 3.55$, $k = 173$). There were no foci where patients exhibited greater activation than control subjects.

Table 4 Activation Peaks, Nonaversive Minus Blanks

Region	Healthy controls			Schizophrenic patients		
	(x, y, z) ^a	Cluster size ^b	Z-score	(x, y, z) ^a	Cluster size ^b	Z-score
Occipital pole (17/18/19)	−14, −84, −12	20517	5.52	10, −82, −8	25110	6.74
	−24, −84, −8		5.05	30, −90, 16		6.58
	14, −84, −6		5.07	−14, −86, −16		6.49
L fusiform gyrus (38/20)				−34, −4, −38	118	3.64
L fusiform gyrus (19/37)	−42, −24, −26	175	3.36			
	−32, −38, −26	178	3.28			
L temporal pole/inf amygdala (38)	−24, 10, −36	210	3.89			
L inferior frontal gyrus (46)	−50, 36, 12	69	3.19			
R inferior frontal gyrus (45)				62, 28, 0	51	3.21
Superior frontal gyrus (6)	0, 18, 60	56	3.67			
Dorsomedial prefrontal cortex (9/10)	−6, 60, 36	769	3.63	−6, 54, 36	338	3.49
	0, 56, 42		3.99	−12, 48, 46		3.18
	24, 62, 28		3.42			

^aStereotactic coordinates from MNI atlas, left/right, anterior/posterior and superior/inferior, respectively.^bCluster size, number of voxels (*k*).

Voxel-by-Voxel Analysis of Phasic Activity in Other Brain Areas

Tables 4–6 show all the regions of activation for each group, above the threshold of $p < 0.001$. Both groups activated the dorsal medial prefrontal cortex (NA–BL), which has been reported in other studies with IAPS stimuli (Liberzon *et al*, 2003; Taylor *et al*, 2003). Comparison of activation between groups showed only a trend for greater activation by the control subjects (10, 48, 50, $Z = 2.97$, $k = 217$); besides this trend, there were no other group differences.

Voxel-by-Voxel Analysis: Effect of Medication

The analyses described above were repeated, without the unmedicated patients. In general, the absence of the unmedicated patients did not change the results, with a few exceptions. In the contrast of NA–BL without the unmedicated patients, the control subjects showed significantly greater activation than medicated patients in a region inferior to and overlapping with the left amygdala (−24, 10, −36, $Z = 3.40$, $k = 256$). Also, with the removal of the unmedicated patients, the significant difference between the patients and controls for the right VS failed to reach significance for the AV–NA contrast. However, for the POS–NA contrast, the group difference in the right VS retained significance for the medicated patients alone (10, 20, −2, $Z = 3.08$, $k = 119$). In general, the medicated patients alone

yielded qualitatively similar patterns of activation as the medicated patients. The five unmedicated patients were compared to a matched subset of five control subjects. In spite of the low power of this comparison, the right VS still showed greater activation for the control subjects, but only for the POS–NA contrast (10, 16, −4, $Z = 3.55$, $k = 197$, for 4 schizophrenic patients). Figure 5 shows differential phasic activation in the right VS between the control subjects and the unmedicated patients ($n = 4$) and a separate comparison with the 13 medicated patients.

DISCUSSION

This experiment used emotionally salient material to probe circuitry central to the pathophysiology of schizophrenia. As predicted, the patients showed smaller phasic changes to emotionally salient stimuli. They exhibited impaired phasic responses to salient stimuli in the right VS, and reduced phasic modulation of visual cortex by salient stimuli. Lateral eye movement measures and online ratings demonstrated good behavioral compliance with the task, arguing against gross performance differences explaining the group differences. In addition to the reduced phasic changes, we also found elevated tonic activity in the amygdala and right VS. Overall, the findings provide evidence that the neural response to emotionally salient stimuli is abnormal in schizophrenia.

Table 5 Activation Peaks, Aversive Minus Nonaversive

Region	Healthy controls			Schizophrenic patients		
	(x, y, z) ^a	Cluster size ^b	Z-score	(x, y, z) ^a	Cluster size ^b	Z-score
Occipital pole (17/18)	−18, −70, −4	5297	4.40	−20, −94, −18	2619	4.05
	−18, −62, 6		4.36	12, −92, −14		3.94
	−20, −80, −14		4.23	28, −76, −16		4.31
R lateral occipital gyrus (18/19)	46, −70, −18	1530	4.09			
	26, −76, 30		3.95			
	40, −80, 16		3.74			
R lateral occipital/inf temp g (19/37)	46, −40, −34	136	3.09			
L lateral occipital gyrus (18/19) inf temp g (19/37)	−50, −50, −30	339	3.39	−42, −74, 0	1528	3.31
	−48, −36, −22		3.29	−38, −52, −16		3.24
				−44, −74, −22		3.23
Retrosplenium				−4, −52, 2	184	3.25
R supramarginal gyrus (40)	56, −28, 26	350	3.24			
L mid-cingulate (24)	−12, 2, 20	68	3.79			
R ventral insula				40, 2, −14	90	3.27
R ventral striatum	20, 24, −4	308	3.07			

^aStereotactic coordinates from MNI atlas, left/right, anterior/posterior and superior/inferior, respectively.

^bCluster size, number of voxels (k).

Response to Salient Stimuli in VS and Amygdala

The brain has evolved systems that select salient stimuli, which signal potential dangers and rewards, and organize appropriate behavioral responses. Limbic neural circuits, such as the VS and amygdala, have key roles in the determination of responses to salient stimuli (Mogenson *et al*, 1980; Davis, 1992; Ledoux, 1992; Stern and Passingham, 1996; Parkinson *et al*, 2000). The fact that these circuits are also implicated in schizophrenic pathophysiology (Grace *et al*, 1998; Heimer, 2000) motivated this study. Phenomenologically, patients with schizophrenia do not respond appropriately to salient stimuli. They fail to express common emotions, clinically evident as negative symptoms, or they read unjustified meaning into stimuli, as in persecutory delusions. Experimentally, the electrophysiology literature shows that schizophrenic patients have impaired responses to salient stimuli, in the form of reduced P300 amplitudes in 'oddball' paradigms (Pfefferbaum *et al*, 1989; McCarley *et al*, 1991). However, this work has not targeted the VS and amygdala, and the P300 stimuli lack emotional content that would elicit appetitive or aversive processing.

The present study represents the first published work, of which are aware, demonstrating abnormal activation of the

VS in schizophrenia. The data parallel and extend prior work showing hypoactive phasic responses in other limbic structures (Schneider *et al*, 1998; Crespo-Facorro *et al*, 2001; Taylor *et al*, 2002; Paradiso *et al*, 2003). Both positive and aversive stimuli activated the VS in healthy subjects, a finding consistent with notions that this structure mediates a general response to emotionally salient stimuli with appetitive or aversive qualities (Berridge and Robinson, 1998; Horvitz, 2000; Liberzon *et al*, 2003). Significant differences between the control subjects with the medicated and unmedicated patients only occurred for the POS stimuli, although the combined group of patients exhibited impaired activation of the VS for both POS and AV stimuli. The stronger effect of POS stimuli may reflect the fact that patients with schizophrenia do not differ from healthy comparison subjects in their ratings of aversive stimuli in the laboratory (Kring *et al*, 1993; Kring and Neale, 1996; Earnst and Kring, 1999) and in the intensity of their aversive life experiences (Myin-Germeys *et al*, 2000). We did find that the patients gave less positive ratings of the positive pictures, consistent with reports of reduced positive life experiences (Myin-Germeys *et al*, 2000). In other words, the POS stimuli may have been better suited to eliciting group differences.

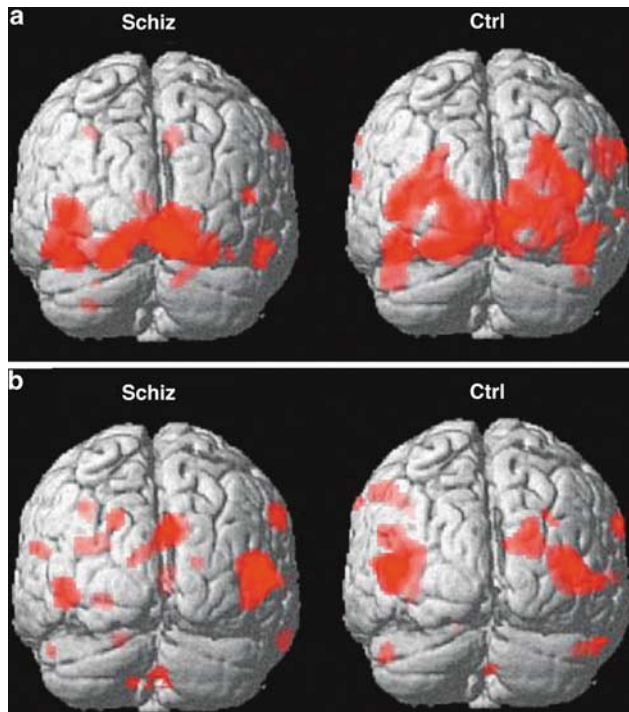


Figure 4 Phasic changes in posterior cortex in response to: (a) aversive or (b) positive pictures, compared to nonaversive pictures, for all schizophrenic (Schiz) and control (Ctrl) subjects. Activated voxels ($p < 0.01$, uncorrected) are projected onto a surface rendering of a reference brain.

Our data did not support the hypothesis that tonic hyperactivity of the amygdala/VS would underlie impaired phasic responses, possibly related to symptom generation. Several investigators have suggested that the amygdala, or VS, produce the positive symptoms of psychosis through aberrant biasing of neural circuits to distort reality construction (Fudge *et al*, 1998; Moore *et al*, 1999; Grossberg, 2000; Kapur, 2003). A specific hypothesis, emanating from these theories and some of our previous work (Taylor *et al*, 2002), would predict that tonic hyperactivity in these limbic regions would directly correlate with positive symptoms. In this formulation, patients would perceive omnipresent threats, and salience-detection circuits would operate continuously, but not selectively. The schizophrenic patients did show greater tonic activity in the right VS (and bilateral amygdala), although the data showed greater positive (and negative) symptoms correlated with less tonic activity—opposite the prediction.

The finding of an inverse correlation between symptoms and activity in the VS/amygdala is useful because it informs us about what tonic hyperactivity is not. However, interpreting the inverse correlation between tonic activity and symptoms presents a challenge. None of the emotionally salient stimuli elicited any symptoms in the patient, and stimuli associated with symptoms could have elicited a very different pattern of tonic and phasic change in the patients. It could reflect greater anxiety in the patients who were less afflicted with positive and negative symptoms. We sought to find third factors, such as education level, age of onset, and medication dose, that might explain these relationships, and

we found no significant correlations. Given the modest strength of these correlations, the small variation in symptom magnitude, and the relatively low severity of the patients in the sample, additional speculation about causality should await replication of the finding.

In the VOI analysis of the VS, tonic hyperactivity appeared as a lack of the functional asymmetry (left > right) found in the healthy subjects. Structural studies of the medial temporal lobe in schizophrenia have also identified a lack of normal asymmetry (Bilder *et al*, 1994, 1999; Pearlson *et al*, 1997), although it is difficult to say whether or not the same process underlies these findings. The unmedicated patients showed a pattern of activity closer to that of the control subjects, and the findings were strengthened somewhat when we removed the unmedicated patients, although the small number of unmedicated patients makes conclusions about the role of medications difficult. Therapy with dopamine-blocking agents does elevate functional activity in the basal ganglia, of which the VS forms the most ventral aspect (Buchsbaum *et al*, 1992; Wolkin *et al*, 1996; Miller *et al*, 1997). However, a medication effect cannot easily explain how the patients had equivalent activity as control subjects on the left and greater activity on the right.

Several other points about the findings require comment. The VOI findings did not show the effect of POS stimuli, relative to NA stimuli, for the healthy subjects because the VOI was several millimeters caudal of the VS focus of activation in the SPM analysis. Our *a priori* placement of this VOI depended upon prior work that only utilized aversive stimuli (Taylor *et al*, 2000). Animal studies (Reynolds and Berridge 2002, 2003) and human neuroimaging studies have suggested that while the VS processes both aversive and appetitive stimuli, the latter may occur in more rostral regions of this structure (Liberzon *et al*, 2003). Hence, we only found activation to POS stimuli in the less-constrained SPM analysis.

Unlike our previous report (Taylor *et al*, 2002), we did not find significant group differences for phasic activity in the amygdala. In the VOI analysis, the patients showed a similar pattern of activation as the control subjects, demonstrating that patients can activate the amygdala in response to emotionally salient stimuli, at least to some degree. In the voxel-by-voxel analysis, changes in the amygdala in the healthy comparison group were present, but not particularly robust, a fact that reduced our power to detect group differences. The amygdalae, as well as the VS, are small structures, making them subject to partial volume effects with this PET camera (effective resolution 12 mm FWHM). Reductions in amygdala volume have been reported in schizophrenia (Nelson *et al*, 1998; Wright *et al*, 2000), although not uniformly (Chance *et al*, 2002). Of course, increased tonic activity cannot be accounted for by a normal or reduced volume of the amygdala.

Modulation of Visual Cortex

The patients showed significantly less modulation in several regions associated with processing visual information, replicating previous work (Taylor *et al*, 2002; Paradiso *et al*, 2003). The modulation of visual cortex by emotional salience is well acknowledged (Phan *et al*, 2002), and the phenomenon may represent top-down modulation to

Table 6 Activation Peaks, Positive Minus Nonaversive

Region	Healthy controls			Schizophrenic patients		
	(x, y, z) ^a	Cluster size ^b	Z-score	(x, y, z) ^a	Cluster size ^b	Z-score
Cuneus (17/18)				10, -84, 28	269	3.45
				4, -76, 26		3.41
R lateral occipital gyrus (18/19)	48, -68, 4	950	4.01	48, -72, 10	634	3.94
	38, -78, 10		3.84			
	24, -76, 20		3.55			
L lateral occipital gyrus (18/19)	-34, -72, 14	1041	4.11			
	-38, -52, 6		3.86			
	-44, -50, 24		3.74			
R precuneus (17/18)				10, -50, 30	220	3.51
L posterior cingulate gyrus (23)				-8, -36, 10	66	3.16
L post-central g (1/2/3)	-48, -30, 48	196	3.45			
L mid-cingulate gyrus (23/24)	-12, 4, 28	67	4.48			
R insula				46, -6, -4	221	3.60
R central sulcus (1/2/3/4)	36, -2, 30	42	3.11			
R ventral striatum	12, 18, -10	332	3.86			
R lateral cerebellum	58, -52, -30	134	3.20			

^aStereotactic coordinates from MNI atlas, left/right, anterior/posterior and superior/inferior, respectively.

^bCluster size, number of voxels (k).

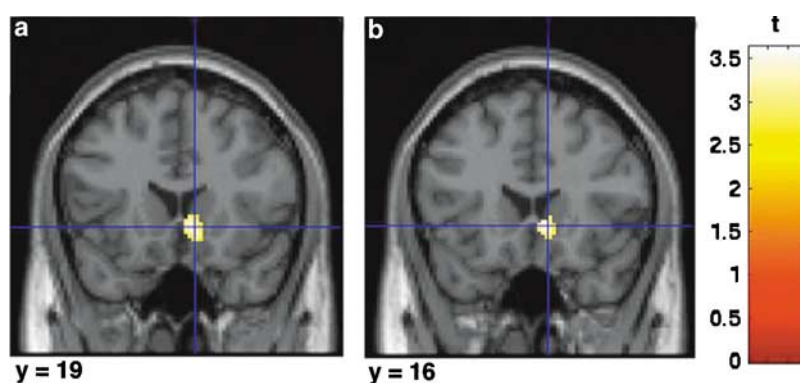


Figure 5 Phasic changes in the right ventral striatum for POS-NA, where control subjects show greater activation than patients. (a) Control subjects ($n = 9$) greater than medicated schizophrenic patients ($n = 13$); (b) Control subjects ($n = 5$) greater than unmedicated schizophrenic patients ($n = 4$). Voxels displayed at $p < 0.01$.

enhance processing of emotional stimuli, that is, salience-mediated attention effects (Pessoa *et al*, 2002). Prior work in schizophrenia has not sufficiently measured eye movements, leaving unanswered the question of whether or not

the patients scanned the pictures in a qualitatively different way, as other studies of visual scanning in schizophrenia have demonstrated (Phillips and David, 1994, 1998; Streit *et al*, 1997). The measurement of lateral EOG activity in the

current study showed an identical pattern of eye movement magnitude across the conditions for the control and medicated schizophrenic subjects. This finding suggests that differences in visual scanning, which might have occurred, would not account for differences in modulation of visual cortex by emotional stimuli. We searched for correlations between EOG parameters and visual cortical modulation and found none. Even if the patients did scan the complex images differently, the similar magnitudes of eye movements between the four conditions suggest that they would scan pictures from the different conditions in the same way. Hence, a contrast of CBF between conditions should not yield phasic CBF activity due to differences in eye movements.

A smaller effect of emotionally salient content on visual cortical processing in schizophrenia may reflect a failure of a process, such as attention, interacting with emotionally salient content. Patients with schizophrenia have well-documented impairments in attention (Nuechterlein and Dawson, 1984; Saykin et al, 1991). If modulation of visual cortex does represent top-down, attentional control, then reduced modulation of visual processing streams by salient content may reflect this attentional impairment. However, equating the strength of the phasic signal with attention may not capture the data accurately. The schizophrenic patients actually exhibited nominally larger magnitude and extent of activation in the visual cortex for the comparison of nonaversive stimuli with blanks. It has been often observed, but infrequently acknowledged, that patients with schizophrenia exhibit significantly greater posterior activity for simple visual stimuli (Siegel et al, 1993; Renshaw et al, 1994; Andreasen et al, 1997; Taylor et al, 1997). In spite of activating more voxels, the patients in the present study still exhibited significantly less phasic activity than controls in the lingual gyrus. One may interpret these results as evidence of a failure of an organizing process, similar to, but not identical with, attention. The ability to organize activity across regions of cortex has been suggested as one of the core deficits in schizophrenia (Andreasen et al, 1998), and the failure to modulate visual cortex to emotionally salient stimuli may reflect this poor organization.

Conclusion

This study used a neurobehavioral probe to target neural circuitry of hypothesized importance for schizophrenia, including brain regions with extensive dopaminergic innervation that process salient, emotional information. The data described in this experiment demonstrate that structures, such as the VS, show a blunted response to emotional salience. Furthermore, some of this same circuitry, along with the amygdala, may be tonically overactive. While many questions remain about the role of this 'salience circuitry' in producing the phenomena of schizophrenia, the use of salience probes can provide important experimental leverage.

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