

ARCHIVAL REPORT

Anhedonia and Emotional Experience in Schizophrenia: Neural and Behavioral Indicators

Erin C. Dowd and Deanna M. Barch

Background: Emotional impairments such as anhedonia are often considered key features of schizophrenia. However, self-report research suggests that emotional experience in response to affect-eliciting stimuli is intact in schizophrenia. Investigation of neural activity during emotional experience may help clarify whether symptoms of anhedonia more likely reflect alterations of in-the-moment hedonic experience or impairments in other aspects of goal-directed behavior.

Methods: Forty individuals with DSM-IV-TR schizophrenia or schizoaffective disorder and 32 healthy control subjects underwent functional magnetic resonance imaging while making valence and arousal ratings in response to emotional pictures, words, and faces. Blood oxygen level-dependent responses were compared between patients and control subjects and were correlated with questionnaire measures of anhedonia.

Results: Patients showed some evidence of blunted valence but not arousal ratings in response to emotional stimuli compared with control subjects. Higher anhedonia scores were associated with blunted valence ratings in both groups and fully mediated the group differences in valence ratings. Functional activity was largely intact in patients, except for regions in right ventral striatum and left putamen, which showed reduced responses to positive stimuli. Higher anhedonia was associated with reduced activation to positive versus negative stimuli in bilateral amygdala and right ventral striatum in patients and in bilateral caudate in control subjects.

Conclusions: Increased anhedonia is associated with a reduced experience of valence in both patients and control subjects, and group differences in experienced valence are likely driven by individual differences in anhedonia. Reduced activation of the striatum and amygdala may contribute to symptoms of anhedonia by failing to signal the salience of positive events.

Key Words: Affect, anhedonia, emotional experience, fMRI, imaging, schizophrenia

Anhedonia, or the inability to experience pleasure, is a long-established feature of schizophrenia (1,2) that significantly impacts functional capacity and is resistant to treatment (3,4). Surprisingly, however, a growing body of self-report (5,6) and behavioral (7) data suggests that emotional experience in schizophrenia is intact. One possible explanation for this discrepancy is that in schizophrenia, clinical measures of anhedonia reflect not a deficit in consummatory pleasure but a deficit in anticipatory pleasure or approach motivation (8–10). To investigate this possibility, we asked whether neural activity during emotional experience is also intact in schizophrenia.

In studying brain responses to affect-eliciting stimuli, several structures are of particular interest. First, the striatum has been associated with responses to “rewarding” or pleasurable stimuli (11–13). Furthermore, reduced ventral striatal activity in response to positive stimuli has been associated with anhedonia in studies with both healthy (14) and depressed (15,16) individuals. Most commonly, the mesolimbic dopamine system and its projections to the striatum are associated with reward prediction and incentive salience (11,17,18), suggesting that this region is instrumental to anticipatory pleasure and approach motivation. Second, dorsomedial prefrontal cortex (dmPFC) and orbitofrontal cortex

(OFC) are active during emotional experience across a wide range of emotion elicitation studies (19). The dmPFC might be involved in the introspective evaluation of one’s feelings, whereas OFC might be involved in establishing the threat or reward value of a stimulus (20). Third, the amygdala is implicated in processing survival-salient, arousing stimuli, both negative and positive (21). Finally, activity in the rostral anterior cingulate cortex (rACC) has been associated with subjective ratings of pleasantness (22,23).

A number of studies have suggested that striatal activity during processing of positive stimuli might be altered in schizophrenia. For example, unmedicated patients have shown reduced ventral striatal activation during reward anticipation, which correlated with negative symptom severity (24). In emotion perception studies, patients failed to modulate nucleus accumbens activation when rating pleasant versus unpleasant odors (25) and demonstrated reduced phasic (but enhanced tonic) activity in the ventral striatum to both positive and aversive stimuli (26).

Studies of activity in dmPFC and OFC during emotional experience in schizophrenia have yielded mixed results. Given evidence of a dissociation between neural activity patterns during emotional experience versus emotion perception (27), we focus here on studies in which participants reported their own experienced emotion. Some of these studies found reduced activation of dmPFC and OFC during sadness in chronic and first-episode schizophrenia (28,29). However, other studies failed to find group differences in these regions in patients (30,31) and relatives (32). Functional neuroimaging studies of amygdala activation in schizophrenia have also given mixed results (33). Some emotional experience studies have shown reductions in amygdala activity in patients compared with control subjects (28,31), whereas others found no group differences (29,30). Similarly, most emotion perception studies have found reduced amygdala activity in response to emotional stimuli in patients relative to control subjects (28,34–38) and in paranoid versus nonparanoid patients (39). However, some studies have shown increased (40,41) or normal (42,43) amygdala activation. The

From the Departments of Psychology (DMB), Psychiatry (DMB), and Radiology (DMB), and the Neuroscience Program (ECD), Washington University, St. Louis, Missouri.

Address correspondence to Erin C. Dowd, B.A., Department of Psychology, Washington University, Box 1125, One Brookings Drive, St. Louis, MO 63130; E-mail: dowde@wusm.wustl.edu.

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disparity in these results might reflect small sample sizes, differences in stimuli, clinical variation across samples, and the need for a low-level control condition given that neutral stimuli might elicit greater limbic activation in patients (44) and their relatives (45) than in control subjects. In the current study, we aimed to address these concerns by using a large sample and several types of stimuli, by conducting individual difference analyses, and by examining the pattern of responses across several emotional conditions rather than comparing emotional conditions to a neutral baseline.

This study aimed to address three questions. First, we asked whether self-reports of emotional experience are intact in patients. In keeping with previous data, we hypothesized that self-reports would be similar between patients and control subjects. Second, we asked whether neural activity during emotional experience was similar in patients and control subjects. If functional magnetic resonance imaging (fMRI) is sensitive to differences in emotional experience not probed by self-report measures, we would expect to see differences in functional activity in regions associated with emotional experience. Third, we asked whether there was a relationship between questionnaire measures of anhedonia and individual differences in self-reported emotion or its associated neural activity.

Methods and Materials

Participants

Participants were 40 outpatients with DSM-IV-TR schizophrenia or schizoaffective disorder and 32 healthy community control subjects. All results reported in the following text remained the same when schizoaffective patients were excluded (see Methods and Materials in Supplement 1). Control subjects were excluded if they had any history of or first-order family member with an Axis I psychotic disorder or any current mood or anxiety disorder other than Specific Phobia. Other exclusions included: 1) DSM-IV substance abuse or dependence within 6 months; 2) any medical disorder that is unstable or severe, would confound the assessment of psychiatric diagnosis, or would make participation unsafe; 3) present or past head injury with neurological sequelae or causing loss of consciousness; and 4) DSM-IV mental retardation (mild or greater). The demographic and clinical characteristics of both participant groups are shown in Table 1. Groups were matched on age, parental education, gender, race, and handedness. All patients were taking antipsychotic medications, which were stable for least 2 weeks.

Participant diagnoses were based on a Structured Clinical Interview for DSM-IV-TR (46) and on information from medical

Table 1. Clinical and Demographic Characteristics

	Mean (SD)		<i>t</i> or χ^2	<i>df</i>	<i>p</i>
	CON	SCZ			
Age	36.25 (10.85)	36.8 (8.99)	.24	70	.82
Education	15.53 (4.29)	13.05 (2.27)	3.15	70	.002 ^a
Highest Parental Education	12.76 (2.76)	13.35 (3.83)	-1.65	65	.1
Gender (% Male)	65.6	65	.003	1	.95
Race (% Caucasian)	53.1	47.5	.225	1	.64
Chapman Social Anhedonia	2.35 (2.06)	5.28 (2.17)	-5.748	69	.001 ^a
Chapman Physical Anhedonia	3.45 (2.99)	7.23 (4.18)	-4.253	69	.001 ^a
SANS Global Anhedonia	—	2.68 (1.21)	—	—	—
Positive Symptoms	—	1.83 (.93)	—	—	—
Negative Symptoms	—	1.81 (1.37)	—	—	—
Disorganization Symptoms	—	1.17 (.80)	—	—	—
Duration of Illness (yrs)	—	17.73 (11.25)	—	—	—
Diagnosis Subtype (%)	—	—	—	—	—
Schizoaffective—bipolar	—	7.5	—	—	—
Schizoaffective—depressive	—	17.5	—	—	—
Schizophrenia—undifferentiated	—	42.5	—	—	—
Schizophrenia—residual	—	15	—	—	—
Schizophrenia—paranoid	—	15	—	—	—
Schizophrenia—disorganized	—	2.5	—	—	—
Medication (% Taking)	—	—	—	—	—
Aripiprazole	—	22.5	—	—	—
Clozapine	—	5.0	—	—	—
Ziprasidone	—	2.5	—	—	—
Haloperidol	—	5.0	—	—	—
Iloperidone	—	2.5	—	—	—
Risperidone	—	30.0	—	—	—
Quetiapine	—	17.5	—	—	—
Trifluoperazine	—	2.5	—	—	—
Olanzapine	—	12.5	—	—	—
Average Dose (CPZ Equivalents)	—	452.20 (369.60)	—	—	—

Positive symptoms were the sum of global scores for hallucinations and delusions; negative symptoms were the sum of global scores for alogia, anhedonia, avolition, affective flattening, and attentional impairment; and disorganization symptoms were the sum of global scores for bizarre behavior, positive thought disorder, and inappropriate affect.

CON, control; SCZ, schizophrenia; SANS, scale for the assessment of negative symptoms; CPZ, chlorpromazine.

^a*p* < .05.

records and corroborative sources. Clinical symptoms were rated with the Scales for the Assessment of Positive Symptoms (SAPS) (47) and Negative Symptoms (SANS) (48). We assessed anhedonia symptoms with the SANS global anhedonia score and the self-report Chapman physical and social anhedonia scales (49) and handedness with the Edinburgh Index (50). See Methods and Materials in Supplement 1 for details.

Materials and Tasks

All participants were scanned while making valence and arousal ratings of their own subjective responses to emotional pictures, words, and faces. Valence (pleasant–unpleasant) and arousal (activation–deactivation) are independent dimensions of affect (51) that are considered vital features of emotional experience (20). Participants rated their experience of each stimulus by button press as positive, negative, or neutral during valence runs or as highly, slightly, or not aroused during arousal runs. Stimuli consisted of 50 each emotional words, pictures, and faces, 10 in each of the following categories: negative high arousal (NHA), negative low arousal (NLA), positive high arousal (PHA), positive low arousal (PLA), and neutral (NEU); see Methods and Materials in Supplement 1. Participants performed the task for six runs; one run each of arousal and valence judgments for each stimulus type (pictures, words, faces). Stimuli were presented for 2000 msec with a jittered interstimulus interval varying from 1000 to 10,000 msec.

Behavioral Data Analysis

Valence and Arousal Ratings. We analyzed the valence and arousal ratings with repeated measures analyses of variance with group (schizophrenia, control) as a between-subjects factor and stimulus (picture, word, face) and condition (NHA, NLA, NEU, PLA, PHA) as within-subjects factors. To further characterize the pattern of responses as a function of condition, we created a priori contrasts that were sensitive to the valence and/or arousal characteristics of the stimuli. To examine the effect of valence irrespective of arousal, we used a linear contrast with weights of $-1, -1, 0, 1,$ and 1 for NHA, NLA, NEU, PLA, and PHA, respectively (valence contrast). To examine the effect of arousal irrespective of valence, we used a quadratic contrast with weights of $2, -1, -2, -1,$ and 2 for NHA, NLA, NEU, PLA, and PHA, respectively (arousal contrast). To examine whether the valence ratings were influenced by both the valence and arousal characteristics of the stimuli, we also created a linear contrast in which valence was amplified by arousal, with weights of $-2, -1, 0, 1,$ and 2 , for NHA, NLA, NEU, PLA, and PHA, respectively (valence \times arousal contrast). We tested the significance of these contrasts with univariate F tests within each group.

Individual Difference Analyses. We conducted linear regression analyses to examine the extent to which anhedonia scores predicted valence ratings within each group. To determine whether the relationship between valence ratings in response to PHA/NHA stimuli and Chapman Physical/Social Anhedonia scores differed between groups, we conducted hierarchical regression analyses with anhedonia score (physical or social) and group entered in Step 1 and group \times anhedonia interaction entered in Step 2. We also examined whether anhedonia scores mediated the effect of group on valence ratings. To do this, we conducted two separate multiple mediation analyses with a Sobel procedure with bootstrapping (52), with PHA or NHA valence ratings as the dependent variable, group as the independent variable, and physical and social anhedonia scores as mediators. Within the patient group, we also conducted correla-

tions between PHA/NHA valence ratings and SANS global anhedonia, and with SANS avolition, alogia, and affective flattening to examine the specificity to anhedonia.

fMRI Analysis

For fMRI acquisition and image analysis, see Methods and Materials in Supplement 1. Functional activation was analyzed with the valence, arousal, and valence \times arousal contrasts in both region of interest (ROI) and whole-brain analyses. We examined voxelwise t tests at the group level within predefined ROI masks, including the amygdala, striatum, dmPFC, OFC, and rACC (Methods and Materials in Supplement 1). Both the whole-brain and ROI analyses were corrected for multiple comparisons with combined p value/cluster size thresholds, determined with Monte Carlo simulations to provide an overall false-positive rate of .05 (53,54). These thresholds were $p < .01$ and 14 voxels for ROI analyses and $p < .003$ and 30 voxels for whole-brain analyses. To identify regions whose activation patterns were consistent with the valence and arousal patterns of interest, we first conducted one-sample t tests for each contrast on both groups combined. To identify regions showing group differences in activation, we also performed group t tests on each contrast. In both analyses, significant regions were followed up with simple effects tests to determine the activation pattern within each group separately. To examine individual differences in functional ac-

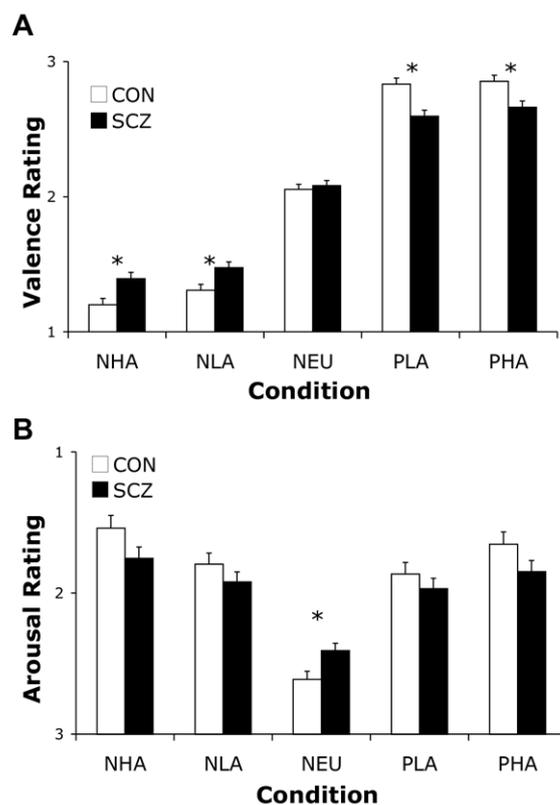


Figure 1. Valence and arousal ratings as a function of condition in individuals with schizophrenia (SCZ) and control subjects (CON). **(A)** Average valence ratings (1 = negative, 2 = neutral, 3 = positive) collapsed across stimulus type (pictures, words, faces) for each emotional condition: negative high arousal (NHA), negative low arousal (NLA), neutral (NEU), positive low arousal (PLA), and positive high arousal (PHA). **(B)** Average arousal ratings (1 = highly aroused, 2 = slightly aroused, 3 = not aroused) collapsed across stimulus type (pictures, words, faces) for each emotional condition. * $p < .05$. Error bars represent standard error.

Table 2. Hierarchical Regression Analyses with Group and Anhedonia Scores to Predict Valence Ratings

Dependent Variable	Predictors	R^2	R^2 Change	β
PHA Valence Rating	Step 1	.229 ^a		
	Group			-.191
	Physical anhedonia			-.360 ^b
	Step 2	.231 ^b	.002	
PHA Valence Rating	Step 1	.192 ^b		
	Group			-.177
	Social Anhedonia			-.313 ^d
	Step 2	.206 ^b	.014	
NHA Valence Rating	Step 1	.199 ^b		
	Group			.191
	Physical anhedonia			.326 ^c
	Step 2	.205 ^b	.006	
NHA Valence Rating	Step 1	.190 ^b		
	Group			.151
	Social anhedonia			.332 ^d
	Step 2	.197 ^c	.007	
	Group \times social anhedonia			-.246

PHA, positive high arousal; NHA, negative high arousal.

^a $p < .001$.

^b $p < .005$.

^c $p < .01$.

^d $p < .05$.

tivity, we also conducted voxelwise correlation analyses between contrast scores and anhedonia scores. Correlations were conducted within each group separately, and correlation coefficients were compared between groups with Fisher r -to- z transformations.

Results

Behavioral Results

Anhedonia Scores. Overall, individuals with schizophrenia had higher anhedonia scores than control subjects on both Chapman scales (Table 1).

Valence and Arousal Ratings. For valence (Figure 1A), there was a significant main effect of condition [$F(4,280) = 659.85, p < .001$] and significant group \times condition [$F(4,280) = 13.49, p < .001$] and stimulus \times condition [$F(8,560) = 12.70, p < .001$] interactions. Simple effects tests revealed significant effects of condition for control subjects [$F(4,280) = 386.85, p < .001$] and patients [$F(4,280) = 273.95, p < .001$]. However, comparisons within each condition revealed that patients' responses to negative stimuli were less negative [$F(1,70) = 9.62, p < .004$ for NHA; $F(1,70) = 7.87, p < .007$ for NLA] and responses to positive stimuli were less positive [$F(1,70) = 15.77, p < .001$ for PLA,

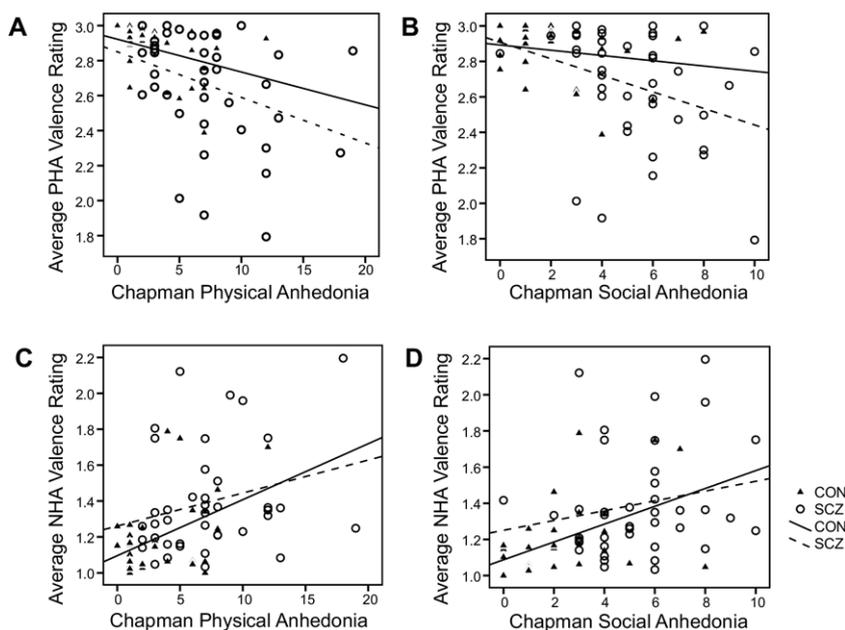


Figure 2. Scatterplots of (A) average valence ratings to PHA stimuli as a function of Chapman physical anhedonia, (B) average valence ratings to PHA stimuli as a function of Chapman social anhedonia, (C) average valence ratings to NHA stimuli as a function of Chapman physical anhedonia, and (D) average valence ratings to NHA stimuli as a function of Chapman social anhedonia, in individuals with SCZ (circles) and CON (triangles). Abbreviations as in Figure 1.

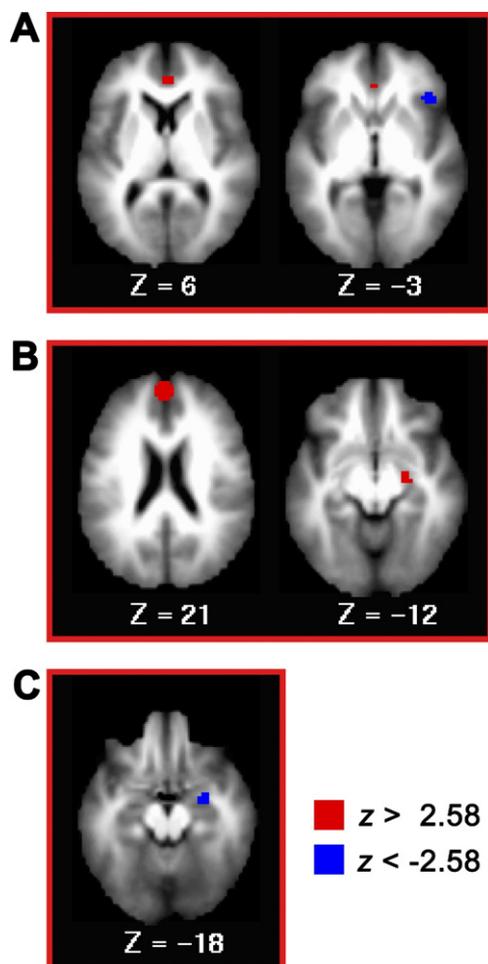


Figure 3. Results of region of interest analyses of valence, arousal, and valence \times arousal contrasts in the total sample (both patients and control subjects). Regions are described in Table 3. Images are shown in neurological orientation. **(A)** Regions showing significant activation in the valence contrast. Positive z scores (red) indicate greater activation to positively valenced stimuli than to negatively valenced stimuli; negative z scores (blue) indicate greater activation to negatively valenced stimuli than to positively valenced stimuli. **(B)** Regions showing significant activation in the arousal contrast. Positive z scores (red) indicate greater activation to high arousal stimuli relative to neutral and low-arousal stimuli. **(C)** Regions showing significant activation in the valence-by-arousal contrast. Negative z scores indicate greater activation to negative high arousal stimuli than to positive and/or low-arousal stimuli.

$F(1,70) = 9.75, p < .004$ for PHA] than control subjects. Both the valence and valence \times arousal contrasts were significant for both groups, with similar effect sizes [valence contrast: $F(1,70) = 521.50, p < .001, \eta_p^2 = .882$ for control subjects, $F(1,70) = 368.23, p < .001, \eta_p^2 = .840$ for patients; valence \times arousal contrast: $F(1,70) = 509.33, p < .001, \eta_p^2 = .879$ for control subjects; $F(1,70) = 364.80, p < .001, \eta_p^2 = .839$ for patients]. Because stimulus type (picture, word, face) did not interact with group in any of our analyses (behavioral or fMRI), stimulus effects are not discussed further here (but see Results in Supplement 1).

For the arousal ratings (Figure 1B), there were significant main effects of stimulus [$F(2,140) = 23.41, p < .001$] and condition [$F(4,280) = 55.96, p < .001$] and significant stimulus \times condition [$F(8,560) = 5.03, p < .001$] and group \times condition [$F(4,280) = 3.15, p < .009$] interactions. Simple effects tests

Table 3. Results of ROI Analyses of Valence, Arousal, and Valence \times Arousal Contrasts in the Total Sample

Brain Region	Talairach Coordinates	Number Voxels	Z	Activation Pattern		Regional Analyses						
				Valence	Arousal	Main Effect of Group	Group \times Condition Interaction	Group Difference in Contrast	Within CON Contrast	Within SCZ Contrast		
Valence Contrast												
R OFC	41, 24, -4	27	-3.98	neu > neg > pos	—	b	NS	NS	b	b	b	b
rACC	1, 35, 3	17	4.61	deactivation: neu = neg > pos	—	NS	NS	NS	a	NS	c	NS
Arousal Contrast												
R amygdala	26, -14, -8	24	3.39	ha > la = neu	ha > la = neu	NS	NS	NS	b	b	d	d
dmPFC	-1, 51, 23	79	3.68	ha > la = neu	ha > la = neu	NS	NS	NS	NS	NS	b	b
Valence \times Arousal Contrast												
R amygdala	28, -10, -15	21	-3.41	neu > neu = pos	nha > nla = neu	NS	NS	NS	d	NS	c	c

ROI, region of interest; BA, Brodmann area; CON, control; SCZ, schizophrenia; R, Right; OFC, orbitofrontal cortex; neu, neutral; neg, negative; pos, positive; rACC, rostral anterior cingulate cortex; ha, high arousal; la, low arousal; dmPFC, dorsomedial prefrontal cortex; nha, negative high arousal; nla, negative low arousal.

^a $p < .001$.

^b $p < .005$.

^c $p < .01$.

^d $p < .05$.

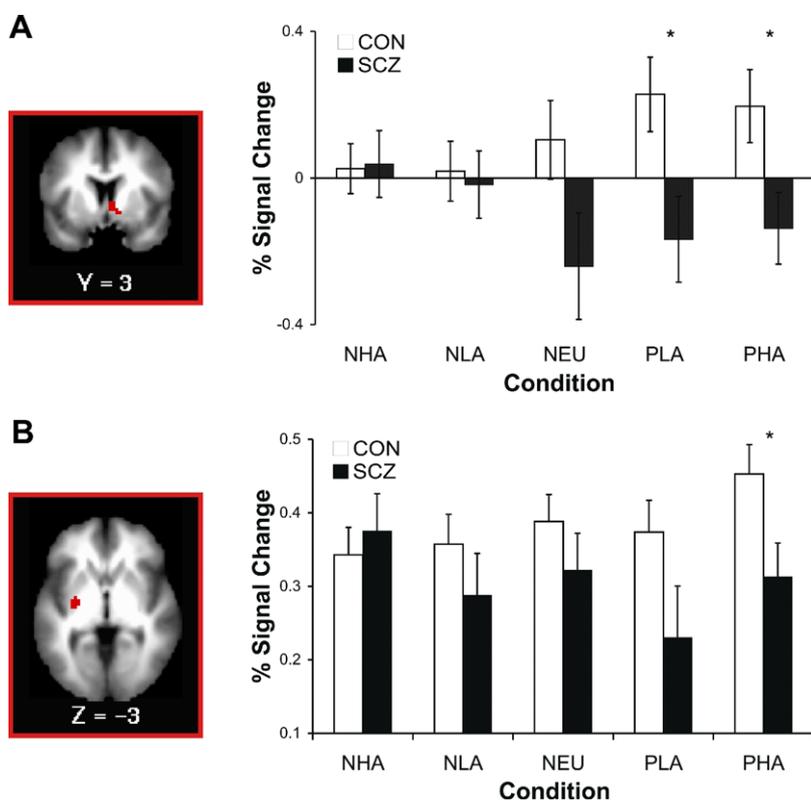


Figure 4. Results of region of interest analyses of group *t* tests between patients and control subjects for the valence and valence \times arousal contrasts. Regions are described in Table 4. Images are shown in neurological orientation. **(A)** Right ventral striatal region demonstrating a group difference in the valence contrast. Activation did not differ significantly in the NHA, NLA, or NEU conditions but was significantly lower in patients than in control subjects for the PLA and PHA conditions. **(B)** Left putamen region demonstrating a group difference in the valence \times arousal contrast. Activation did not differ significantly in the negative, neutral, or PLA conditions but was significantly lower in patients than in control subjects in the PHA condition. * $p < .05$. Error bars represent standard error. Abbreviations as in Figure 1.

revealed significant effects of condition within each group [$F(4,280) = 39.35$, $p < .001$ for control subjects, $F(4,280) = 17.72$, $p < .001$ for patients]. Furthermore, group comparisons within each condition revealed a significant group difference only for the NEU condition: compared with control subjects, patients showed higher arousal in response to neutral stimuli [$F(1,70) = 6.87$, $p < .02$]. The arousal contrast was significant for both groups [$F(1,70) = 151.45$, $p < .001$, $\eta_p^2 = .654$ for control subjects; $F(1,70) = 68.76$, $p < .001$, $\eta_p^2 = .496$ for patients]. Taken together, these results indicate that patients showed blunted valence ratings in response to emotional stimuli. However, the patterns of both valence and arousal ratings as a function of emotional condition were similar between groups.

Individual Difference Analyses. We conducted hierarchical regression analyses with Chapman anhedonia scores predicting valence ratings to PHA and NHA stimuli in patients and control subjects (Table 2). In all of these analyses, anhedonia score and group accounted for a significant portion of the variance in the valence ratings, and adding a group \times anhedonia interaction term failed to account for significantly more variance. As expected, higher physical and social anhedonia scores were associated with less-positive responses to PHA stimuli and less-

negative responses to NHA stimuli in both groups (Figure 2). Similarly, within the patient group, SANS anhedonia correlated negatively with PHA valence ratings ($r = -.37$, $p < .03$), although it failed to correlate with NHA valence ratings ($p > .16$). Together, these results suggest that, within both patients and control subjects, higher levels of anhedonia are associated with less-valenced experiences of emotional stimuli.

Multiple mediation analyses revealed that for both PHA and NHA valence ratings, the effect of group was fully mediated by physical and social anhedonia scores [effect of group on valence rating, controlling for physical and social anhedonia: $t(69) = -1.2$, $p > .24$ for PHA, $t(69) = 1.0$, $p > .31$ for NHA]. The total mediated effect was significant in both models (95% confidence interval: $-.27$, $-.01$ for PHA; $.02$, $.25$ for NHA). For PHA ratings, only physical anhedonia was significant as a specific mediator (95% confidence interval: $-.16$, $-.003$), and for NHA ratings, neither specific mediator was significant alone.

To evaluate the specificity of these results to anhedonia, we correlated PHA and NHA valence ratings with SANS global avolition, alogia, and affective flattening in patients and found that avolition also correlated negatively with PHA valence ratings ($r = -.34$, $p < .04$) and positively with NHA valence ratings ($r = .36$, $p < .03$). Aside from a trend-level correlation between alogia and NHA ratings ($r = .30$, $p < .07$), alogia and affective flattening failed to correlate with either measure ($p > .16$). Therefore, a reduced experience of positive and negative emotion seems to be related to symptoms of anhedonia and amotivation but not to other negative emotional symptoms.

fMRI Results

ROI Analyses: One-Sample *t* Tests. As shown in Figure 3, one-sample *t* tests identified several regions within the ROIs with activity patterns significant for the valence, arousal, and valence \times

Table 4. Results of ROI Analyses of Group *t* Tests Between Patients and Control Subjects for the Valence and Valence \times Arousal Contrasts

Brain Region	Talairach Coordinates	Number Voxels	Z
valence contrast			
R ventral striatum	7, 3, -4	14	2.80
Valence \times Arousal Contrast			
L putamen	-28, -14, -1	17	3.44

ROI, region of interest; R, Right; L, Left.

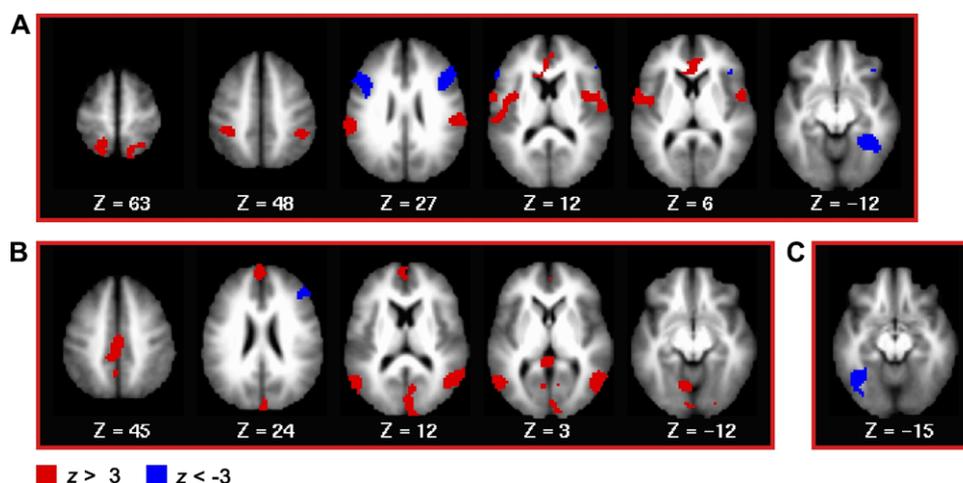


Figure 5. Results of whole-brain analyses of valence, arousal, and valence \times arousal contrasts in the total sample (both patients and control subjects). Regions are described in Table S5 in Supplement 1. Images are shown in neurological orientation. **(A)** Regions showing significant activation in the valence contrast. Positive z scores (red) indicate greater activation to positively valenced stimuli than to negatively valenced stimuli; negative z scores (blue) indicate greater activation to negatively valenced stimuli than to positively valenced stimuli. **(B)** Regions showing significant activation in the arousal contrast. Positive z scores (red) indicate greater activation to high arousal stimuli relative to neutral and low-arousal stimuli; negative z scores (blue) indicate greater activation to neutral and low-arousal stimuli than to high-arousal stimuli. **(C)** Regions showing significant activation in the valence \times arousal contrast. Negative z scores indicate greater activation to negative high arousal stimuli than to positive and/or low-arousal stimuli.

arousal contrasts. These regions and their activation patterns are detailed in Table 3.

Group t Tests. One region in right ventral striatum demonstrated a significant group difference in the valence contrast, and one in left putamen showed a group difference in the valence \times arousal contrast (Figure 4, Table 4). As shown in Figure 4, in both of these regions, patients showed reduced activation compared with control subjects for the positive conditions. Post hoc tests revealed that, in left putamen, PHA activation differed significantly between groups [$F(1,70) = 5.05, p < .04$]. In right ventral striatum, there were significant group differences in both PHA [$F(1,70) = 5.58, p < .03$] and PLA [$F(1,70) = 6.14, p < .03$].

Whole-Brain Analyses

As shown in Figure 5 (and Table S5 in Supplement 1), a number of regions were identified by the valence, arousal, and valence \times arousal contrasts in whole-brain one-sample t tests. In the group t tests, however, we did not find a single region that showed a significant group difference in any of the contrasts. To further examine whether the activity patterns were similar between groups, we conducted follow-up group analyses on each region identified in the one-sample t tests. As shown in Table S5 in Supplement 1, overall activity differed between patients and control subjects in a number of these regions. However: 1) in every region, both patients and control subjects showed signifi-

cant within-group effects of the relevant contrast; 2) in every region, there were no significant group differences in the magnitude of the contrast; and 3) in all but two regions, the pattern as a function of emotional condition was the same for both patients and control subjects. Thus, outside of the striatum, patients and control subjects demonstrated similar neural responses to both valence and arousal.

Individual Difference Analyses. We first conducted correlations between anhedonia scores and average activation contrast scores within the regions showing group differences in the contrasts. This analysis revealed a negative correlation between physical anhedonia and valence \times arousal contrast score in the right ventral striatum in patients ($r = -.36, p < .04$), indicating that patients with higher anhedonia scores showed less activation in this region in response to positive stimuli compared with neutral and negative stimuli. This correlation was not significant in control subjects ($r = -.17, p > .34$), although the group difference in correlation coefficients was not significant ($p > .77$). We next conducted voxelwise ROI analyses (Table 5), in which physical anhedonia correlated negatively with the valence contrast in left amygdala and with the valence \times arousal contrast in right amygdala in patients. In control subjects, social anhedonia correlated negatively with the valence contrast in bilateral caudate. Comparison of correlation coefficients between groups revealed a significant difference in the right caudate ($p < .02$)

Table 5. ROI Results of Correlation Analyses Between Anhedonia Scores and fMRI Valence and Valence \times Arousal Contrast Scores

Contrast	Anhedonia Measure	Talairach Coordinates	Region Name	Number Voxels	r	Z
Control	Valence	8, -1, 14 -13, -2, 18	R caudate	14	-.550	-3.26
			L caudate	28	-.539	-3.18
Schizophrenia	Valence	-14, -9, -15 17, -14, -11	L amygdala	17	-.446	-2.89
	Valence \times Arousal		R amygdala	15	-.413	-2.58

ROI, region of interest; fMRI, functional magnetic resonance imaging; R, Right; L, Left.

and a trend level difference in left caudate ($p < .08$) but no difference in either amygdala region ($p > .70$).

Discussion

Behavioral Measures of Emotional Experience

We found that individuals with schizophrenia self-reported more anhedonia than control subjects, in agreement with most clinical data. Behaviorally, there was a group \times condition interaction in the valence ratings, and post hoc tests revealed that patients rated their experience of the valenced stimuli as less valenced than control subjects. This finding is at odds with most studies, which have shown intact responses to emotional stimuli. However, although the arousal ratings also showed a group \times condition interaction, the only post hoc group difference was heightened arousal ratings in response to neutral stimuli in patients. This finding suggests that patients' experience of arousal in response to emotional stimuli is intact, in agreement with previous literature. Furthermore, patients clearly showed modulation of both valence and arousal ratings as a function of the emotional content of the stimuli: when we conducted contrast analyses sensitive to valence, arousal, and valence \times arousal interaction, the relevant contrasts were significant within both groups, with similar effect sizes. Overall, although these findings suggest that the range of experienced emotion might be narrowed in patients, they also show that evoked arousal is relatively intact and that affective stimuli modulate emotional experience in similar ways in patients and control subjects.

Individual difference analyses revealed that higher anhedonia was associated with blunted responses to emotional stimuli within both patients and control subjects. Furthermore, the group differences in valence ratings were fully mediated by anhedonia scores. Together, these results indicate that the level of anhedonia rather than simply the diagnosis of schizophrenia might underlie the blunted responses to emotional stimuli seen in patients. This finding highlights the importance of including sufficiently powered individual difference analyses in future work.

fMRI Measures of Emotion-Processing

The fMRI analysis revealed that brain activity is largely intact during emotional experience in schizophrenia. On whole-brain analysis, we did not find any regions that showed group differences in any contrast, suggesting similar patterns of neural activity in patients and control subjects. On ROI analysis, however, right ventral striatum and left putamen showed reduced activation to positive stimuli in patients compared with control subjects. Given past research showing that striatal activation is associated with the anticipation (55) and receipt (23) of pleasurable stimuli, this finding might represent a failure to respond to positive experiences that contributes to an inability to anticipate or want such experiences in the future (56).

In support of this interpretation, reduced activation to positive versus negative stimuli in the same ventral striatal region was also associated with higher physical anhedonia in patients. This finding suggests that the group differences in activation seen in this region might be driven by individual differences in anhedonia. Similarly, bilateral amygdala activation to positive versus negative stimuli was reduced in patients who were higher in physical anhedonia. Within control subjects, greater social anhedonia was associated with decreased bilateral caudate activation in response to positive relative to negative stimuli. Because the amygdala (21) and striatum (57) are thought to be involved in

salience attribution, these results might indicate that these regions fail to mark positive events as salient in anhedonic individuals, leading to a blunted experience of emotion and a reduced ability to seek out similar events in the future.

Given that the ventral striatum is typically associated with reward processing, it is interesting to speculate on how these results relate to findings of reduced ventral striatal activation during reward anticipation in schizophrenia (24). Notably, the reduced ventral striatal activation to positive stimuli seen here in patients might represent a deficit in motivational or reward-prediction processes rather than in hedonic processes per se. During learning, dopaminergic neurons initially fire to unexpected positive stimuli, shifting over time to fire to cues that predict these rewards (18). Thus, the deficient right ventral striatal activation reported here could reflect a failure of this initial dopaminergic firing to unpredicted positive stimuli, potentially impairing reward prediction/incentive salience and leading to reduced anticipatory activation. Importantly, this impairment in predictive or motivational processes might be independent of the hedonic response to the reward, allowing a normal experience of "liking" combined with reduced "wanting." This is consistent with the view that consummatory pleasure is intact in schizophrenia while anticipatory pleasure is impaired (10).

Given the finding of group differences in striatal activity, a major limitation of this study is that all patients were taking medications that block dopamine receptors, potentially altering striatal function. However, most patients were taking atypical antipsychotics, which have a lesser effect on striatal activity during reward processing than typical antipsychotics (58,59). Furthermore, when we removed from analysis all patients taking typical antipsychotics or risperidone (which are pharmacologically similar), the group differences and correlations remained significant. In addition, neural activity did not correlate with antipsychotic dose within the regions showing group differences (Results in Supplement 1). Although the possibility of medication effects cannot be ruled out without examination of unmedicated patients, we feel that these results provide reasonable evidence that the findings reported here were not driven by medications.

In summary, this study makes several important contributions to the literature on emotional experience and its related brain activity in schizophrenia. First, although patients showed blunted responses to emotional stimuli compared with control subjects, these group differences in ratings were clearly mediated by the level of anhedonia displayed by the participants. Second, the pattern of brain activity in response to emotional stimuli was largely intact, with the exception of two striatal regions that showed reduced responses to positive stimuli. Third, blunted activation to positive versus negative stimuli correlated with anhedonia in the amygdala and right ventral striatum in patients and in the caudate in control subjects, suggesting that failure to mark stimuli as salient or rewarding might contribute to symptoms of anhedonia. Clinically, these results highlight the importance of individual differences, suggesting that optimal treatment strategies are best tailored to the individual symptomatology of the patient. Future work examining the relationship between reduced neural responses to positive stimuli and deficits in motivated behavior, with paradigms that probe for reward anticipation and reinforcement learning in anhedonic individuals, might shed additional light on the questions raised here.

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Supplementary material cited in this article is available online.

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