Event-Related Functional Magnetic Resonance Imaging Measures of Neural Activity to Positive Social Stimuli in Pre- and Post-Treatment Depression

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Background: *Relationships between aberrant social functioning and depression have been explored via behavioral, clinical, and survey methodologies, highlighting their importance in the etiology of depression. The neural underpinnings of these relationships, however, have not been explored.*

Methods: *Nine depressed participants and 14 never-depressed control subjects viewed emotional and neutral pictures at two functional magnetic resonance imaging (fMRI) scanning sessions approximately 22 weeks apart. In the interim, depressed patients received the antidepressant Venlafaxine. Positively rated images were parsed into three separate comparisons: social interaction, human faces, and sexual images; across scanning session, activation to these images was compared with other positively rated images.*

Results: *For each of the three social stimulus types (social interaction, faces, sexual images), a distinguishable circuitry was activated equally in non-depressed control subjects and post-treatment depressed subjects but showed a hypo-response in the depressed group pre-treatment. These structures include regions of prefrontal, temporal, and parietal cortices, insula, basal ganglia, and the hippocampus.*

Conclusions: *The neural hypo-response to positively valenced social stimuli that is observed in depression remits as response to antidepressant medication occurs, suggesting a state-dependent deficiency in response to positive social incentives. These findings underscore the importance of addressing social dysfunction in research and treatment of depression.*

Key Words: Depression, functional MRI, positive affect, psychosocial factors, antidepressant treatment, prefrontal cortex

It is well-known that social and interpersonal factors are important in both the etiology and expression of depression. Many studies have found social dysfunction to be among the best predictors of low positive affect, remission, and relapse in depression (Brugha et al 1997; Paykel 2002), above attributional style, self-esteem, number of previous depressive episodes (Staner et al 1997), and other behavioral factors (Schelde 1998b)—a relationship that holds in sub-clinical adult (Nezlek et al 1994) and adolescent populations (Cheng and Furnham 2003). Although neuroimaging investigations of generally defined positive affect have found attenuated activation in the depressed state in response to picture-caption pairs (Kumari et al 2003) and positively rated International Affective Picture System (IAPS) slides (Mitterschiffthaler et al 2003), little is known about the neural underpinnings of the connection between positive social factors, depression, and its treatment. We have examined this relationship in terms of three types of socially relevant content that are strongly tied to depression: social interaction, human faces, and erotica, in pre- and post-treatment depression relative to never-depressed control subjects.

Difficulty in social interaction has emerged as a key component of the depressed state; depression and its recurrence have been connected to reduced social contact, loneliness, and dissatisfaction with social interaction (Cheng and Furnham 2003; Joiner 1997; Joiner et al 2002), whereas treatment response has been linked to increased social activity (Lenderking et al 1999; Schelde 1998a). To examine these relationships via neuroimaging, we presented positively valenced scenes showing people engaged in social interaction and contrasted the reaction obtained to similarly rated scenes showing no social interaction (i.e., showing a single person). We predicted that depressed persons would exhibit a hypo-responsiveness to scenes depicting positive social interaction that normalizes with treatment in brain networks responsible for social reinforcers and in the left prefrontal cortex (PFC), given the relationship between depression and hypoactivion in this region (Davidson 1994; Drevets 1999; Gotlib et al 1998; Gray et al 1987; Tomarken et al 1990) and its putative role in approach-related behavior (Davidson 1992; Henriques and Davidson 1991).

Human faces and expressions are vital facets of interpersonal interactions as they convey nuances and emotions in interpersonal situations. Social dysfunction in depression extends to this arena, because people with depression show a negative bias in the judgment of facial affect (Davidson et al 1985; Surguladze et al 2004), display blunted facial affect themselves when viewing positive stimuli (Berenbaum and Oltmanns 1992; Sloan et al 2001), are slower to detect happy faces amongst a crowd of neutral expressions (Suslow et al 2004), and exhibit reduced eye contact and social smiling in interpersonal situations (Segrin and Abramson 1994). We compared neural networks activated, in pre- and post-treatment depression, in response to positively rated scenes showing human faces with similarly rated scenes with people but without visible human faces. Happy faces have been found to activate the fusiform gyrus selectively in control subjects and not in those currently depressed (Surguladze et al 2005), and a wide array of paradigms presenting facial stimuli to normal subjects have implicated the fusiform gyrus and amygdalae (Breiter et al 1996; Critchley et al 2000; Hariri et al 2002; Iidaka et al 2001; Kanwisher et al 1997; Kesler-West et al 2001;

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Keightley et al 2003; Puce et al 1996); on the basis of this work we predicted that the depressed state would be associated with a hypo-activation of these regions.

Of the myriad symptoms present in depression, sexual dysfunction can also have major implications for interpersonal relationships and is manifested in a variety of physical and emotional symptoms, either before or after onset of the depressive episode (Baldwin 2001). It is also remarkably common, presenting in an estimated 70% of depressed patients (Clayton 2001; Clayton et al 2002). Neuroimaging investigations of sexual stimuli in normal populations and in depression, relative to nondepressed control subjects, have found activation in normal subjects and hypo-activation in depression in reward networks and regions involved in global vigilance, including the anterior cingulate, inferior PFC, insula, hypothalamus, striatum, anterior temporal cortex, and components of the visual stream (Arnow et al 2002; Beauregard et al 2001; Ferris et al 2001; Mouras et al 2003; Yang 2004). We aimed to extend the work of Yang (2004) by probing the neural response to sexual stimuli before and after antidepressant treatment and predicted that the aforementioned regions would show a hypo-response in depressed patients that would return to a normal level of functioning with the remittance of depressive and sexual symptoms.

Methods and Materials

Participants

Study participants were recruited through newspaper ads and posters displayed throughout the community requesting volunteers for a study of depression. All participants gave written informed consent in agreement with the Human Subjects Committee of the University of Wisconsin and were paid for participation. Potential participants received a Structured Clinical Interview for DSM-IV (First et al 1995) interview, conducted by masters- or doctorate-level clinicians to assess for Axis I disorders, and completed several rating scales, including the Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960), the Beck Depression Inventory (BDI) (Beck et al 1961), and the Positive and Negative Affect Schedule (PANAS), General Form (Watson et al 1988). Exclusion criteria included: magnetic resonance imaging (MRI) contraindicated (e.g., pacemaker); significant medical or neurological disorder; head injury; loss of consciousness exceeding 1 min; left-handed; or any first-degree family history of psychoses. Participants in the depressed group met DSM-IV criteria for either current (single or recurrent) Major Depressive Disorder with a minimum HRSD score of 22 or current Dysthymia, were free of antidepressant medication for at least 1 month before enrollment, and were further excluded for any of the following: primary anxiety disorder; history of psychosis, mania, or hypomania; substance abuse or dependence in the past year; any severe history of substance abuse or dependence; history of electroconvulsive therapy; or clinical instability (i.e., acute risk for self harm or suicidal or violent behavior). All depressed participants were assessed by the treating psychiatrist (RMB) to be medically and clinically appropriate for treatment with the study medication, Venlafaxine. Exclusion criteria for control participants included: current or past Axis I or Axis II disorder; or any Axis I disorder in a first-degree relative.

A total of 16 depressed and 17 control participants were enrolled in the study. Four depressed participants did not complete the protocol: one remitted immediately after the first MRI scan and discontinued enrollment, two discontinued their enrollment between MRI scans 1 and 2, and one was dropped from the study owing to medication noncompliance. Technical problems caused MRI data from one depressed subject to be unusable. Three control subjects were excluded: two owing to excessive movement during MRI scans and one because of self-reported sleep during the functional runs. Two depressed subjects were additionally excluded from the primary analyses concerning functional (f)MRI change pre- to post-treatment: one showed no treatment response with a considerable increase in HRSD and BDI scores over a 22-week treatment period; and another met criteria for dysthymia, but low HRSD and BDI scores precluded treatment with Venlafaxine as per the treating psychiatrist. This patient was not given Venlafaxine but went through time 2 testing after symptoms abated. Additional analyses correlating change in clinical variables to change in neural activation included these two depressed participants. Thus the final sample size for the main analyses of treatment response was 9 depressed (6 women, average age 35.9 years) and 14 control subjects (10 women, average age 28.2). Table 1 lists the demographic and clinical characteristics of the final sample.

Clinical Treatment and Assessment

After enrollment, depressed participants were treated with 37.5–75 mg of Venlafaxine (Effexor or Effexor XR; Wyeth, Madison, New Jersey) for 1 week. The dose was then increased by 37.5–75 mg/week to a total of at most 225 mg, assuming minimal side effects, and then maintained for 4 weeks. At week 5, if there had been $< 20\%$ decrease in HRSD score, the dose was increased to 300 mg, assuming minimal side effects. The mean daily dose prescribed was 205 mg/day (range:128–264 mg/day, SD = 46.4).

Follow-up appointments were scheduled every 2 weeks after onset of treatment and with the study psychiatrist when clinically indicated. During these sessions, all patients completed the BDI, PANAS, and HRSD. The second scan was scheduled after patients entered remission, defined as an HRSD score of 10 or better for four continuous follow-up visits; if subjects did not meet remission criteria by week 13, the second scan was scheduled and a treatment plan developed with the study psychiatrist. The average time between scanning sessions for depressed patients was 21.8 weeks (range = 15.6–32 weeks); control subjects averaged 21.5 weeks (range = 17.8–26 weeks).

All study participants completed the BDI and PANAS and were interviewed with the HRSD before MRI scanning at each session. To assess treatment effects, paired *t* tests were run within the depressed group, contrasting scan 1 and scan 2 HRSD, BDI, and PANAS scores as well as two specific BDI items with specific relevance to these analyses: social functioning and sexual interest.

MRI Acquisition/Scanning Protocols

All subjects underwent a simulation session before the real MRI scan to familiarize them with the scanning environment, during which they were placed in a mock MRI scanner and shown pictures similar to those in the real functional runs. Pre- and post-treatment MRI scans followed an identical protocol. Subjects first completed clinical questionnaires and then were positioned in the MRI (GE Horizon 1.5 Tesla scanner, GE Medical Systems, Waukesha, Wisconsin). First, a high-resolution, T1-weighted volume was acquired for localization of functional activity (124 axial slices, voxel size = $1 \times 1 \times 1.1$–1.2 mm). Three runs of whole-brain, echo-planar (EPI) functional data were then collected, with 409 functional images per run in volumes of 23 7-mm coronal slices with 1-mm gap (repetition time = 3 sec, echo time = 50 msec, field-of-view = 240 mm, 64×64 matrix, voxel size $3.75 \times 3.75 \times 8$ mm). These acquisition parameters

Table 1. Clinical and Demographic Characteristics of Subjects

Characteristic	Depressed Subjects, n = 9 Mean (SD)	Control Subjects, n = 14 Mean (SD)	*t* Statistic (*df*)	*p*-Value
Mean Age	36.5 (9.9)	28.2 (7.9)	2.07 (21)	.051
Gender, No, % M	3 M, 6 F, 33.3% M	4 M, 10 F, 28.6% M	NA	NA
HRSD				
Scan 1	23.4 (7.2)	0.4 (0.6)	9.56 (8.1)	<0.001
Scan 2	7.3 (10.4)	0.4 (0.6)	2.00 (8.0)	.08
BDI				
Scan 1	24.3 (8.5)	0.1 (0.3)	8.56 (8.0)	<0.001
Scan 2	2.7 (3.4)	0.2 (0.6)	2.15 (8.3)	.063
PANAS (Positive)				
Scan 1	2.1 (0.8)	3.6 (0.7)	−4.69 (21)	<0.001
Scan 2	3.1 (0.8)	3.7 (0.7)	−1.92 (21)	.069

Diagnoses of Depressed Subjects

Age	Gender	Primary Diagnosis	Secondary Diagnosis	No. of Previous Depressive Episodes
31	F	MDD with neither melancholic nor atypical features	None	7
45	M	Dysthymia	None	0
32	F	MDD with atypical features	None	>10
19	F	MDD with neither melancholic nor atypical features	GAD	4
41	F	MDD with atypical features	GAD	5
33	M	Dysthymia	MDD with melancholic features	>10
35	F	MDD with neither melancholic nor atypical features	None	1
33	F	MDD with melancholic features	Binge Eating Disorder	6
54	M	MDD with atypical features	None	4
Subjects Included in Correlation Analyses Only				
31	F	Dysthymia	None	1
43	F	Dysthymia	None	1

For the HRSD and BDI *t* statistics, Levene's Test for Equality of Variance indicated that an unpooled estimate of variance was appropriate. A pooled estimate was used for mean age and PANAS *t* tests.

M, male; F, female; HRSD, Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; PANAS (Positive), Positive and Negative Affect Scale – General Version, Positive Subscale; MDD, major depressive disorder; GAD, generalized anxiety disorder.

were found to minimize signal dropout in orbitofrontal and amygdalar regions while retaining whole-brain coverage. Pictures were displayed via fiber-optic–driven stereoscopic goggles mounted inside the headcoil (Silent Vision system; Avotec, Jensen Beach, Florida); each picture was presented for 3 sec, followed by 16 sec of black screen to allow the hemodynamic response to return to baseline. No task was required of subjects during the picture presentations; to ensure subjects indeed viewed the pictures, functional data from primary visual cortex was inspected. All subjects showed robust activation except for the subject who reported sleep and was thus dropped from analyses.

Stimuli

Picture stimuli were selected from the IAPS (Lang et al 1997); a total of 189 pictures were presented at each fMRI session, 63 of each high-arousal positive, negative, and low-arousal neutral images. To present a set of images with maximal arousal and valence ratings across both genders, five positively rated pictures differed by gender. Images were presented, across the three runs, in a random order that was the same for both MRI scanning sessions. For the purpose of this report, only positively rated pictures are considered and were grouped by content three different ways.

Social Interaction Analysis. Images depicting two or more people interacting were compared with images containing only one person and with images of nonhuman but otherwise appetitive content (e.g., food and money). Erotica were excluded, as were two pictures depicting people far apart in the background of the image. Analyses compared the three picture groups: social interaction, one person (no interaction), and appetitive items.

Facial Stimuli Analysis. Images containing a human face were compared with pictures containing people with no visible faces and also to images containing non-social appetitive content. Erotica were again excluded. Analyses compared the three picture groups: faces, people but no visible faces, and appetitive items.

Erotic Scenes Analysis. Sexual images were compared with pictures containing at least one person but with no romantic or erotic content and to images containing general appetitive content. Analyses compared the three picture groups: erotica, people/non-erotic, and appetitive items.

Given these categorizations, the reaction to the target social stimulus (i.e., social interaction, faces, or erotica) was directly contrasted with non-target images also containing people and also to positively valenced nonhuman images in order to isolate regions that react uniquely to the desired attribute from those that respond to humans or positive scenes generally. The total number of pictures and standard IAPS ratings (Center for the Study of Emotion and Attention 1995) for each categorization are given in Table 2. Analyses of variance and post hoc paired *t* tests were run among the different groups on the published ratings for each categorization.

Table 2. Standard Ratings of the IAPS Pictures Selected for Each Comparison

	Women			Men		
	No. of Images	IAPS Rating: Valence	IAPS Rating: Arousal	No. of Images	IAPS Rating: Valence	IAPS Rating: Arousal
Positive (All Images)	63	7.3	6.0	63	7.2	6.0
Social Interaction	16	7.7[a]	6.3[b]	14	7.3[a]	6.2
No Interaction (Single Person)	18	7.0[a]	5.7[b]	18	6.9[a]	5.8
Appetitive Items	19	7.5[a]	5.7[b]	22	7.5[a]	5.7
Faces	19	7.4	5.9	16	7.0	5.7
People, No Faces Visible	17	7.1	6.0	18	7.0	6.1
Appetitive Items	19	7.5	5.7	22	7.5	5.7
Erotica	9	6.8[c]	6.1	9	7.2	6.3
People, Non-erotic	35	7.3[c]	5.9	35	7.0	5.9
Appetitive Items	19	7.5[c]	5.7	22	7.5	5.7

Ratings taken from Lang et al (1997).

IAPS, International Affective Picture System; HSD, Honestly Significant Differences.

[a]No Interaction rated significantly less pleasant. Women: $F(2,50) = 5.48$, $p = .007$; No Interaction versus App. Items and No Interaction versus Social Interaction Tukey HSD $p = .047$ and .009, respectively. Men: $F(2,51) = 4.13$, $p = .022$, No Interaction versus App. Items Tukey HSD $p = .031$.

[b]Social rated significantly more arousing. $F(2,50) = 3.39$, $p = .042$; Social Interaction versus One Person Tukey HSD $p = .054$.

[c]Erotica rated significantly less pleasant. $F(2,61) = 3.27$, $p = .045$; Erotica versus App. Items Tukey HSD $p = .034$.

Data Processing and Analysis

Data Reduction. Data processing and analysis were performed with the Analysis of Functional NeuroImages software suite, version 2.51e (Cox 1996). Data processing steps included: offline reconstruction with a 1-voxel full-width-at-half-maximum in-plane Hanning window, slice-dependent linear shift of the time series to correct for interleaved acquisition, 6-parameter rigid-body motion correction, 1/60 Hz highpass filtering to remove signal drift, and removal of ghost and skull artifacts. To determine an ideal hemodynamic response function (HRF) that best represented the unique response-shape of the individual subject, the time series for each stimulus type was averaged for each subject across a region of visual cortex. A least-squares fit of this subject-derived HRF was applied to the whole-brain time series data, with the motion parameters entered in as covariates, the resultant β-weights for each stimulus type converted to percentage signal change, and the maps transformed into standardized Talairach space (Talairach and Tournoux 1988).

Statistical Region-of-Interest Identification. These percentage signal change maps were entered into voxel-by-voxel repeated-measures analyses of variance (ANOVAs): stimulus group (target social, non-target, appetitive items) × participant group (de-

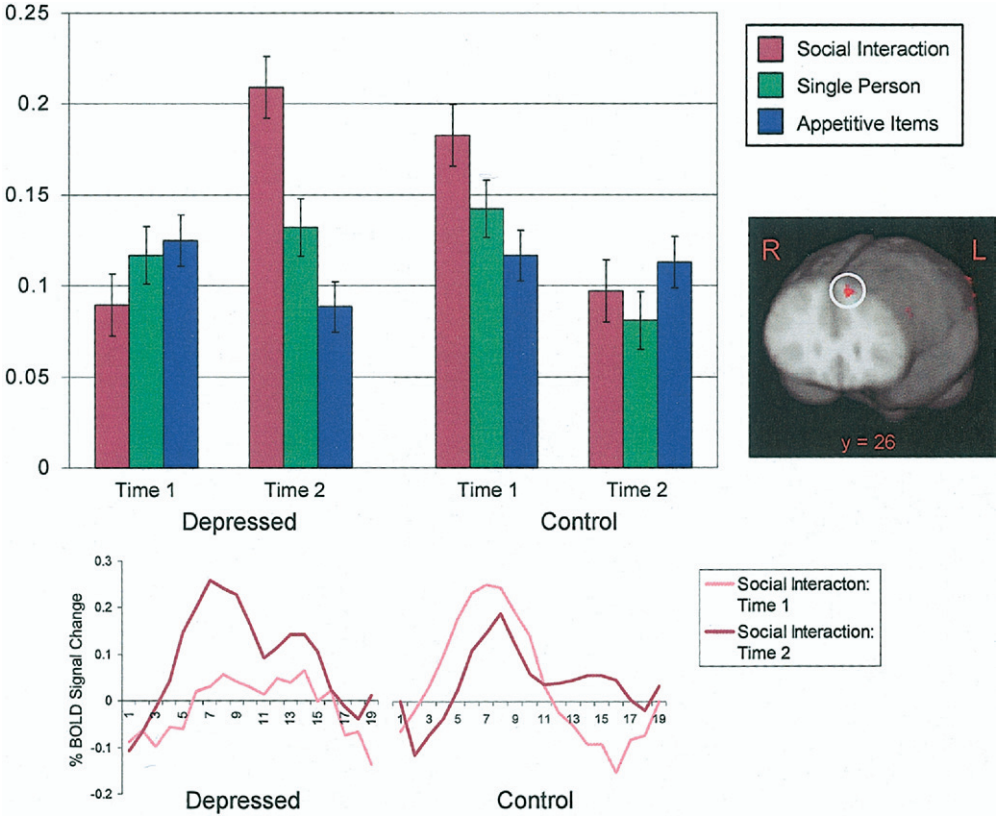

Figure 1. Pattern of activation from an example cluster in the social interaction analysis (left superior frontal gyrus, $y = 26$). Depressed subjects show a decreased response to stimuli depicting social interaction at the first scan versus control subjects and versus their own response at the second scan. Error bars show ± 1 SE. All clusters demonstrated this pattern of significance in post hoc testing and hemodynamic activation. Time series show the 19-sec raw average time series for the cluster in response to stimuli depicting social interaction, in depressed and control subjects at time 1 and time 2. BOLD, blood oxygenation-level dependent.

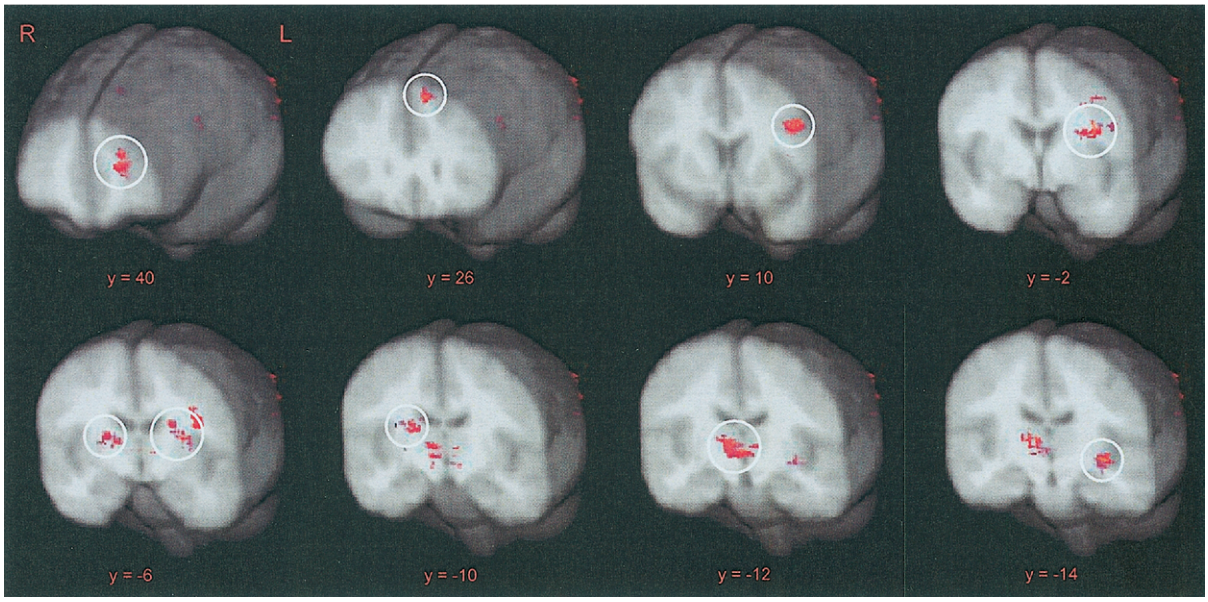

Figure 2. Frontal and subcortical clusters from the social interaction analysis. Y-coordinate for each slice is shown.

pressed, control) × scan (time 1, time 2). Independent ANOVAs were run for each of the aforementioned stimulus groupings: social interaction, faces, and erotic scenes. Monte Carlo simulations estimated the false-detection rate and corrected for multiple testing; given the spatial correlation of the input data, an individual voxel threshold of $p = .005$ and a minimum cluster size of 130 mm^3 achieved a corrected mapwise $p = .05$ (Xiong et al 1995). For clusters meeting these thresholds for interaction effects of interest, average percentage signal change values were extracted for each participant, scan, and stimulus group, and the values were entered into traditional simple effects analyses to determine the source of the interaction.

Covariate and Laterality Analyses. Because the control and depressed participants differed in average age, region-of-interest (ROI) values were entered into stimulus group (target social, non-target, appetitive items) participant group (depressed, con-

Table 3. Regions Showing a Significant Group × Scan × Stimulus Group Interaction for the Social Interaction Analysis

Location	L/R	BA	Talairach Coordinates			Cluster Volume	*F*	*p*-Value	Laterality Test
			x	*y*	*z*				
Frontal									
Medial frontal gyrus	L	10/46	−22	49	23	705	6.34	.0039	4.17 (0.031)
Superior frontal gyrus	L	6	−12	26	50	288	7.61	.0015	2.00 (0.162)
Inferior frontal gyrus	L	6/8	−44	10	29	386	5.58	.0071	4.532 (0.024)
	L	6	−39	−2	25	713	5.38	.0083	3.921 (0.037)
Subcortical									
Putamen	L		−27	−6	18	252	5.38	.0083	
	L		−32	−14	1	571	7.86	.0013	
	R		24	−8	7	174	5.27	.0091	
Caudate	R		19	−10	20	167	5.32	.0087	0.552 (0.58)
Ventolateral thalamic nucleus	R		10	−12	7	1535	5.23	.0094	
Hippocampus[a]	L		−31	−18	−7	113	5.92	.0054	0.837 (0.44)
Parahippocampal gyrus	L		−29	−36	−5	230	5.84	.0058	2.93 (0.077)
Temporal									
Middle temporal gyrus	R	37	61	−44	3	208	6.32	.0040	4.083 (0.033)
Superior temporal gyrus	L	22	−54	−47	22	287	6.08	.0048	1.476 (0.252)
Inferior temporal gyrus	R	37	42	−53	−8	617	6.59	.0032	3.792 (0.040)
Parietal									
Posterior cingulate gyrus	L	23	−6	−45	18	545	6.21	.0043	
Supramarginal gyrus	L	19	−48	−65	30	612	6.12	.0047	0.745 (0.488)

Laterality test refers to the *F*-statistic (*p* value in parentheses) for the hemisphere × patient group × scan × stimulus group analysis of variance and was not run for structures that crossed the midline or had homologous significant clusters in the opposite hemisphere.

All clusters meet $p < .05$ mapwise corrected and are listed in anterior-to-posterior order within each region.

L/R: left or right hemisphere; BA: Brodman's Area; Cluster volumes are in mm^3; *F*-statistic and corresponding *p* value based on (2,42) degrees of freedom.

[a]The hippocampal cluster itself is smaller than the cluster threshold of 130 mm^3, but represents the posterior end of the second left putamen cluster, and was manually separated and the 2 clusters analyzed separately.

trol) × scan (time 1, time 2) analyses of covariance (ANCOVAs), with age entered as a covariate to determine post hoc whether age differences accounted for a significant portion of the interaction. Laterality was tested for relevant ROIs by dilating respective clusters to twice their original size, then extracting the average percentage signal change for the same and homologous hemisphere. Dilation of the cluster is a more conservative test of laterality, because it allows for identification of a homologous region that is active but not precisely opposite the original cluster. The percentage signal change values for each hemisphere, stimulus group, and scan for each participant were then entered into four-way repeated-measures ANOVAs; ROIs were considered lateralized if this four-way interaction achieved $p < .05$ significance and a corresponding three-way ANOVA within the homologous region revealed that the stimulus group × participant group × scan interaction was not significant at $p = .05$. Within the depressed group, statistical ROIs were then tested for a relationship between pre- to post-treatment change in activation (time 2 - time 1) and average daily dose of Venlafaxine. Repeated-measures ANCOVAs tested for an interaction between average daily dose and T2-T1 activation to each stimulus type (target social, non-target, appetitive items). The source of the interaction was determined by inspection of the individual correlations between dose and change in activation to each stimulus type as described by Aiken and West (1991). To rule out correlations due to clinical change and not drug dose specifically, hierarchical regressions were run on activation, entering change in BDI or HRSD first and then testing the effect of average dose on variance in activation after the effect of BDI or HRSD was removed. Finally, analogous ANCOVAs tested for an interaction between stimulus type and change in clinical measures BDI and PANAS-Positive, adding in the two subjects not suitable for previous analyses addressing treatment response to add to the generalizability of the resultant relationships. The HRSD was used to screen patients for entry to the study and did not provide sufficient variability for correlational analyses.

Results

Self-Report and Clinical Change in Depressed Participants

Significant clinical improvement was seen in depressed patients from pre- to post-treatment, in self-report measures, and in evaluations made by the clinician (Table 1). A 68% reduction was seen in HRSD scores, and an 89% reduction was seen in the BDI [HRSD: Time 1 = 23.4, Time 2 = 7.3, $t(8) = 4.83$, $p = .0013$; BDI: Time 1 = 24.3, Time 2 = 2.7, $t(8) = 7.08$, $p = .0001$]. Of the nine

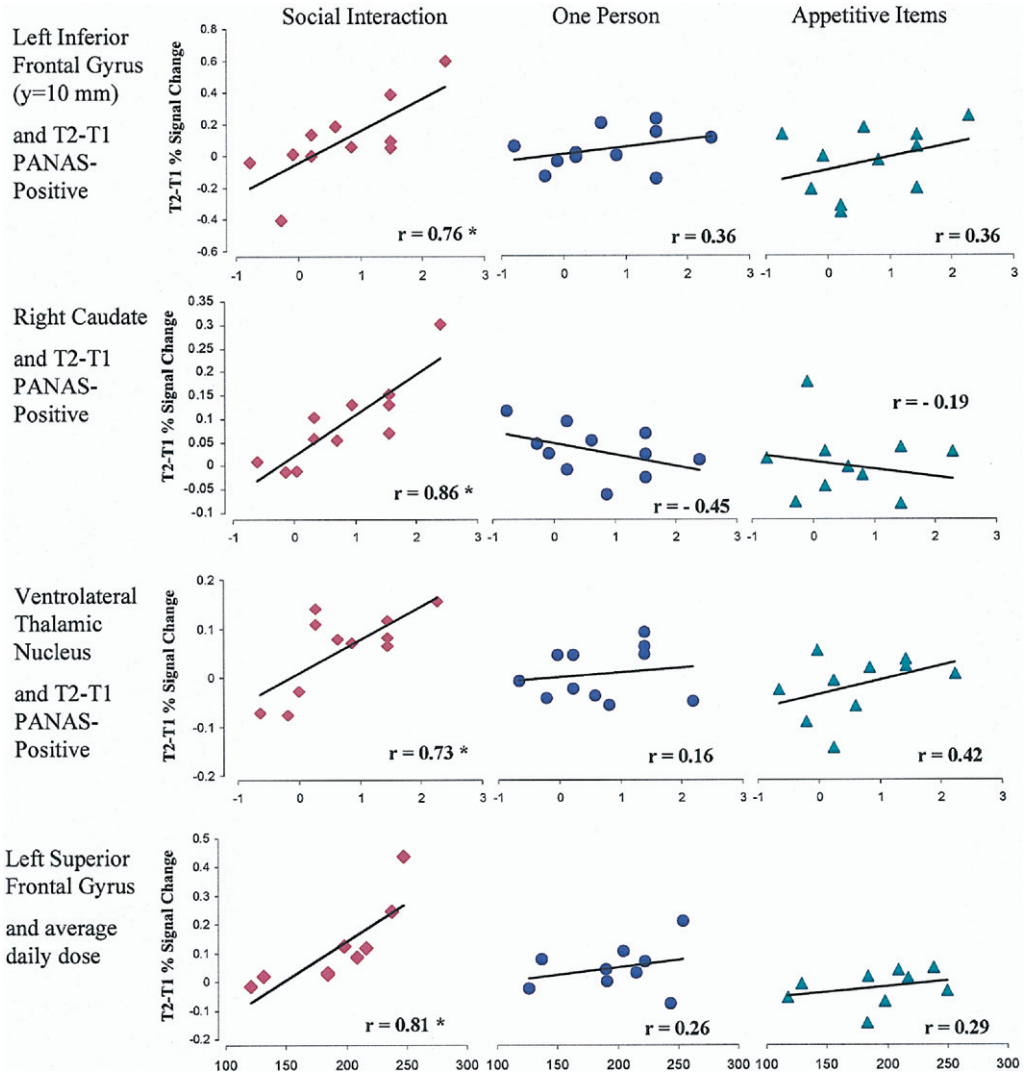

Figure 3. Clusters from the social interaction analysis demonstrating a significant interaction ($p < .05$) between T2-T1 change in activation and T2-T1 Positive and Negative Affect Schedule (PANAS)-Positive or average dose of Venlafaxine (mg/day). Significant individual Pearson correlations are indicated with an asterisk.

depressed subjects, six met our criteria for remission and all saw a decrease in HRSD and BDI scores. There was a significant increase in the positive affect subscale of the PANAS; subjects reported an average 44% increase in general positive affect [Time 1 = 2.1, Time 2 = 3.1, $t(8) = 3.30$, $p = .0109$]. Given the current interest in social and sexual functioning, of note are two specific items on the BDI concerning sexual interest and interest in other people. Patients reported a significant improvement, from the first scan to the post-treatment scan, in both of these items [sexual interest: Time 1 = 1.78, Time 2 = .0, $t(8) = 4.44$, $p = .0022$; social interest: Time 1 = 1.44, Time 2 = .11, $t(8) = 4.62$, $p = .0017$].

FMRI Results

IAPS Classification No. 1—Social Interaction. The social interaction analysis compared positively valenced images split into three groups: pictures depicting at least two people interacting, images showing just one person, and images containing only non-social appetitive items such as food and money. A stimulus group (social interaction, no social interaction, appetitive items) × patient group (depressed, control) × scan (time 1, time 2) repeated-measures ANOVA revealed a series of clusters with a significant three-way interaction. Simple effects analyses revealed the following significant effects: within the depressed group, activation to social interaction is significantly higher than to other images at time 2 only, and the activation to social interaction is greater at time 2 versus time 1; control subjects show the reversed pattern: at time 1, the response to social interaction is greater than to non-social images or appetitive items, whereas at time 2 the response to social interaction is smaller versus time 1. Comparing control subjects and depressed patients, control subjects show greater activation to social interaction at time 1 only, and the response to social interaction images in depressed subjects at time 2 is not significantly different from that in control subjects at time 1. All clusters showed this same pattern of significance (Figure 1). A number of left hemisphere regions were part of this network, specifically localized in inferior, medial, and superior frontal gyri, superior temporal gyrus, supramarginal gyrus, caudate, and hippocampus (Figure 2). Additional significant clusters were found in the right ventrolateral thalamic nucleus, bilateral putamen, right middle and inferior temporal gyri, and posterior cingulate (Table 3). Regions that did not cross the midline or have homologous, significant clusters were tested for laterality of activation. Clusters in the left medial and inferior frontal gyri and right middle and inferior temporal gyri were significantly more active than in the opposite hemisphere; the left superior frontal gyrus, right caudate, left hippocampus, left superior temporal gyrus, and left supramarginal gyrus were not. Age did not account for a significant amount of variance in the aforementioned interaction; the four-way age × patient group × stimulus group × scan was not significant for any cluster, nor did the addition of age alter the original interaction. A significant interaction between Time 2-Time 1 activation and improvement in PANAS-Positive was found in the left inferior frontal gyrus [$F(2,18) = 3.89$, $p = .039$], right caudate [$F(2,18) = 8.47$, $p = .003$], and thalamus[$F(2,18) = 5.58$, $p = .013$] (Figure 3). In all cases the interaction was due to a significant positive correlation between T2-T1 PANAS-Positive and T2-T1 activation to social interaction (respectively: $r = .76$, $p = .007$; $r = .86$, $p = .001$; and $r = .73$, $p = .01$). A significant interaction between Time 2-Time 1 activation and average daily dose was found in the left superior frontal gyrus [$F(2,14) = 3.85$, $p = .047$], owing to a significant correlation between average dose and T2-T1 activation to social interaction ($r = .81$, $p = .008$) (Figure 3). A hierarchical regression entering T2-T1 BDI or HRSD first and testing the effect of dose on residualized variance in T2-T1 activation to social interaction indicated a significant relationship between dose and change in activation even when

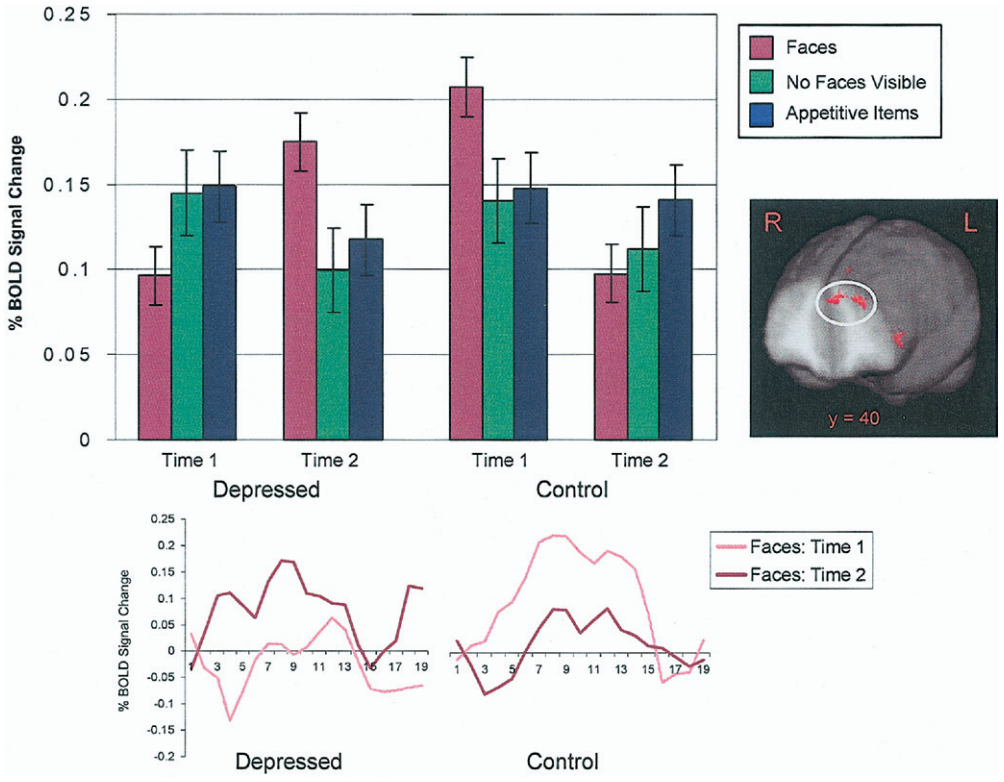

Figure 4. Pattern of activation and significant post hoc contrasts from an example cluster in the faces analysis (left medial frontal gyrus, $y = 40$). Depressed subjects respond less to images of human faces at the first scan in comparison with the second scan or control subjects. All clusters demonstrated this pattern of significance. Error bars show ± 1 SE. Time series show the 19-sec raw average time series for the cluster in response to images of faces, in depressed and control subjects at time 1 and time 2. BOLD, blood oxygenation-level dependent.

Table 4. Regions Showing a Significant Group × Scan × Stimulus Group Interaction for the Facial Stimuli Analysis

Location	L/R	BA	Talairach Coordinates			Cluster Volume	*F*	*p*-Value	Laterality Test
			x	*y*	*z*				
Frontal									
Medial frontal gyrus	L	8	−3	40	38	367	6.39	.0038	8.27 (0.002)
Inferior frontal gyrus	L	45	−48	35	7	215	6.51	.0034	6.45 (0.007)
Superior frontal gyrus	L	6	−7	24	44	311	7.01	.0024	10.63 (0.001)
Medial frontal gyrus	L	6	−46	0	30	287	6.26	.0042	4.006 (0.034)
Subcortical									
Insula	L		−36	18	8	224	6.70	.0030	
	R		39	5	−5	263	6.70	.0030	
Medial dorsal thalamic nucleus	R		8	−21	4	574	6.51	.0034	3.82 (0.039)
Occipital									
Fusiform gyrus	R	18	19	−74	−14	452	6.86	.0026	3.37 (0.055)

Laterality test refers to the *F*-statistic (*p*-value in parentheses) for the hemisphere × patient group × scan × stimulus group analysis of variance and was not run for structures that crossed the midline or had homologous significant clusters in the opposite hemisphere.

All clusters meet $p < .05$ mapwise corrected and are listed in anterior-to-posterior order within each region.

L/R, left or right hemisphere; BA, Brodman's Area; Cluster volumes are in mm^3; *F*-statistic and corresponding *p* value based on (2,42) degrees of freedom.

T1-T2 BDI [$F(1,6) = 8.47$, $p = .027$] or T1-T2 HRSD [$F(1,6) = 8.07$, $p = .030$] was accounted for.

IAPS Classification No. 2—Faces. The next classification of positive social stimuli compared the three groups: images containing human faces, images containing people but showing no faces, and positive images containing appetitive items but not people. A similar stimulus group (faces, no faces, appetitive items) × patient group (depressed, control) × scan (time 1, time 2) ANOVA was run. For clusters with a significant three-way interaction, simple-effects analyses demonstrated an analogous pattern to the social interaction analysis (Figure 4), that is, images of human faces produced greater activation than positive images without human faces or appetitive items for depressed participants after treatment and control participants at the first scan. This pattern was found in regions of the left inferior, medial, and superior frontal gyri, bilateral insulae, medial dorsal nucleus of the thalamus, and right fusiform gyrus (Table 4, Figure 5). The ANCOVAs for each cluster again demonstrated that the addition of age into the analysis did not alter the interaction. All clusters except the insula, which was originally activated bilaterally, were tested for laterality, and all were significantly lateralized except the right fusiform gyrus. No regions demonstrated a reliable interaction between clinical improvement or drug dose and change in activation over time.

IAPS Classification No. 3—Erotica. The last analysis split positively rated images into the three groups: sexual images, non-sexual stimuli containing at least one person, and appetitive items. Again, clusters achieving a significant stimulus group (erotic, non-erotic human, appetitive items) × patient group (depressed, control) × scan (time 1, time 2) interaction were found, showing the same general pattern of significance as

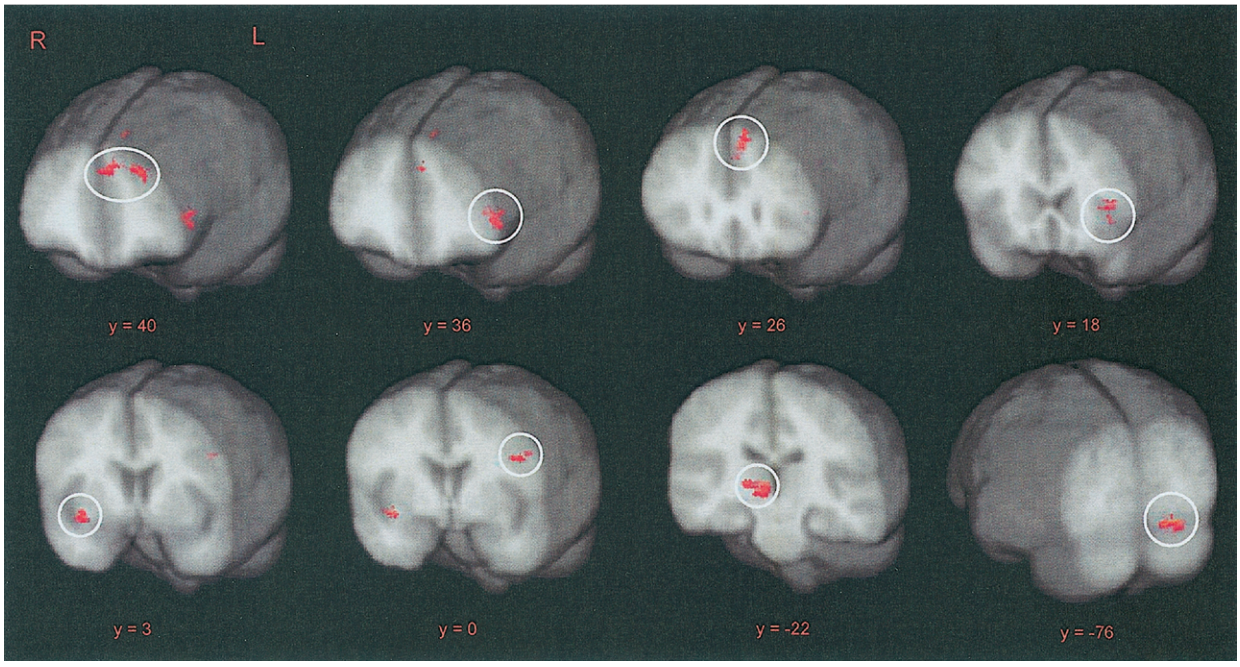

Figure 5. Significant clusters from the faces versus no faces versus appetitive items analysis. Y-coordinate for each slice is shown.

previous analyses: erotica garnered greater activation than non-erotic stimuli or appetitive items for depressed participants after treatment and control participants at the first scan (Figure 6). Significant regions included a series of prefrontal cortical zones, namely the left superior rostral gyrus, bilateral medial frontal gyri, and right inferior frontal gyrus, as well as the anterior cingulate, bilateral insula, left superior temporal gyrus, hypothalamus, left pre- and post-central gyri, bilateral supramarginal gyri, primary visual cortex, and middle and posterior sections of the cingulate gyrus (Figure 7, Table 5). The ANCOVAs with age as a factor did not show a significant interaction with age and preserved the original three-way interaction effect. Again, relevant clusters were tested for laterality of activation, with significant left-sided lateralization for the superior rostral gyrus, medial frontal gyrus, precentral gyrus, and postcentral gyrus. Significantly right-sided activations included the more posterior medial and inferior frontal gyri loci. A significant interaction between Time 2-Time 1 activation and improvement in PANAS-Positive was found in the anterior cingulate gyrus [$F(2,18) = 3.53$, $p = .050$], and a nonsignificant trend was found in the hypothalamus [$F(2,18) = 3.52$, $p = .06$] (Figure 8). Both regions showed a significant positive Pearson correlation between T2-T1 PANAS-Positive and T2-T1 activation to erotic images (respectively: $r = .61$, $p = .046$; $r = .68$, $p = .022$). A significant interaction between Time 2-Time 1 activation and T1-T2 BDI was found in the left insula [$F(2,18) = 4.53$, $p = .026$]; the Pearson correlation between T1-T2 BDI and T2-T1 activation to erotic images showed a nonsignificant trend ($r = .49$, $p = .13$) (Figure 8). No significant relationships were found with average daily dose of Venlafaxine.

Discussion

This investigation is unique in its exploration of different categories of positive affect in pre- and post-treatment depressed patients. The findings from this study indicate that depressed patients before treatment and in a current episode exhibit hyporeactivity to several classes of positive social stimuli compared with never-depressed control subjects in a variety of networks, including several regions of PFC, temporal and parietal cortex, insula, basal ganglia, and hippocampus. These structures were activated more in control subjects and remitted depressed patients compared with the depressed patients at scan 1. Many of these networks were significantly asymmetric, the most common pattern being greater activation to the positive social stimuli among the control subjects and remitted depressed

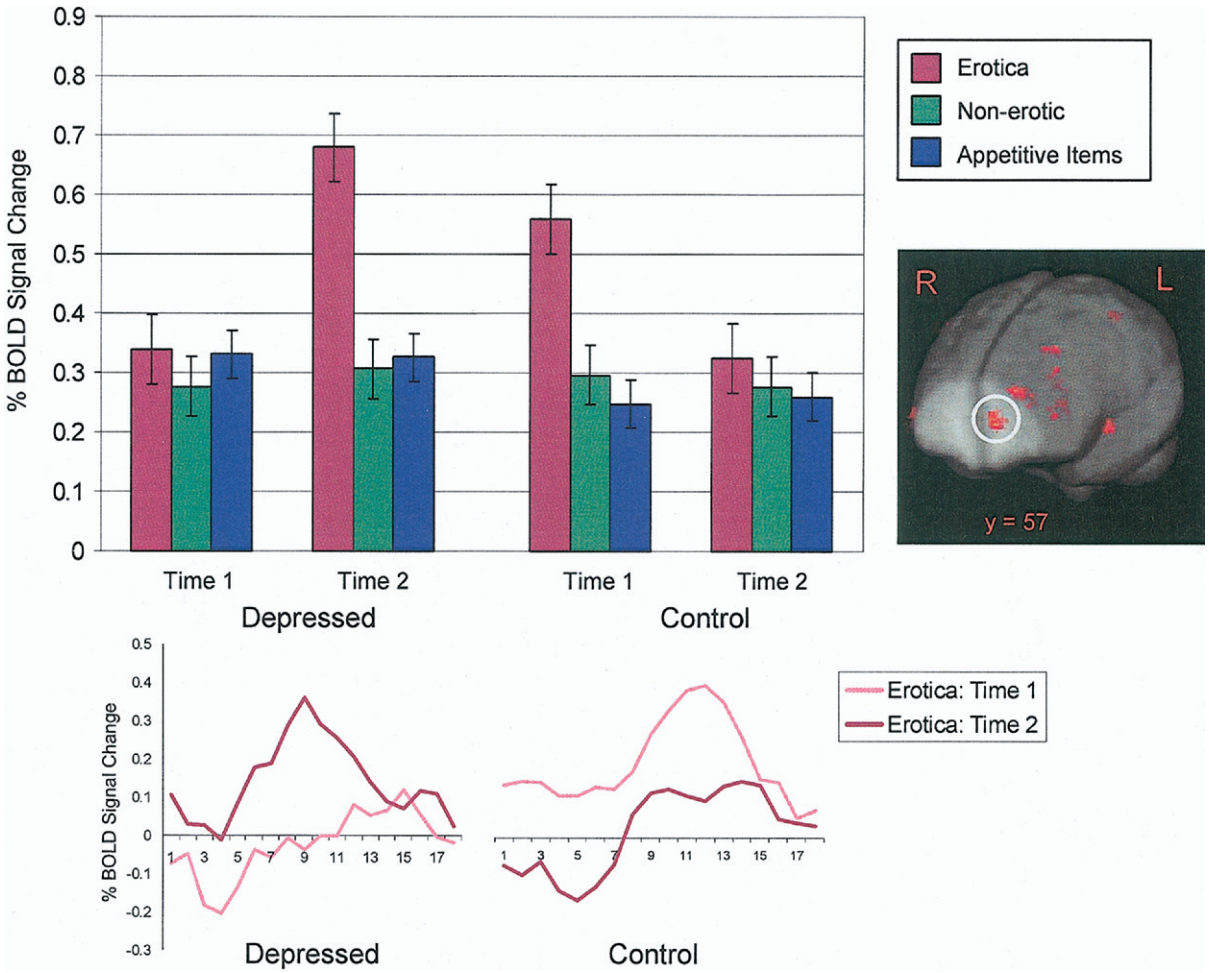

Figure 6. Pattern of activation and significant post hoc contrasts from an example cluster in the erotica analysis (left rostral superior frontal gyrus, y = 57). Depressed subjects show a decreased response to erotic images at the first scan versus the comparison control subjects and versus their own response at the second scan. Error bars show +/− 1 SE. All clusters demonstrated this pattern of significance. Time series show the 19-sec raw average time series for the cluster in response to erotic images, in depressed and control subjects at time 1 and time 2. BOLD, blood oxygenation-level dependent.

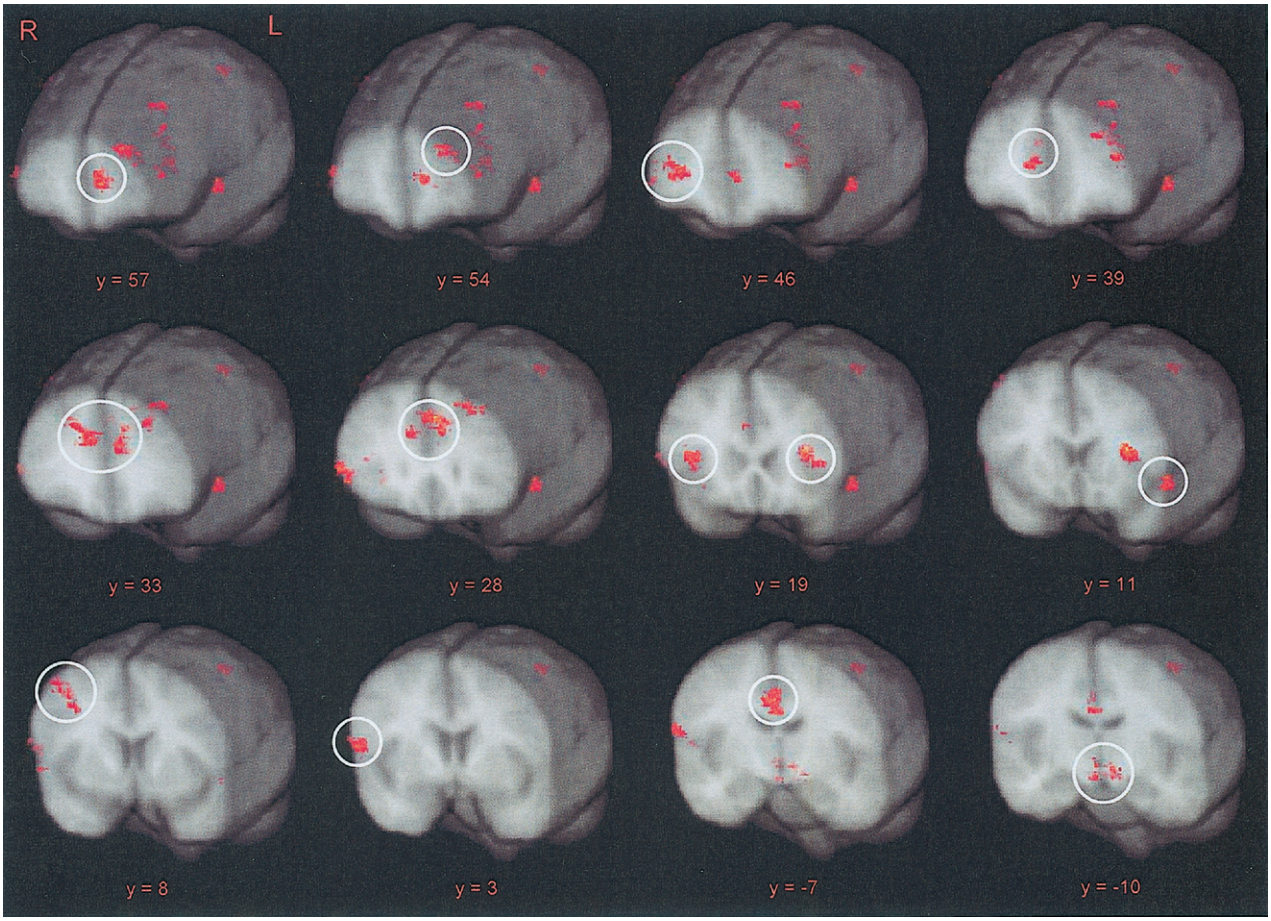

Figure 7. Selected frontal and subcortical clusters from the erotic stimuli analysis. Y-coordinate for each slice is shown.

patients in regions of left PFC. What is unique about the analyses presented in this study is the rigorous comparison of specific types of positive social stimuli with other non-social appetitive stimuli that were similar in valence and arousal. Thus, these effects underscore the specificity of our findings to specific features of positive social stimuli. The fact that the group differences we observed at scan 1 normalized after treatment with Venlafaxine and, moreover, responded as highly in post-treatment depression as in the first scan of control subjects suggests that these are state-related effects of the depressed state rather than characteristics of those vulnerable to depression. In control subjects, the response to positive social stimuli decreased from the first to the second scan, a result likely due to habituation, because the identical pictures were presented at both scans.

The pattern of left-lateralized prefrontal change that accompanied treatment and remission of symptoms in depressed patients is consistent with much of our prior data and theorizing (e.g., Davidson et al 2002). Regions of the left PFC have been implicated in approach-related behavior and goal-directed positive affect (Davidson 1992), and hypoactivation of this region has been implicated in depression (Davidson et al 2002; Pizzagalli et al 2005). In response to all three classes of positive stimuli, we observed hypoactivation in several regions of left PFC at Time 1 when the patients were scanned in episode. The deficit in left-lateralized PFC activation to social, facial, and erotic positive images was found to be significantly asymmetric with rigorous tests of the asymmetry of activation, a procedure that is rarely invoked although critical to establish the laterality of an imaging finding (Davidson and Irwin 1999). Moreover, in one region of left PFC, activation in response to social interaction correlated with average daily dose of Venlafaxine, even when variance accounted for by clinical improvement was statistically removed. Venlafaxine specifically has been associated with improvement in social functioning above clinical response (Gorenstein et al 2002; Lenderking et al 1999); here we find this same relationship as an improvement in neural response to images of social interaction in a brain region associated with approach-related affect. In a more inferior and posterior region of left PFC, a relationship was found in patients between improvement in the PANAS-Positive and increase in activation to social images, further reinforcing the connection between left PFC, positive affect, and approach-related behavior.

In addition to the prefrontal changes, a network of other regions also changed in response to treatment, including the caudate, putamen, and thalamus—all structures that have additionally been implicated in components of positive affect (Berridge and Robinson 2003). Furthermore, the caudate and thalamus showed a correlation between change in activation to social interaction and improvement in the PANAS-Positive, demonstrating a quantitative relationship between response to positive images and positive affect and providing a possible neural basis for the connection between social functioning and self-reported positive affect, as reported by Berry (Berry and Hansen 1996). Territories in parietal and temporal cortex also showed signifi-

Table 5. Regions Showing a Significant Group × Scan × Stimulus Group Interaction for the Erotic Stimuli Analysis

Location	L/R	BA	Talairach Coordinates			Cluster Volume	*F*	*p*-Value	Laterality Test
			x	*y*	*z*				
Frontal									
Superior rostral gyrus	L	10	−9	57	10	906	6.78	.0028	7.98 (0.003)
Medial frontal gyrus	L	10	−23	54	28	271	6.70	.0030	1.87 (0.18)
Inferior frontal gyrus	R	46	32	46	5	735	6.70	.0030	1.49 (0.25)
Anterior cingulate gyrus	R	32	9	39	12	197	6.91	.0025	
	R	24/32	10	28	26	727	7.01	.0024	
Medial frontal gyrus	L	8	−27	33	38	763	6.49	.0035	7.34 (0.004)
Anterior cingulate gyrus	L	24	−6	26	35	839	8.06	.0011	
Inferior frontal gyrus	R	45	50	28	3	316	7.55	.0016	7.77 (0.003)
Medial frontal gyrus	R	6	38	7	44	371	6.51	.0034	7.60 (0.004)
Inferior frontal gyrus	R	44/6	56	3	12	631	6.65	.0031	2.15 (0.15)
Cingulate gyrus	R	24	1	−7	39	610	7.08	.0022	
Precentral gyrus	L	4	−44	20	52	266	6.93	.0025	5.75 (0.011)
Subcortical									
Insula	R		35	20	9	596	6.94	.0025	
	L		−33	16	13	674	8.06	.0008	
Hypothalamus	L		−7	−9	−3	296	6.41	.0037	
Temporal									
Superior temporal gyrus	L	38	−53	11	−2	140	7.54	.0016	0.30 (0.75)
Parietal									
Postcentral gyrus	L	7	−27	−42	53	297	8.09	.0011	3.90 (0.037)
Supramarginal gyrus	L	40	−40	−46	36	463	6.94	.0025	
	R	40	37	−51	29	380	6.88	.0026	
Posterior cingulate gyrus	R	30	3	−49	23	468	6.21	.0043	
Occipital									
Primary visual cortex	R	18	1	−69	30	211	6.35	.0039	
Occipital gyrus	R	19	3	−73	−8	374	6.50	.0035	2.33 (0.12)

Laterality test refers to the *F*-statistic (*p*-value in parentheses) for the hemisphere × patient group × scan × stimulus group analysis of variance and was not run for structures that crossed the midline or had homologous significant clusters in the opposite hemisphere.

All clusters meet $p < .05$ mapwise corrected and are listed in anterior-to-posterior order within each region.

L/R, left or right hemisphere; BA, Brodman's Area; Cluster volumes are in mm^3; *F*-statistic and corresponding *p* value based on (2,42) degrees of freedom.

cant change and suggest that remission of depressive symptoms is associated with increased activation in perceptual processing regions as well.

The pattern of neural changes exhibited in response to human faces included both regions typically associated with face processing (e.g., fusiform) but also regions implicated in affective responding (PFC, insula). These findings might elucidate the deficit in responsivity to positive facial stimuli that has been observed in depression (Lawrence et al 2004; Sloan et al 2002; Surguladze et al 2004). The precise face-processing networks found by Lawrence (2004) were not replicated; our facial images were embedded in complex scenes and were thus quite different (although arguably more ecologically valid) than the usual facial stimuli presented. This distinction might account for the differences in circuitry identified in our study versus those that have studied processing of isolated, posed, emotional faces. Contrary to expectations, this investigation did not yield a significant treatment effect in the amygdala for the faces–versus–no faces analysis, which could also be a result of the complexity of the images used.

Like reduced interest toward social activity and cues, sexual dysfunction represents a reduction in previously rewarding behavior (Frohlich and Meston 2002). This sample of depressed participants experienced a significant improvement in their self-reported level of sexual dysfunction over the treatment period and, likewise with treatment, showed a differential neural reaction to erotic images versus pictures containing people without erotic content and to pictures containing non-social appetitive items. A large array of regions emerged that responded significantly more in control subjects versus pre-treatment depressed patients, replicating the finding of Yang (2004). Furthermore, at the second scan these same regions responded in the previously depressed subjects, whereas in control subjects they habituated somewhat. Three regions often implicated in the response to erotic images in normal populations, the anterior cingulate, insula, and hypothalamus (Arnow et al 2002; Beauregard et al 2001; Park et al 2001), showed a significant positive relationship between change in neural activation to erotic images and improvement in PANAS-Positive or BDI within depressed patients, suggesting that these regions respond to sexual stimuli in post-treatment depression as a function of more general clinical improvement.

Despite intriguing results, there are important limitations in this study. Of greatest importance is the small sample size, reflecting the difficulty in recruitment for such a time-intensive longitudinal study; this precluded analyses that co-vary variables such as gender, diagnosis, initial severity, and residual symptoms. The groups were also marginally different in age, although the addition of age as a covariate did not alter results. In minimizing the duration of the experiment and keeping the functional scans passive-viewing, no real-time affect or ratings were collected. It is thus unclear whether increased activation in patients is due to increased attentional resources or a true change in positive affect or some combination thereof. These are all potentially important moderating variables that require additional study.

In conclusion, the major finding from this study is that depressed patients in episode are hyporesponsive in prefrontal, cingulate, insula, and several subcortical regions in response to

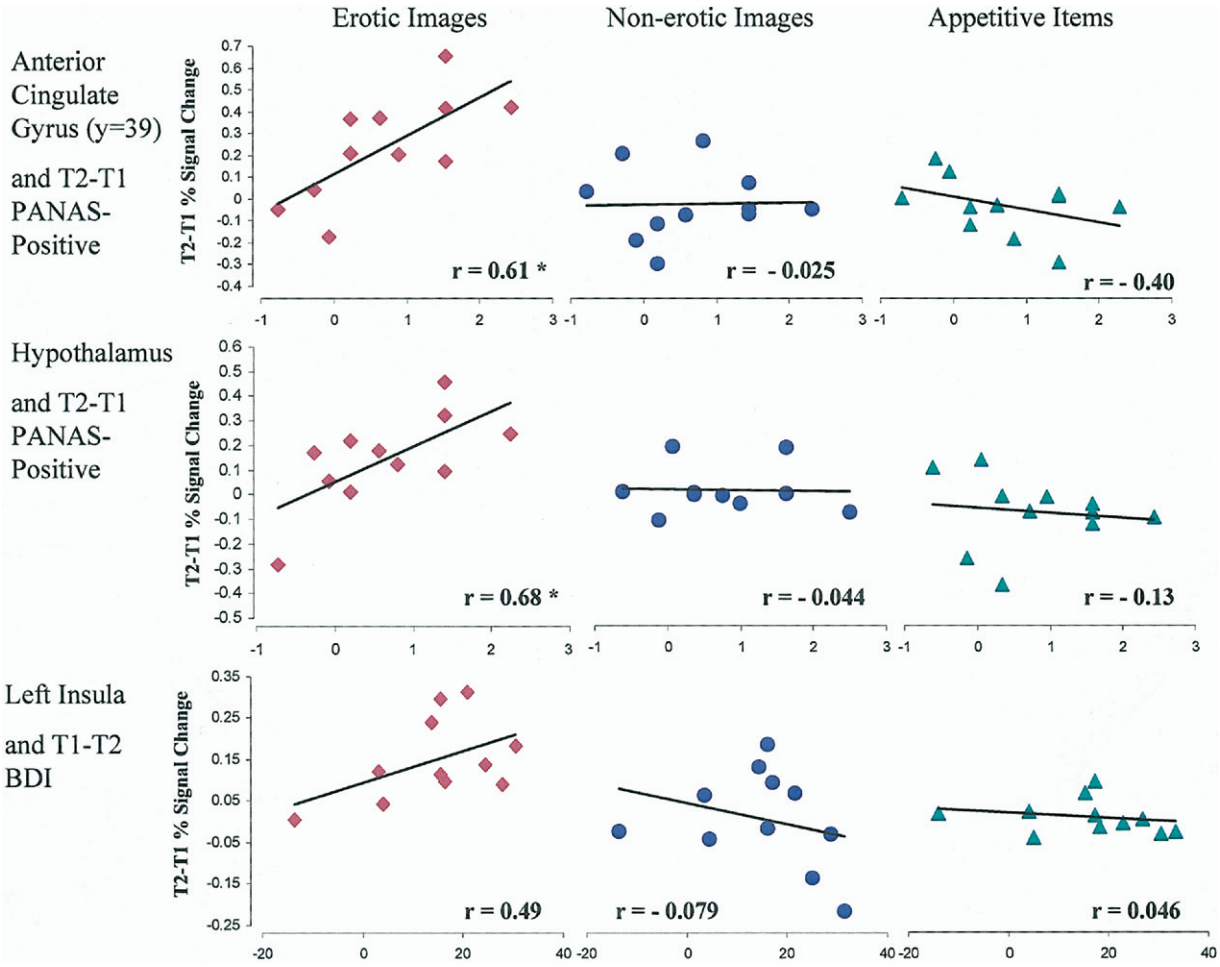

Figure 8. Clusters from the erotic stimuli analysis demonstrating a significant interaction ($p < .05$) between T2-T1 change in activation and T2-T1 Positive and Negative Affect Schedule (PANAS)-Positive or T1-T2 Beck Depression Inventory (BDI). Significant individual Pearson correlations are indicated with an asterisk; note the left insula shows a significant interaction across stimulus type, but the correlation with erotic images does not meet significance ($p = .13$).

social, facial, and erotic positive stimuli compared with other forms of positive stimuli without these characteristics. Such neural differences normalize after treatment; in several key regions this change correlates with clinical improvement or drug dose. These findings underscore the importance of circuitry underlying positive affect as a therapeutic target in antidepressant treatment.

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