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ORIGINAL ARTICLE

Attenuation of the Neural Response to Sad Faces in Major Depression by Antidepressant Treatment

A Prospective, Event-Related Functional Magnetic Resonance Imaging Study

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Background: Depression is associated with interpersonal difficulties related to abnormalities in affective facial processing.

Objectives: To map brain systems activated by sad facial affect processing in patients with depression and to identify brain functional correlates of antidepressant treatment and symptomatic response.

Design: Two groups underwent scanning twice using functional magnetic resonance imaging (fMRI) during an 8-week period. The event-related fMRI paradigm entailed incidental affect recognition of facial stimuli morphed to express discriminable intensities of sadness.

Setting: Participants were recruited by advertisement from the local population; depressed subjects were treated as outpatients.

Patients and Other Participants: We matched 19 medication-free, acutely symptomatic patients satisfying *DSM-IV* criteria for unipolar major depressive disorder by age, sex, and IQ with 19 healthy volunteers.

Intervention: After the baseline assessment, patients received fluoxetine hydrochloride, 20 mg/d, for 8 weeks.

Main Outcome Measures: Average activation (capacity) and differential response to variable affective intensity (dynamic range) were estimated in each fMRI time series. We used analysis of variance to identify brain regions that demonstrated a main effect of group (depressed vs healthy subjects) and a group × time interaction (attributable to antidepressant treatment). Change in brain activation associated with reduction of depressive symptoms in the patient group was identified by means of regression analysis. Permutation tests were used for inference.

Results: Over time, depressed subjects showed reduced capacity for activation in the left amygdala, ventral striatum, and frontoparietal cortex and a negatively correlated increase of dynamic range in the prefrontal cortex. Symptomatic improvement was associated with reduction of dynamic range in the pregenual cingulate cortex, ventral striatum, and cerebellum.

Conclusions: Antidepressant treatment reduces left limbic, subcortical, and neocortical capacity for activation in depressed subjects and increases the dynamic range of the left prefrontal cortex. Changes in anterior cingulate function associated with symptomatic improvement indicate that fMRI may be a useful surrogate marker of antidepressant treatment response.

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THE FIRST FUNCTIONAL NEUROIMAGING studies of depression measured resting cerebral blood flow using xenon Xe 133 inhalation during a resting state.[1] Since then, researchers have used single-photon emission tomography and positron emission tomography to correlate abnormalities in resting state activity with clinical symptoms[2-4] and to examine trait abnormalities and state changes after a variety of treatments.[5-10] More recent studies have examined specific cognitive[11-13] and affective[13-16] processes and, using functional magnetic resonance imaging (fMRI), have combined cognitive activation paradigms with antidepressant treatments.[17,18]

A fundamental neuropsychological impairment in depression is a mood-congruent processing bias such that ambiguous or positive events tend to be perceived as negative.[19-23] In particular, depressed patients show a diminished ability to discern affective, eg, happy and sad,

Table 1. Demographic and Clinical Characteristics of the Sample*

	Comparison Subjects (n = 19)	Depressed Subjects (n = 19)
Mean age, y	42.8 (6.7)	43.2 (8.8)
Sex, No. M/F	8/11	6/13
IQ		
Full	116.4 (18.8)	109.2 (14.5)
Verbal	111.6 (16.3)	105.6 (15.8)
Performance	117.5 (18.0)	106.9 (14.0)
HRSD score		
Week 0	0.3 (0.7)	21.1 (2.3)
Week 8	0.0 (0.0)	8.5 (4.8)

Abbreviation: HRSD, Hamilton Rating Scale for Depression.
*Unless otherwise indicated, data are expressed as mean (SD). There was no significant difference in age, sex, full IQ, or verbal or performance IQ between groups. The depressed patients had significantly greater HRSD scores than normal comparison subjects at baseline (independent-samples t test, $t_{33}=34.1$; $P<.001$) and showed significant reduction in symptom severity during the course of 8 weeks of treatment (paired t test, $t_{18}=10.6$; $P<.001$).

facial expressions.[24-27] This impairment contributes significantly to psychosocial and interpersonal difficulties commonly observed during an acute depressive episode,[24,25] and its persistence during remission of clinical symptoms is associated with a vulnerability for future episodes.[27,28]

The neurocognitive systems involved in identifying affective facial expressions have been well studied in healthy individuals.[29-31] Key nodes in this network[32] include the fusiform face area in the ventral occipitotemporal cortex, which shows a selective response for faces[29-31]; the superior temporal sulcus, which is responsive to mouth and eye movements involved in facial expressions[33]; and the amygdala (usually the left amygdala), which shows a selective response to emotional facial expressions[34] such as fear,[35-37] sadness,[38,39] anger,[40] and disgust.[41,42]

In depression, neural correlates of negative affective visual processing were investigated using fMRI in 2 recent studies. Davidson et al[18] observed activation by negative visual stimuli, greater in the left fusiform gyrus in acutely depressed patients compared with healthy volunteers, and in the amygdala bilaterally in both groups. With masked emotional faces, Sheline et al[17] found increased left amygdala activity in acutely depressed patients. These findings are consistent with studies of healthy individuals that found greater activation in the fusiform gyrus during explicit processing of sad relative to neutral facial expressions[43] and in the amygdala with sad faces.[38,39] Sheline et al[17] also found that increased activation of the left amygdala resolved after 8 weeks of antidepressant treatment with a selective serotonin reuptake inhibitor (sertraline hydrochloride, 100 mg/d).

This effect of antidepressant treatment on amygdala activation is complemented by the findings of other studies, which indicate reverse of brain functional abnormalities by antidepressant treatments.[5-8] In particular, the subgenual component of the anterior cingulate cortex shows increased activity with provocation of sadness in normal volunteers[44] and attenuation of initially enhanced basal metabolic activity in patients with depression after effective antidepressant treatment.[15] Higher resting metabolism at baseline in the anterior cingulate cortex has been replicably associated with a better symptomatic response to antidepressant treatment[6,18,45-48] (reviewed by Fu et al[9]).

In this study, we used fMRI to study brain systems activated specifically by incidental processing of sad facial affect in the following 2 parallel groups of participants who underwent imaging twice in 8 weeks: 19 depressive patients treated with fluoxetine hydrochloride after baseline assessment and 19 healthy volunteers. On the basis of 2 key previous fMRI studies,[17,18] we hypothesized that an abnormally enhanced amygdala response to sad facial affect processing in the patients at baseline would be attenuated by 8 weeks of antidepressant treatment. On the basis of previous data implicating the anterior cingulate cortex in recovery from depression,[6,18,45-48] we also predicted an association between symptomatic response and changes in activation of the pregenual anterior cingulate cortex.

There are methodological distinctions between this study and its immediate predecessors[17,18] in terms of design and analysis. We used an event-related fMRI paradigm and presented sad faces at 3 discriminable degrees of affective intensity. This allowed us to map the dynamic range of brain response to affective stimuli, as well as the overall capacity or mean difference between affective and baseline trials. Also, we used whole-brain analysis by nonparametric statistical methods to address the following 2 key questions: (1) do patients with depression differ from comparison subjects in activation of negative affect–processing systems? and (2) do patients with depression show antidepressant treatment–related changes in activation of such systems? These questions were tested by means of mixed-effects modeling of a balanced factorial design consisting of a larger number of participants (n = 19 in each group) than previously described in comparable studies.

METHODS

SUBJECTS

Twenty-one participants (15 women; age range, 29-58 years) meeting *DSM-IV* criteria for major depressive disorder[49] according to the Structured Clinical Interview for *DSM-IV* Axis I Disorders[50] were recruited through local newspaper advertisements. Inclusion criteria were an acute episode of major depressive disorder of the unipolar subtype[49] and a score of at least 18 on the 17-item Hamilton Rating Scale for Depression (HRSD).[51] Exclusion criteria were a history of neurological trauma resulting in loss of consciousness; current neurological disorder; current comorbid Axis I disorder, including bipolar disorder and anxiety disorder; or a history of substance abuse within 2 months of study participation. All patients were free of psychotropic medication for a minimum of 4 weeks at recruitment. Functional MRI data from 2 patients were subsequently excluded because of a neuroradiological abnormality (age-inappropriate ventriculomegaly and periventricular leukoaraiosis) in one case and failure to attend follow-up appointments in the other. Therefore, 19 patients constitute the sample reported herein (**Table 1**).

Nineteen healthy comparison subjects (11 women) with HRSD scores of less than 8 and no history of any psychiatric dis-

order, neurological disorder, or head injury resulting in a loss of consciousness were recruited by advertisement from the local community and matched to the patients in terms of age, sex, and IQ.

All participants provided written, informed consent. The project was approved by the Ethics Research Committee, Institute of Psychiatry, London, England.

EXPERIMENTAL DESIGN

We adopted a parallel-group, repeated-measures design in which all subjects underwent imaging in 4 separate sessions. The first session served to acquire a structural MRI data set for neuroradiological examination and to familiarize subjects with the MRI unit and imaging environment. Then, 3 separate 60- to 90-minute sessions were scheduled to acquire fMRI data sets at baseline or week 0, 2 weeks after baseline, and 8 weeks after baseline. During each session, subjects participated in a number of activation paradigms, but (for the sake of brevity and clarity) only data acquired at weeks 0 and 8 for the sad facial affect recognition task and the visual stimulation task will be presented herein. The sad facial affect recognition task was always the final cognitive task presented in each imaging session to prevent any possible residual effect of an induced negative mood state on performance of subsequent tasks.[52]

CLINICAL ASSESSMENT AND TREATMENT OF SUBJECTS WITH DEPRESSION

Patients received antidepressant treatment with oral fluoxetine hydrochloride, a selective serotonin reuptake inhibitor, 20 mg/d in a single dosage, starting as soon as possible (typically <1 day) after the baseline fMRI session and continuing until their completion of the study protocol 8 weeks later. For the duration of their participation in the study, the patients underwent a clinical assessment every 2 weeks with a psychiatrist (C.H.Y.F.), and depressive symptoms were serially rated using the HRSD.[51] Some patients reported minor adverse effects (nausea/vomiting or headache) soon after the initiation of treatment, but all patients recruited into the study were able to complete the protocol satisfactorily. Subjects were reimbursed for their travel expenses for each clinical session and received £20 (approximately US $35) for the initial MRI session and £30 (US $45) for each fMRI session.

IMPLICIT SAD FACIAL AFFECT RECOGNITION PARADIGM

Ten faces (5 male) from a standardized series of facial expressions of sadness[53] were morphed to represent low, medium, and high intensities of sadness (**Figure 1**). Further detail on prior behavioral validation of these stimuli is available as supplemental material at http://www-bmu.psychiatry.cam.ac.uk/DATA (accessed July 5, 2004). For the event-related fMRI paradigm, facial stimuli and baseline trials (crosshair fixation) were presented in random order. Each facial stimulus was presented twice at each intensity of sadness (60 faces in total), along with 12 baseline trials (crosshair visual fixation point), for a total of 72 trials. Each trial was presented for 3 seconds, and the intertrial interval was randomly varied according to a Poisson distribution with mean intertrial interval of 5 seconds. Total duration of the experiment was therefore 360 seconds. The same stimulus set was used at baseline and at 8 weeks.

For each facial trial, subjects were asked to indicate the sex of the face (male or female) by lateral movement of a joystick; no hand movement was required in response to a baseline trial. Latency (or reaction time) and accuracy of the sex decision during imaging were recorded for each trial. We used this strategy to elicit incidental or implicit affective processing

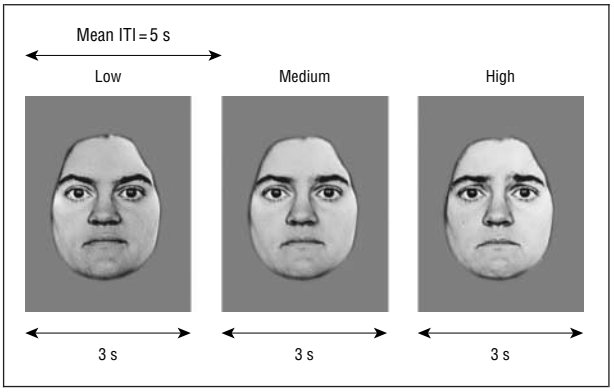

Figure 1. Sad facial stimuli used in event-related functional magnetic resonance imaging paradigm. Twenty standard faces were morphed by computer to express discriminable intensities of sadness (low, medium, and high). These 60 stimuli were presented in random order with 12 baseline trials of crosshair fixation. During facial trials, subjects indicated by a right-handed movement of a joystick whether the face was male or female. Each stimulus was shown for 3 seconds, and there was a randomly jittered interval between trials so that the mean intertrial interval (ITI) was 5 seconds.

because of previous data suggesting that the affective evaluation of facial expressions initially occurs at an implicit level,[54-56] before explicit judgments of the type or intensity of affect, which involve further cognitive processing.[57,58] The level of processing also appears to have a significant effect on neural activation, as a greater amygdalar signal has been observed with implicit compared with explicit affective facial expression tasks in most[40,54,56] but not all[55,59] studies.

VISUAL STIMULATION PARADIGM

Alternating checkerboard stimuli were visually presented in a graded block design with 32-second blocks of stimulation alternating periodically with 32-second blocks of darkness. Frequency of checkerboard alternation was varied between blocks as 2, 4, or 8 Hz. A total of 9 cycles of visual stimulation/darkness was presented in the course of an experiment lasting 9 minutes 36 seconds in total. The participants were instructed to lie quietly in the imaging unit with their eyes open throughout the experiment. Three patients were unable to tolerate the extra imaging time required for acquisition of these data at both time points; subsequent analysis of this experiment, therefore, uses only data from 16 patients and 16 matched comparison subjects.

fMRI DATA ACQUISITION

Gradient-echo single-shot echoplanar imaging was used to acquire T2-weighted image volumes on a neuro-optimized 1.5-T IGE LX System (General Electric, Milwaukee, Wis) at the Maudsley Hospital, South London, and Maudsley NHS Trust, London. We acquired 180 volumes for the sad facial affect task and 144 volumes for the visual auditory stimulation control task. For each volume, 16 noncontiguous axial planes parallel to the intercommissural plane were collected with the following parameters: repetition time, 2000 milliseconds; echo time, 40 milliseconds; section thickness, 7 mm; section skip, 0.7 mm; and in-plane resolution, 3×3 mm.To facilitate later coregistration of the fMRI data in standard space, we also acquired in the first fMRI session a 43-section, high-resolution inversion recovery echo planar image of the whole brain in the intercommissural plane with the following parameters: repetition time, 16000 milliseconds; echo time, 73 milliseconds; inversion time,180 milliseconds; and section thickness, 3 mm.

fMRI DATA ANALYSIS

Following correction of section-timing differences and head movement–related effects in the fMRI time series,[60] linear regression was used to estimate experimentally induced signal changes. Regression analysis modeled the following 2 mutually orthogonal aspects of brain activation at each voxel: (1) average facial-processing capacity, ie, the response elicited by the difference on average between baseline trials and all facial trials taken together; and (2) facial-processing dynamic range or load response, ie, the response elicited by the difference between facial trials presented at low, medium, and high intensities of sadness or levels of negative affective load. Before model fitting, each column of the regression matrix was convolved with a pair of Poisson kernels ($\lambda = 4$ or 8 seconds) to model locally variable hemodynamic response functions. Statistic maps or *t* maps representing each of these 2 standardized effects for each individual at each imaging session were registered in the standard space of Talairach and Tournoux[61] by means of an affine transformation to a template image.[62]

Factorial effects of interest were identified in a second stage of analysis; methodological detail and validation have been provided by Suckling and Bullmore.[63] A 2×2 analysis of variance (ANOVA) model was specified, including a main effect of time (weeks 0 vs 8), a main effect of group (depressed patients vs healthy comparison subjects), and a group × time interaction. This ANOVA model was fitted at all intracerebral voxels in standard space (n = 76 at each voxel), and a set of 3 F maps was estimated, 1 map for each factorial F statistic.

To identify brain regions associated with symptomatic response, the change in HRSD symptom score for each patient during 8 weeks of treatment was regressed on the change in the affective load response estimated during the same period by subtracting the *t* map for polynomial load response at week 0 from the corresponding map at week 8.

The statistical significance of these (ANOVA and regression) effects was decided by means of a cluster-level permutation test that involved applying a preliminary probability threshold ($P < .05$) to the corresponding voxel statistic maps and setting all subthreshold voxels to 0, thus creating a set of suprathreshold voxel clusters that were spatially contiguous in 3 dimensions. The sum of the suprathreshold voxel statistics, or cluster mass M, was tested by means of a permutation test[64] with clusterwise probability of a type I error of $P < .005$. At this size of test, and over the search volume of clusters tested (typically in the range 100-1000), we expect less than 1 false-positive cluster per map.

Further methodological details and software for nonparametric analysis of factorial designs can be accessed at http://www-bmu.psychiatry.cam.ac.uk/BAMM (accessed July 5, 2004).

RESULTS

Anatomical aspects of the fMRI results are summarized below and in **Figures 2**, **3**, and **4**. Further details, including tables of Talairach coordinates and whole-brain ANOVA maps, are available as supplemental material at http://www-bmu.psychiatry.cam.ac.uk/DATA.

MAIN EFFECTS OF GROUP

Do patients with depression differ from comparison subjects in activation of negative affect–processing systems?

There was increased capacity in the patients compared with the healthy comparison subjects in the following regions of the left brain: hippocampus extending to amygdala and parahippocampal gyrus, hypothalamus, ventral striatum (putamen/globus pallidus), insula, caudate nucleus, thalamus, dorsal cingulate gyrus, and inferior parietal cortex (Figure 2; **Table 2**).

There was increased dynamic range in the patients compared with the healthy comparison subjects in the bilateral cerebellum and anterior cingulate gyrus extending bilaterally to rostral prefrontal cortex (**Table 3**).

EFFECTS OF GROUP × TIME

Do patients with depression show antidepressant treatment–related changes in activation of negative affect–processing systems?

For capacity of activation, there was a significant interaction between group and time in the following regions of the left brain: the amygdala, ventral striatum (putamen/globus pallidus), insula, caudate nucleus, thalamus, anterior, dorsal and posterior cingulate cortex, precentral gyrus (approximate Brodmann area [BA] 4) extending to the lateral premotor cortex, postcentral gyrus, and inferior parietal lobule. There was also a significant interaction in the right ventral striatum and thalamus and right inferior parietal lobule (Figures 2 and 3; **Table 4**).

Post hoc analysis showed that amplitude of response to sad faces was significantly increased in patients compared with healthy volunteers at baseline (independent samples $t_{36} = -4.32$; $P < .001$) and reduced significantly in patients during the course of 8 weeks of treatment (repeated-samples $t_{18} = 4.75$; $P < .001$).

For dynamic range of activation, there was a significant interaction in the following left brain regions: the inferior and middle frontal gyri (BAs 44 and 9), postcentral gyrus, and putamen/globus pallidus (**Table 5**).

Post hoc analysis showed that the dynamic range or affective load response in these regions was reduced in patients compared with healthy comparison subjects at baseline (independent-samples $t_{36} = 3.17$; $P = .003$) and increased significantly in patients during the course of 8 weeks of antidepressant treatment (repeated-samples $t_{18} = -3.16$; $P = .005$).

CORRELATED FACTORIAL EFFECTS ON CAPACITY AND DYNAMIC RANGE OF AFFECTIVE PROCESSING

The effect of group on facial-processing capacity in limbic, subcortical, and neocortical regions was positively correlated with group effects on the dynamic range of response in anterior cingulate and prefrontal cortex ($r = 0.26$; n = 76; $P = .02$). Thus, depression tended to enhance both measures of activity in these systems.

There was also a strong negative correlation between the group × time effect on facial-processing capacity in limbic and subcortical regions and the group × time effect on dynamic range of response in frontal and striatal regions ($r = -0.36$; n = 76; $P = .001$) (Figure 3A). In other words, as limbic and subcortical activation by sad faces was reduced on average by antidepressant treatment, so the dynamic range of neocortical (frontal) regions was increased. This coupling between complementary treatment effects occurred because

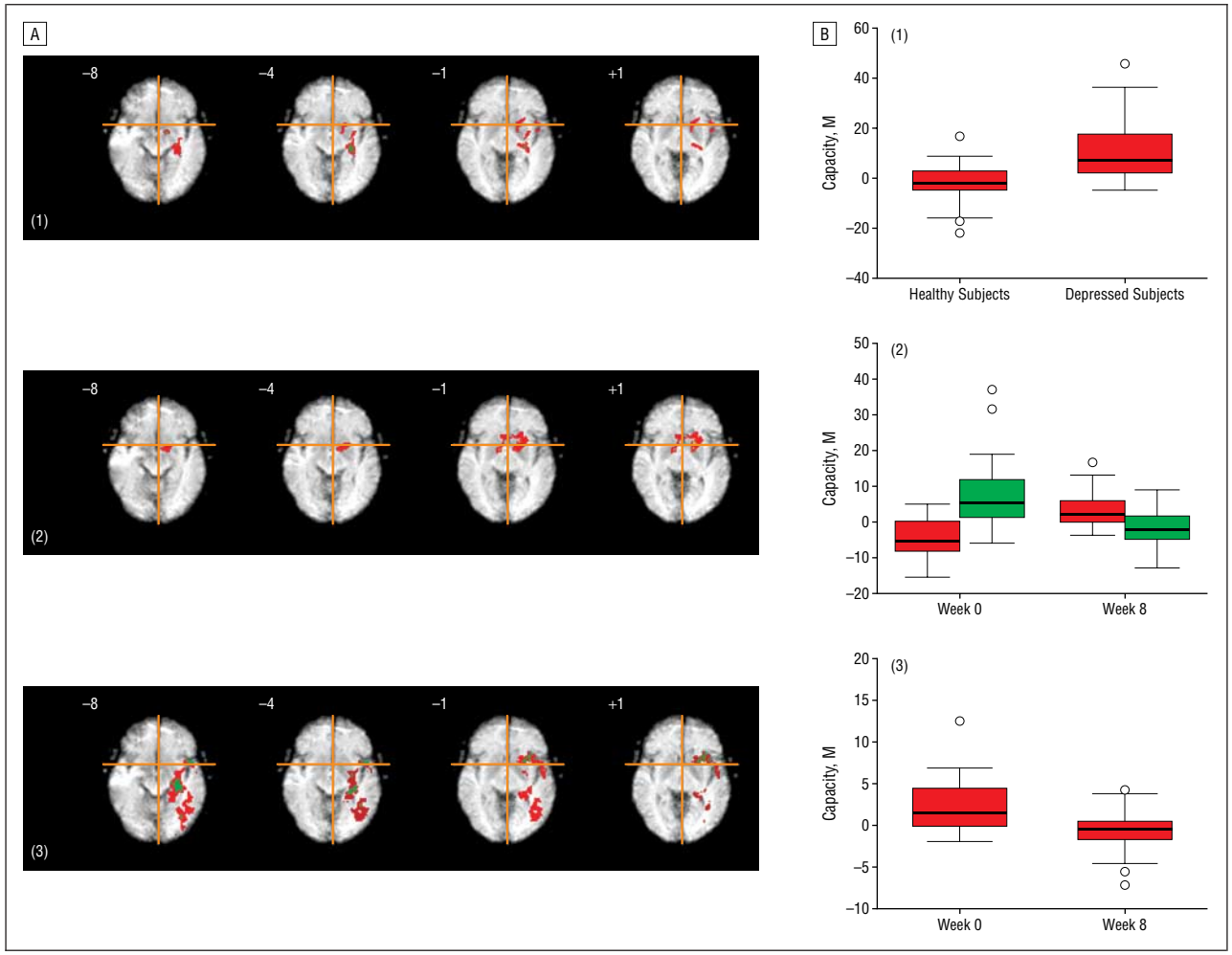

Figure 2. Limbic and subcortical effects of time, depression, and antidepressant treatment exposure on sad facial affect–processing capacity. A, Selected sections of analysis of variance F maps illustrate (1) main effects of group (healthy vs depressed subjects); (2) group × time interaction; and (3) main effect of time (weeks 0 vs 8). For each map, the left brain is depicted on the right side of the image; the crosshairs locate the origin of the x and y dimensions, and the numeral indicates location in the z dimension of Talairach space. B, Box plots illustrating that the main effect of group is enhanced sad facial affect–processing capacity (cluster mass statistics, M) in the left medial temporal, ventral striatal, and insular regions; (2) the group × time interaction shows enhanced capacity for activation (*t* statistics) in patients (green boxes) compared with healthy volunteers (red boxes) at baseline, which normalizes in the course of 8 weeks of antidepressant treatment; and (3) the main effect of time is the attenuated capacity of activation at 8 weeks compared with baseline. Boxes indicate interquartile range; horizontal lines, median; limit lines, range excluding outliers; and open circles, outliers (defined as points >1.5 times the interquartile range from the upper [or lower] limit of the interquartile range).

the prefrontal cortical load-response curve at baseline was flat at the high level of activation (response ceiling). As sad facial affect–processing capacity was generally reduced by antidepressant treatment exposure, prefrontal activation by low-intensity faces was selectively reduced, and the gradient of the load-response curve became correspondingly steeper.

RELATIONSHIPS BETWEEN SYMPTOMATIC RESPONSE AND DYNAMIC RANGE OF AFFECTIVE PROCESSING

There was a significant association between the changes in HRSD scores and the dynamic range of activation in the following brain regions: the bilateral (right>left) pregenual anterior cingulate cortex (BAs 24 and 32), right ventral striatum, and bilateral (left>right) cerebellum. This association was such that patients who showed the greatest reduction in depressive symptoms after treatment also tended to show the greatest reduction in dynamic range in the cingulate and cerebellar regions (Figure 4).

MAIN EFFECTS OF TIME ON AFFECTIVE-PROCESSING SYSTEMS

There was a reduction of capacity over time in the following regions of the left brain: the hippocampus extending to the amygdala and parahippocampal gyrus, ventral striatum extending dorsally to the head of the caudate nucleus, and ventral occipital cortex (fusiform and lingual gyri) extending anteriorly to the inferior temporal cortex (BA 37) and superiorly to the inferior parietal cortex (Figure 2; **Table 6**). There was a reduction of dynamic range over time in the cerebellum, ventral occipital cortex (fusiform and lingual gyri), posterior cingulate gyrus, thalamus, and left inferior parietal cortex (**Table 7**). There was a signifi-

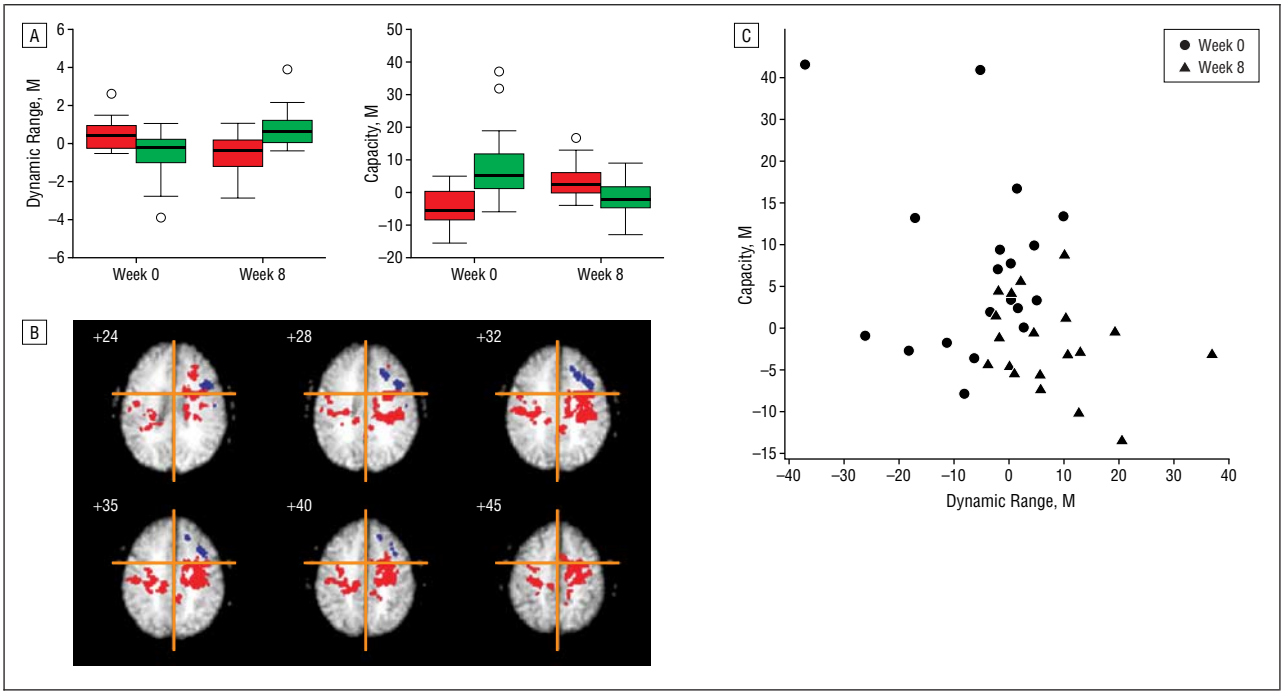

Figure 3. Neocortical effects of antidepressant treatment exposure on sad facial affect–processing capacity and dynamic range. A, Box plots demonstrate the individual cluster mass statistics (M) for dynamic range and overall capacity estimated in patients (green boxes) and comparison subjects (red boxes) at different time points, illustrating the group × time interaction. B, Selected sections of analysis of variance F maps depict the group × time effects on capacity and dynamic range of sad facial affect processing. Red voxels indicate neocortical (frontal and parietal) loci of significant group × time effect on sad facial affect–processing capacity; blue voxels, prefrontal loci of significant group × time interaction on dynamic range or affective load response. For each section, the left brain is depicted on the right side of the image; the crosshairs locate the origin of the x and y dimensions, and the numeral indicates location in the z dimension of Talairach space. C, Scatterplot of data from depressed subjects only showing the negative correlation between antidepressant exposure–related changes in facial affect–processing capacity and dynamic range. During the course of 8 weeks of treatment, depressed subjects tended to move from the top left to the bottom right quadrant of the plot as overall capacity for sad facial affect processing was reduced and the dynamic range of response in prefrontal cortex was increased.

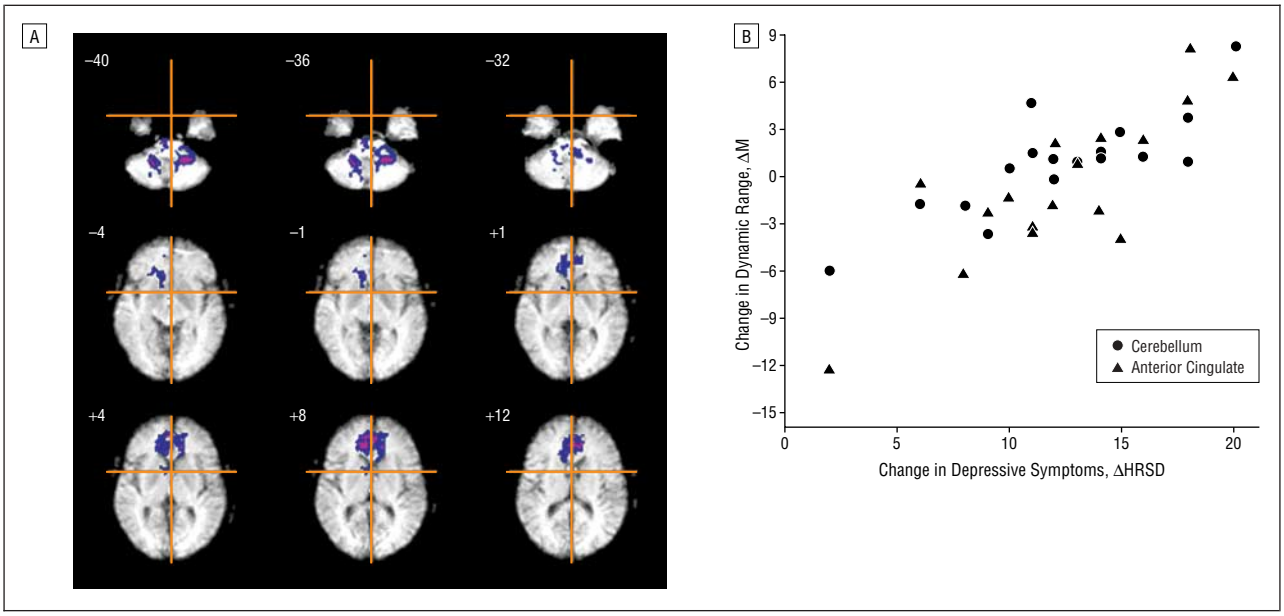

Figure 4. Brain correlates of symptomatic response. A, Selected sections of the map of brain regions (pregenual anterior cingulate cortex, ventral striatum, and cerebellum) where reduction in the dynamic range of sad facial affect processing is significantly associated with reduction in depressive symptoms. For each section, the left brain is depicted on the right side of the image; the crosshairs locate the origin of the x and y dimensions, and the numeral indicates location in the z dimension of Talairach space. B, Scatterplot of data from depressed subjects only illustrates that reduction in depressive symptoms over time (Hamilton Rating Scale for Depression [HRSD] score at baseline minus HRSD score at 8 weeks; Δ HRSD) is associated with reduction in dynamic range of sad facial affect processing (baseline minus 8 weeks; ΔM) in the cingulate and cerebellar regions of interest.

cant positive correlation between the effect of time on facial-processing capacity in the medial temporal and subcortical regions and the effect of time on affective load response in the cerebellum, thalamus, and ventral occipital and posterior cingulate cortices ($r = 0.34$; n = 76; $P = .003$).

Table 2. Anatomical Locations of Main Effect of Group (Depressed Patients vs Healthy Comparison Subjects) on Sad Facial Affect–Processing Capacity*

Cerebral Region	BA	Hemisphere	Cluster Size, Voxels	Talairach Coordinates, mm		
				x	y	z
Cingulate gyrus						
Anterior	33/24	L	54	–15	10	24
				–15	12	20
Middle	24/23	L	191	–14	–9	35
				–14	–43	24
	24	R	8	24	–14	35
Posterior	31	L	361	–25	–36	40
				–22	–57	24
	33/23	L	86	–18	–53	20
				–18	–53	16
Inferior parietal cortex	40	L	565	–40	–29	50
				–52	–32	28
	39	L	31	–45	–58	28
Superior temporal cortex	22	L	126	–54	–35	20
				–40	–4	–4
Inferior temporal cortex	37	L	45	–25	–35	–12
				–25	–38	–16
Precuneus	7		612	–25	–40	50
				–10	67	35
Premotor cortex	6	L	117	–28	2	20
				–44	0	8
Precentral gyrus	4	R	164	5	–25	50
				40	–20	45
Insula	NA	L	152	–29	2	16
				–41	2	–1
Amygdala	NA	L	26	–11	–10	–8
				–11	–10	–12
Parahippocampal gyrus	27/30	L	164	–22	–30	1
				–26	–32	–8
Putamen/globus pallidus	NA	L	206	–25	–1	12
				–15	–4	–4
Caudate	NA	L	149	–20	17	16
				–22	12	4
Thalamus	NA	L	142	–10	–14	16
				–19	–28	4

Abbreviations: BA, approximate Brodmann area; L, left; NA, not applicable; R, right.
*In all regions, there was significantly enhanced activation by patients compared with controls.

BEHAVIORAL DATA RECORDED DURING INCIDENTAL FACIAL AFFECT PROCESSING

There was a main effect of group on latency (ANOVA; $F_{1,34}=5.1$; $P=.03$); patients with depression were slower to respond on average over all trials in both sessions. There were no other significant effects of group or group × time on latency or accuracy of explicit sex recognition. There was a significant main effect of affective intensity or load (repeated-measures ANOVA; $F_{2,33}=3.9$; $P=.03$); participants in both groups were slower to respond to facial stimuli depicting more intense degrees of sadness (**Table 8**).

Table 3. Anatomical Locations of Main Effect of Group (Depressed Patients vs Healthy Comparison Subjects) on Sad Facial Affect–Processing Dynamic Range*

Cerebral Region	BA	Cluster Size, Voxels	Talairach Coordinates, mm		
			x	y	z
Anterior cingulate gyrus	32	741	–4	37	17
Cerebellum	NA	590	9	–66	–33
		162	–24	–59	–38

Abbreviations: See Table 2.
*In all regions, there was significantly enhanced load-response by patients compared with controls.

VISUAL STIMULATION CONTROL EXPERIMENT

A region of occipital (calcarine) cortex activated by photic stimulation on average across all checkerboard frequencies in the comparison subjects at baseline was defined as a region of interest. There were no significant effects of group ($F_{1,30}=0.11$; $P=.74$) or group × time ($F_{1,30}=1.05$; $P=.31$) on capacity or dynamic range of response to photic stimulation in this region of occipital cortex.

Table 4. Anatomical Locations of Group × Time Interaction (Indicative of Antidepressant Treatment Effects) on Sad Facial Affect–Processing Capacity*

Cerebral Region	BA	Hemisphere	Cluster Size, Voxels	Talairach Coordinates, mm		
				x	y	z
Cingulate gyrus						
Anterior	32	L	42	–25	26	24
Middle	23/24	L	336	–28	–14	35
				–16	–23	24
		R	22	26	–27	24
Posterior	23/31	L	415	–25	–12	40
				–29	–30	24
	29/31	R	248	27	–28	40
				17	–34	20
Medial premotor cortex	6	L	21	–7	5	45
Inferior parietal cortex	40	R	156	38	–23	32
				32	–42	24
Precuneus	7	L	32	–13	–38	45
				–6	–44	35
			19	9	–29	45
Precentral gyrus	4	L	601	–12	–31	65
				–24	–12	45
		R	217	14	–21	65
				29	–24	45
Postcentral gyrus	1, 2, 3	L	250	–33	–16	32
				–36	–15	24
	1, 2, 3	R	42	47	–13	24
				50	–18	20
Insula	NA	L	411	–27	3	20
				–37	–22	4
Amygdala	NA	L	45	–12	–5	–8
				–11	–7	–12
Putamen/globus pallidus	NA	L	154	–23	–12	12
				–17	4	4
	NA	R	172	–22	–10	16
				–37	–22	4
Caudate	NA	L	269	–26	12	16
				–20	13	8
			281	–9	4	1
				–9	4	–1
	NA	R	16	18	–14	20
Thalamus	NA	L	110	–29	–14	16
				–22	–11	8
	NA	R	70	18	–8	8

Abbreviations: See Table 2.
*In all regions, there was significantly enhanced activation by patients at week 0 that was significantly attenuated by week 8.

COMMENT

EFFECTS OF ANTIDEPRESSANT TREATMENT

Response to sad faces in the patients was abnormally exaggerated at baseline but significantly reduced during the course of treatment. The amygdala has been identified as a fundamental component of neuropsychological models of depression.[65,66] Of more direct relevance to our results, Sheline et al[17] reported greater activation of the left amygdala by fearful faces in acutely depressed patients that was reduced after 8 weeks of treatment with sertraline hydrochloride, 100 mg/d. Similarly, Davidson et al[18] reported greater bilateral amygdalar activation by aversive visual stimuli in patients with depression at baseline that was significantly reduced after 8 weeks of treatment with venlafaxine hydrochloride, 225 mg/d. The Talairach coordinates for left amygdalar treatment effects in their report,[18] namely x=–18 mm, y=–6 mm, z=–10 mm, are comparable to the following coordinates for a left amygdalar effect reported herein (Table 4): –12, –5, and –8 mm and –11, –7, and –12 mm. Thus, we conclude that there is now convergent evidence from 3 independent fMRI studies that antidepressant drugs generically act to reduce abnormal amygdalar responsivity to negatively affective faces in patients with depression.

We also found evidence in patients with depression for reduction of an initially exaggerated response to sad faces in the ventral striatum and thalamus. Decreased activity in the basal ganglia and thalamus of depressed patients after treatment has been noted in other studies with the serotonin reuptake inhibitors sertraline,[45] fluoxetine,[6] and paroxetine,[7,48] but some earlier studies did not report a treatment effect.[5,67-69] This may be a

Table 5. Anatomical Locations of Group × Time Interaction (Indicative of Antidepressant Treatment Effects) on Sad Facial Affect–Processing Dynamic Range*

Cerebral Region	BA	Hemisphere	Cluster Size, Voxels	Talairach Coordinates, mm		
				x	y	z
Anterior cingulate gyrus	24/32	L	56	–23	24	28
				–23	23	20
Medial prefrontal cortex	8	L	24	–17	32	40
				–17	31	35
Middle frontal gyrus	9	L	130	–35	13	40
				–31	19	32
Inferior frontal gyrus	44	L	243	–41	11	28
				–40	12	12
Superior temporal cortex	42	L	61	–50	–16	12
				–53	–20	8
Postcentral gyrus	43	L	32	–47	–17	20
Insula	NA	L	97	–39	–13	16
Putamen/globus pallidus	NA	L	214	–20	11	16
				–29	–7	4

Abbreviations: See Table 2.
*In all regions, there was significantly attenuated load-response by patients at week 0, which was significantly enhanced by week 8.

Table 6. Anatomical Locations of Main Effect of Time (Week 0 vs Week 8) on Sad Facial Affect–Processing Capacity*

Cerebral Region	BA	Hemisphere	Cluster Size, Voxels	Talairach Coordinates, mm		
				x	y	z
Inferior parietal cortex	39	L	12	–41	–52	24
Superior temporal cortex	22	L	20	–40	–53	20
	22	L	72	–44	1	–4
				–43	2	–8
Occipital gyrus	19	L	305	–32	–67	12
				–32	–70	4
Inferior temporal gyrus	37	L	16	–35	–59	1
	37	L	294	–30	–49	–12
Parahippocampal gyrus	36	L	123	–29	–35	–16
Fusiform gyrus	18	L	26	–29	–91	–16
Lingual gyrus	19	L	362	–38	–63	–1
				–37	–63	–8
Insula	NA	L	337	–34	17	12
				–35	3	–1
Parahippocampal gyrus	28/35	L	412	–20	–40	4
				–25	–30	–8
Putamen/globus pallidus	NA	L	127	–33	3	1
				–23	–11	–1
Caudate	NA	L	53	–18	15	12
				–18	14	8
		L	47	–27	–43	16
				–23	–40	8

Abbreviations: BA, approximate Brodmann area; fMRI, functional magnetic resonance imaging; L, left; NA, not applicable.
*Data are expressed as mean (SD) for low, medium, and high intensities of sad facial expressions. In all regions, there was significantly attenuated activation at week 8 compared with week 0.

diagnostically nonspecific effect of serotonin reuptake inhibitors, as similar reductions in caudate activity have been observed in obsessive-compulsive disorder after treatment with paroxetine and may be mediated by posttreatment reductions in serotonin transporter density in the striatum.[70]

These treatment effects on sad facial affect–processing capacity in limbic and subcortical regions were associated with comparable changes in frontal and parietal neocortical regions that have also been repeatedly implicated in the functional neuroanatomy of depression.[6] Mayberg et al[46] have proposed that experimental or pathological changes in mood state are associated with reciprocal changes in activity of limbic-subcortical systems and a frontoparietal attentional system,[71] ie, limbic-subcortical regions are more activated and frontoparietal circuits are less activated by sadness or lowering mood. Some of our results are consistent with this formulation. As overall capacity for activation by sad faces was decreased by treatment in limbic-subcortical systems,

Table 7. Anatomical Locations of Main Effect of Time (Week 0 vs Week 8) on Sad Facial Affect–Processing Dynamic Range*

Cerebral Region	BA	Hemisphere	Cluster Size, Voxels	Talairach Coordinates, mm		
				x	y	z
Posterior cingulate gyrus	23/31	L	56	–3	–30	28
				–8	–60	20
Inferior parietal cortex	40	L	24	–35	–69	40
				–35	–69	35
Inferior parietal cortex	39	L	45	–44	–64	28
Middle temporal cortex	39			–40	–69	16
Occipital cortex	18/19	L	702	–35	–71	32
				–13	–92	–4
Fusiform gyrus	18	L	47	–18	–88	16
Lingual gyrus	18/19	L	280	–11	–76	1
				–8	–88	–12
	18	R	221	4	–66	4
				10	–72	–8
Brainstem	NA	R	107	10	–20	–1
				5	–14	–8
Cerebellum	NA	L	107	–10	–71	–12
				–24	–71	–16
Putamen/globus pallidus	NA	R	39	15	–4	8
				15	–15	4
Thalamus	NA	R	241	4	–15	12
				13	–19	1

Abbreviations: See Table 2.
*In all regions, there was significantly attenuated load response at week 8 compared with week 0.

Table 8. Behavioral Performance Data Recorded During fMRI*

Intensity of Sad Expressions	Comparison Subjects (n = 19)		Depressed Subjects (n = 19)	
	Baseline	Week 8	Baseline	Week 8
Reaction time, s				
Low	1.01 (0.25)	0.91 (0.15)	1.12 (0.28)	1.04 (0.24)
Medium	1.00 (0.22)	0.90 (0.13)	1.10 (0.24)	1.05 (0.25)
High	1.02 (0.20)	0.92 (0.15)	1.16 (0.20)	1.07 (0.26)
Accuracy, %				
Low	80.0 (7.6)	82.4 (6.3)	79.5 (8.0)	76.3 (14.2)
Medium	87.9 (7.3)	83.6 (17.0)	84.7 (6.6)	79.7 (15.8)
High	85.8 (9.8)	86.3 (8.31)	85.8 (7.7)	81.8 (13.9)

Abbreviations: BA, approximate Brodmann area; fMRI, Functional magnetic resonance imaging; L, left; NA, not applicable.
*Data are expressed as mean (SD).

there was a reciprocal increase in differential activation of prefrontal cortex by the highest levels of affective load (most intensely sad faces). This was a significant (negative) correlation that can be explained in terms of antidepressant treatment exposure reducing prefrontal activation selectively at the lowest levels of affective load and therefore increasing the dynamic range available for differential activation by the highest levels of affective load.

When dynamic range was considered, the most interesting result was found in the subgenual anterior cingulate cortex. Increased dynamic range in acutely depressed, medication-free patients at baseline was associated with a greater symptom reduction at 8 weeks. Increased activity in the rostral pregenual anterior cingulate cortex has been observed in depressed patients who subsequently respond to treatments, including antidepressant drugs,[6,7,18,45,46,48] the mood-stabilizing agent carbamazepine,[47] or sleep deprivation.[72] Activation of the rostral anterior cingulate cortex has been elicited by a number of affectively challenging paradigms, including induction of anxiety,[73-75] sadness,[15,72,76] anger,[38] fear,[36] and affective "unpleasantness" associated with pain.[77] Mayberg et al[6] have suggested that the rostral anterior cingulate facilitates interactions between dorsal cortical and ventral paralimbic systems and has a significant role in the regulation of mood and cognitive and somatic functions. Our finding further implicates pregenual anterior cingulate function as a surrogate marker for symptomatic response in depression and adds to the growing body of support for baseline neural activity in this region as an important predictor of antidepressant treatment response.[78]

Two additional regions showed a relationship between change in the HRSD scores and dynamic range changes, ie, the ventral striatum and the cerebellum. The ventral striatum also showed increased activation capacity at baseline in depressed patients that decreased after treatment. The striatum is typically associated with reward[79] and has been elicited by most neuroimaging mood-induction studies of happiness, as reviewed by Phan et al.[80] However, the striatum has also been recruited in studies of disgust[80] and in response to aversive stimuli.[81,82] It has been proposed that engagement of the striatum occurs with the initiation of action in response to a relevant stimulus, rather than to reward itself.[79] The overall reduction in activation of the striatum in patients likely reflects an effect of fluoxetine treatment.[6]

The cerebellum is classically associated with motor control. However, its activation is frequently reported in neuroimaging studies of mood induction,[44,80] and degenerative cerebellar diseases are associated with mood dis-

orders and personality changes.[83] These data are compatible with our observation and suggest the cerebellum may be a major component of dysfunctional circuits in mood disorders.[84]

MAIN EFFECTS OF GROUP

Depressed patients tended to have greater capacity and greater dynamic range of response in sad facial affect–processing systems. In future studies, it will be interesting to test the hypothesis that recognition bias for negative stimuli is directly related to enhanced activation of limbic and subcortical brain regions in depressed subjects.

MAIN EFFECTS OF TIME

Attenuation of medial temporal and ventral occipital fMRI signals in response to repeated presentation of affectively valent stimuli has been previously reported.[35] Our results confirm that regions of the left medial temporal lobe, consisting of the hippocampus and parahippocampal gyrus, and of the left ventral occipital cortex are sensitive to repeated presentation of negative affect in faces for a longer period than previously investigated. The implicit nature of our affect-processing task precluded investigation of the subjective correlates of these broadly habituating effects, but it is interesting to speculate that longer-term physiological attenuation of response to affectively valent stimulation may be correlated with subjective blunting of response to repeated presentation of emotive material.

SOME METHODOLOGICAL ISSUES

We have used a comparison group of untreated, healthy volunteers to control for the major effects of task repetition over time. Consequently, we have interpreted the group × time interaction as indicative of antidepressant treatment. Although we regard this interpretation as tenable, such an interaction could also occur because of nontherapeutic, trait differences between the groups. The ideal control would have been a group of untreated (or placebo-treated) patients with depression. We considered this possibility initially, but ruled it out on ethical grounds because it would entail withholding an effective treatment from symptomatic patients for the duration of the study.

We chose to use an implicit or incidental facial affect–processing task in which participants were not explicitly instructed to pay attention to the sadness of stimuli. However, the behavioral data recorded during scanning indicates that the degree of sadness modified the participants' responses to the explicit sex discrimination task, suggesting that awareness of affect may have been conscious or at least able to interfere with simultaneous performance of a conscious task.

The biophysical basis for drug-related changes in fMRI signals has not been entirely elucidated yet. It is possible that some drug-related effects on blood oxygenation level–dependent (BOLD) signal may be a neuronally nonspecific consequence of altered cerebral hemodynamics.[85] Arguing against this interpretation of our data, we note first that we have described graded antidepressant treatment–related BOLD signal changes in anterior cingulate cortex that are associated with graded symptomatic recovery from depression in subjects receiving the same drug dose. Second, there was no significant antidepressant drug effect on the BOLD signal in primary visual cortex (as noted also in healthy volunteers[86]), indicating a degree of region and task specificity compatible with a neuronal mechanism for treatment-related signal change.

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