Altered Emotional Interference Processing in Affective and Cognitive-Control Brain Circuitry in Major Depression

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Background: Major depression is characterized by a negativity bias: an enhanced responsiveness to, and memory for, affectively negative stimuli. However, it is not yet clear whether this bias represents 1) impaired top-down cognitive control over affective responses, potentially linked to deficits in dorsolateral prefrontal cortex function; or 2) enhanced bottom-up responses to affectively laden stimuli that dysregulate cognitive control mechanisms, potentially linked to deficits in amygdala and anterior cingulate function.

Methods: We used an attentional interference task using emotional distracters to test for top-down versus bottom-up dysfunction in the interaction of cognitive-control circuitry and emotion-processing circuitry. A total of 27 patients with major depression and 24 control participants was tested. Event-related functional magnetic resonance imaging was carried out as participants directly attended to, or attempted to ignore, fear-related stimuli.

Results: Compared with control subjects, patients with depression showed an enhanced amygdala response to unattended fear-related stimuli (relative to unattended neutral). By contrast, control participants showed increased activity in right dorsolateral prefrontal cortex (Brodmann areas 46/9) when ignoring fear stimuli (relative to neutral), which the patients with depression did not show. In addition, the depressed participants failed to show evidence of error-related cognitive adjustments (increased activity in bilateral dorsolateral prefrontal cortex on posterror trials), but the control group did show them.

Conclusions: These results suggest multiple sources of dysregulation in emotional and cognitive control circuitry in depression, implicating both top-down and bottom-up dysfunction.

A primary feature of major depressive disorder (MDD) is a preoccupation with negative ideation. Many behavioral studies have documented an enhanced attention to, and memory for, negative emotional stimuli in depression (1–4). However, the source of this bias is unclear. One possibility is that this negativity bias reflects a top-down deficit in the control of attention (for example, a failure to suppress distracting emotional influences), potentially linked to deficits in brain regions supporting cognitive control such as dorsolateral prefrontal cortex (DLPFC) or dorsal anterior cingulate cortex (ACC) (5,6). Alternatively, this bias may reflect an enhanced bottom-up response to emotional stimuli that dysregulates cognitive control mechanisms potentially linked to deficits in amygdala and ventromedial prefrontal cortex function.

Recent research (7) has identified a network of emotion-processing areas that might drive bottom-up influences of emotion on cognitive functioning in depression. These include the amygdala and ventromedial prefrontal cortex (subgenual and pregenual cingulate). It has been proposed that these areas are involved in the perception, evaluation, and response to emotion-inducing stimuli and that they mediate the experience of fear, sadness, and other negative emotions (8–10). Both ventromedial areas and the amygdala are normally deactivated during cognitive processing and increase activation during the experience of fear, anxiety, or sadness (11). Individuals with major depression show hyperactivity of the amygdala when processing emotionally evocative information (12–14). In addition, resting-state overactivity in the subgenual cingulate is consistently found in major depression (9,15,16). If these emotion regions are hyper-responsive in major depression, they may bias individuals toward the processing of affectively negative stimuli.

A negativity bias might also reflect primary dysfunction in cognitive control areas of the brain. Some studies have shown that the DLPFC plays an important role in the top-down regulation of emotional processing (5,17). In addition, the dorsal ACC is thought to monitor for errors or processing conflicts that could disrupt performance and to recruit the DLPFC to reallocate attentional resources as needed (18–25). Importantly, some research suggests that MDD is characterized by hypoactivity in DLFPC and dorsal ACC (6,26), as well as in rostral cingulate (27).

As noted above, both excessive activity in the amygdala and reduced activity in the DLPFC have been documented in MDD patients (6,12,13). For example, MDD patients have long been found to show elevated activity in the amygdala during passive resting or during sleep (9,28). They have also shown excessive amygdala activity when exposed to stimuli with negative valence that are presented outside of conscious awareness (12). However, less is known about amygdala function in depression when patients are actively engaged in demanding cognitive processing. In such situations, processing in cognitive-control regions of the brain may suppress emotion-processing regions such as the amygdala, since these two circuits are known to work in opposition to each other (11). Recently, Siegle et al. (29) tested MDD patients on a demanding executive task and a separate

emotion-processing task. They found reduced activation in dorsolateral prefrontal cortex in the executive task, as well as increased amygdala activity in the emotional task. However, these findings do not address the issue of amygdala reactivity in MDD when there could be direct competition between cognitive and emotion circuitry. Such conflict can occur in cognitive tasks that include task-irrelevant emotional information, since these tasks should evoke activity in two networks that would normally suppress each other. Thus, the goal of the current study was to investigate the pattern of recruitment seen in these two networks when individuals with MDD were asked to either ignore or directly attend to emotionally negative stimuli. In doing so, we hoped to examine top-down and bottom-up influences when cognitive control was needed and when it was not.

To investigate these questions, we performed an event-related functional magnetic resonance imaging (fMRI) study in which MDD patients and control subjects performed a matching task while exposed to emotional interference (30,31). Stimuli were fearful or neutral faces or houses, and the face stimuli were either targets or distracters. Trials with fearful faces as distracters were considered to generate emotional interference and would therefore require cognitive control. In addition, we considered error trials as possible sources of emotional conflict. As a second test of cognitive control, we examined activation on trials following emotional conflict trials, since in healthy control subjects both error and conflict trials usually induced increased cognitive control on subsequent trials (32–34).

We made several predictions based on the two hypotheses about the source of negative bias in depression. If this bias reflects deficits in the top-down control of attention, then compared with healthy control subjects, individuals with MDD should show: 1) on correct trials, impaired activity in DLPFC and the dorsal ACC on all trials; 2) on correct trials, enhanced activity in the amygdala and ventromedial prefrontal cortex (PFC) when ignoring fearful faces (and possibly also when attending to them) because of inadequate suppression by cognitive control regions; 3) on error trials, enhanced activity in the amygdala and ventromedial PFC, because negative affect associated with errors could not be appropriately regulated by the DLPFC and the dorsal cingulate; 4) on error trials, reduced dorsal ACC responses; and 5) on trials following errors, reduced DLPFC response, reflecting impaired control recruitment.

If the negativity bias in MDD reflects abnormal bottom-up responses to emotional stimuli, we would predict: 1) on correct trials, enhanced activity in the amygdala and subgenual/pregenual ACC when ignoring fearful faces and possibly also when attending to them (similar to the top-down model but not because of reduced cognitive control); 2) in contrast to the top-down model, for correct trials, impaired DLPFC but only on trials in which the participant shows enhanced amygdala response to negative stimuli; 3) on error trials, possibly either reduced or enhanced dorsal ACC responses to errors, depending on whether MDD participants experience suppressed cognitive control or instead more readily detect conflict from emotionally evocative events; and 4) on posterror trials, impaired recruitment of DLPFC if the enhanced bottom-up processing of the negative stimuli impairs DLPFC recruitment.

Among all these predictions, we viewed the behavior of DLPFC as key to the distinction between top-down and bottom-up influences, since it might show dysfunction either on all trials (top-down) or only when the amygdala was overactive (bottom-up).

Methods and Materials

Participants

Participants were 27 patients with major depression (M/F: 10/17, mean age: 33.4 years [SD 8], mean education: 15 years [SD 2.2]), and 24 demographically matched control subjects (M/F: 12/12, mean age: 36.4 years [SD 9], mean education: 16 years [SD 2.3]). Inclusion criteria for depressed subjects were a current episode of unipolar recurrent major depression by DSM-IV criteria (35). All participants were free of psychotropic medication for a minimum of 4 weeks and were administered the 17-item Hamilton Rating Scale for Depression (HRSD) (36) to determine depression severity. Depressed participants were included with HRSD scores 18 or above (mean: 20, SD 2.3) and control participants were included with scores less than 8 (mean: .3, SD .6). Patients were excluded for any Axis I disorder (other than MDD) that preceded the onset of MDD. Additional exclusion criteria were acute physical illness, history of trauma resulting in loss of consciousness, current neurological disorder, and lifetime psychiatric disorder (other than major depression for the patients). All participants provided written informed consent in accordance with criteria established by the Washington University Human Subjects Committee. Seven additional participants (six patients, one control subject) completed behavioral testing but withdrew from the study before undergoing scanning. The two groups did not differ significantly in age or gender (proportion of female participants). However, the control participants showed a tendency to have greater educational attainment ($p = .07$). Participants were paid $25.00 per hour for their participation.

Procedure

The emotional interference experiment was carried out as part of a larger study that included two other scanning tasks (data for which will be reported separately). Scanning for the emotional interference task occurred on a second day and was always carried out before the other tasks. At the beginning of the session, participants were instructed on how to do the task, to emphasize speed and not worry about mistakes. They were given practice trials inside the scanner, using neutral faces only.

The emotion-interference task (30,31) presented participants with a pair of houses and a pair of faces in each trial, with one pair arranged horizontally and the other vertically around a central fixation cross (Figure 1). Participants were instructed to fixate on the cross and attend to the horizontal or vertical axis for a given block (four blocks total, counterbalanced order). Positioning of face-pairs or house-pairs was random. For each trial, the task was to tell whether the two items in the target axis were the same or different. Participants responded by button-press on a fiber optic response box interfaced with PsyScope (37). Each block contained 13 trials for each attention × emotion condition, pseudo-randomly interleaved throughout the block. Thus, trial types were attend-fearful-faces, attend-neutral-faces, ignore-fearful-faces (attend-houses), and ignore-neutral-faces (attend-houses). For each trial, the two faces displayed were either both neutral or both fearful, with the two expression types occurring equally often in a block. Each trial lasted 3200 milliseconds, starting with a fixation (displayed for 1000 milliseconds), after which the four stimuli appeared for 250 milliseconds. Participants had 2200 milliseconds to make a response. An intertrial interval (ITI) then took place that varied randomly between five possible lengths (2150, 4660, 7170, 9680, or 12,190 milliseconds).

fMRI Imaging and Analysis

Image Acquisition.   Functional MRI images were collected on a Siemens 3T Allegra MRI scanner (Siemens, Erlangen, Germany). The protocol included localizer images, a high-resolution structural image (magnetization prepared rapid gradient echo [MPRAGE]), and a series of functional images. The structural images were acquired with $1 \times 1 \times 1.25$ resolution using a sagittal three-dimensional (3-D) T1-weighted sequence with repetition time (TR) of 1.9 seconds, time-to-echo (TE) of 3.93 milliseconds, flip angle = 7 degrees, and inversion time (TI) of 1000 milliseconds. Functional images were collected using an asymmetric spin-echo echo-planar sequence with volume TR = 2.5 seconds (slice TR = 64.10 milliseconds), TE = 25 milliseconds, flip angle = 90 degrees, and field of view (FOV) of 205 cm. One acquisition consisted of 39 transverse slices, 3.2 mm thick (no gap), and with an in-plane resolution of 3.2×3.2 mm. Each functional run began with four volume images that were not analyzed, followed by 160 acquisitions for the paradigm.

Image Analysis.   The functional imaging data were preprocessed to correct for asynchronous slice acquisition and odd/even slice intensity differences caused by interleaving. Following this, the data were rigid body motion corrected (38,39). Atlas transformation (12 parameter affine) of the functional data was computed via the structural images. Our atlas representative target image conforms to the space of Talairach and Tournoux (40) as defined by Lancaster *et al.* (41). The final preprocessing step combined motion correction and atlas transformation in one resampling to 3 mm isotropic voxels. Before statistical analysis, the data were smoothed using a Gaussian filter with 9-mm full-width at half maximum.

For each participant, a general linear model (GLM) was used to estimate hemodynamic model-independent (42) event-related responses over 17.5 seconds (seven frames). Separate regressors were used to estimate response to each facial emotion (fear vs. neutral), attention condition (attend to house, attend to face), and trial type (same or different), yielding a total of eight response types. Preliminary analyses showed no effects attributable to the same versus different dimension. Accordingly, all present analyses were collapsed across this dimension, leaving four main conditions: 1) attend to fearful faces, 2) attend to neutral faces, 3) ignore fearful faces, and 4) ignore neutral faces. We computed a response magnitude estimate for each condition based on the cross-correlation of the time series with an assumed canonical hemodynamic response shape (43). All analyses reported below were based on analyses of variance (ANOVAs) and *t* tests conducted with subject as a random factor.

Regions of Interest Identification.   To test our hypotheses, we used a priori defined regions of interest (ROI), including left and right amygdala, subgenual cingulate, pregenual cingulate, more superior rostral cingulate, dorsal anterior cingulate, and right and left dorsolateral prefrontal cortex. The dorsolateral ROIs were defined on an atlas-representative image using the boundaries described by Rajkowska and Goldman-Rakic (44). The more superior area of rostral ACC (which we call superior rostral in this article) has been implicated in cognitive control, especially the detection of errors, while the more ventral pregenual region has been linked with more overtly emotional processes (45). To separate these two, we used a Talairach z-coordinate of 6 as a boundary. Voxels within the a priori defined ROIs showing effects of interest were identified using a two-stage process. To protect against type II error, we required voxels to show significant effects at $p < .025$ and to belong to clusters of at least nine contiguous voxels (46). We then conducted regional analyses based on the clusters identified in the previous step and (to protect against type I error) required region results to show post hoc effects at $p < .006$.

Exploratory Analyses.   To look for nonpredicted effects in regions outside the a priori ROIs, we conducted a whole-brain three-way ANOVA. The ANOVA results were thresholded to obtain a whole-brain false-positive rate of .05 ($p < .0001$ and a minimum cluster extent of 14 or more contiguous voxels). As this ANOVA revealed no significant group-related effects, the whole-brain analysis was not pursued further.

Results

Behavioral Results

To examine data, we used three-way repeated-measures analyses of variance with attention (attended or ignored faces), emotion (fearful or neutral), and group (control or depressed) as factors. No significant group-related effects were found for accuracy: main effect of group and all group interactions, $p > .2$. There was a main effect of group [$F(1,49) = 6.575$, $p = .013$, $\eta^2 = .118$] on response times, with depressed participants slower than control subjects. Behavioral results are summarized in Table 1. We also carried out posterror analyses to examine group differences in error-related performance adjustment (Table 1). Posterror trials were significantly faster than postcorrect trials [$F(1,49) = 6.110$, $p = .017$, $\eta^2 = .111$]. There was also a trend toward a significant interaction of trial type by group [$F(1,49) = 2.692$, $p = .107$, $\eta^2 = .052$], such that depressed patients showed a speedup of approximately 60 milliseconds for posterror versus postcorrect

Table 1. Performance in the Conflict Task and the Posterror Analysis (Means and SEs)

	Conflict Task							
	Percent Accuracy				Response Times			
Group	AF	AN	IF	IN	AF	AN	IF	IN
Control	.83 ± .02	.82 ± .02	.85 ± .02	.85 ± .02	805 ± 36	770 ± 32	754 ± 35	753 ± 38
Depressed	.80 ± .02	.80 ± .02	.81 ± .02	.83 ± .02	922 ± 34	888 ± 30	883 ± 33	871 ± 36

	Posterror Analysis			
	Percent Accuracy		Response Times	
Group	Postcorrect	Posterror	Postcorrect	Posterror
Control	.85 ± .02	.84 ± .02	777 ± 37	763 ± 29
Depressed	.80 ± .02	.81 ± .02	906 ± 35	839 ± 27

AF, attend-fear; AN, attend-neutral; IF, ignore-fear; IN, ignore-neutral.

trials, while control subjects showed almost no difference between the two trial types. Effects of group, trial type, or their interaction on accuracy were nonsignificant. Thus, no conventional posterror effects were found for this task but instead a speedup on posterror trials that was mostly driven by performance in the depressed group.

fMRI Results

In this section, we describe findings for all regions showing significant group-related effects. Significant effects that were not group-related are presented in Table 2 but not further discussed here.

Effects of Attended and Unattended Fear.   To test the hypothesis that depressed participants are more sensitive than control subjects to unattended fear-related stimuli, we looked at activation in the three-way interaction of attention × emotion × group. Only two regions showed significant three-way effects (Table 2, Figure 2, with details provided in Supplement 1). As predicted, we found that the MD patients ($p = .05$), but not the control subjects ($p > .1$), showed significantly increased activation in the left amygdala in the contrast of the ignore-fear versus ignore-neutral conditions. Further, this fear-related increase in the ignore condition was significantly larger for the MD patients than control subjects ($p < .05$). The opposite pattern was found for the attend condition. Control subjects ($p < .05$), but not MD patients ($p > .1$), showed significant activation of left amygdala in the contrast of attend-fear versus attend-neutral. In a direct

contrast of the two groups, this fear-related increase in the attend condition was significantly larger in control subjects than in MD patients ($p < .01$). We found a different pattern in the right DLPFC. The control subjects ($p < .01$), but not the MD patients ($p > .10$), showed a significant increase in right DLPFC activity for ignore-fear versus ignore-neutral, with this increase significantly greater in control subjects than MD patients ($p < .05$). Neither group showed a significant difference in right DLPFC activity for the attend-fear versus attend-neutral contrast ($p > .1$) nor were there significant group differences for this contrast.

Group Effects of Depression.   We found (Table 2, Figure 3) a significant main effect of group in subgenual cingulate (Brodmann area [BA] 25) and in a second region spanning from superior rostral cingulate (BA 24, at Talairach z-coordinate 28–30) up into the lower dorsal ACC (BA 32, z = 34). In the subgenual area, depressed patients showed significantly greater activation (less deactivation) than control subjects. In the superior rostral ACC region, activation was significantly lower for the depressed than control subjects.

Effects of Attending Versus Ignoring Faces.   One region showed a significant interaction between attention and group (Table 2, Figure 3). This was an area in pregenual cingulate that showed deactivations overall. The interaction with group reflected a crossover pattern such that the control group showed greater deactivation (lower activation) in pregenual ACC than the

Table 2. Group and Nongroup-Related Effects for the Conflict Task

Brain Region	BA	Voxels	Side	x	y	z	Z-Value	Effect
Attention × Emotion × Group								
Amygdala		28	L	−18	−5	−19	3.02	(See text)
Middle frontal gyrus	9/46	41	R	36	27	29	2.58	(See text)
Attention × Group								
Pregenual cingulate	24	33	L	−10	35	−2	2.73	Control: Attend > Ignore
								Depressed: Ignore > Attend
Emotion × Group								
Dorsal cingulate	32	57	R	4	17	41	2.52	Control: Neutral > Fear
								Depressed: Fear > Neutral
Main Effect of Group								
Subgenual cingulate	25	40	L	−6	13	−13	2.66	Depressed > Control
Superior-rostral cingulate	24	25		0	13	29	2.92	Control > Depressed
Dorsal cingulate	24	29		0	13	34	2.92	Control > Depressed
Effect of Attention								
Amygdala		67	L	−21	−6	−14	3.34	Attend > Ignore
Amygdala		59	R	21	−6	−12	4.08	Attend > Ignore
Middle frontal gyrus	9	128	R	40	20	27	3.75	Attend > Ignore
Superior frontal gyrus	9	65	R	18	40	30	2.7	Attend > Ignore
Inferior frontal gyrus	44	16	L	−38	16	26	2.61	Attend > Ignore
Middle frontal gyrus	9,8	36	L	−39	22	42	3.25	Ignore > Attend
Dorsal cingulate	32	141	R	3	21	38	3.13	Attend > Ignore
Dorsal cingulate	32	57	R	4	17	41	2.83	Attend > Ignore
Effects of Emotion								
Pregenual cingulate	32	83	L	−3	40	−3	3.24	Neutral > Fear
Superior-rostral cingulate	32	23	R	11	39	20	2.63	Neutral > Fear
Superior frontal gyrus	8	14	L	−20	30	43	3.01	Neutral > Fear
Middle/superior frontal gyrus	8	181	L	−24	24	44	3.6	Neutral > Fear
Middle frontal gyrus	8,32	202	R	20	28	41	3.79	Neutral > Fear
Attention × Emotion								
Superior-rostral cingulate	24	63	R	4	28	21	2.61	Attend: Neutral > Fear
								Ignore: Fear > Neutral

BA, Brodmann area; L, left; R, right.

Figure 1. Example of a stimulus screen used in the emotional conflict task.

depressed group in the ignore face conditions, while in the attend conditions, the control group showed less deactivation than the depressed group.

Error Analysis. We looked for group differences in the contrast of correct-trial processing versus error-trial processing. An area in the dorsal cingulate region (BA 32 and 24, Talairach z = 33–45) showed significantly increased activation for error versus correct trials, but this effect did not differ by group. Only one area, in the pregenual cingulate, showed an interaction between trial type and group. In this region, both groups showed deactivation for correct trials and both increased activation (lost deactivation) on errors; however, the depressed group increased activation more sharply than the control subjects.
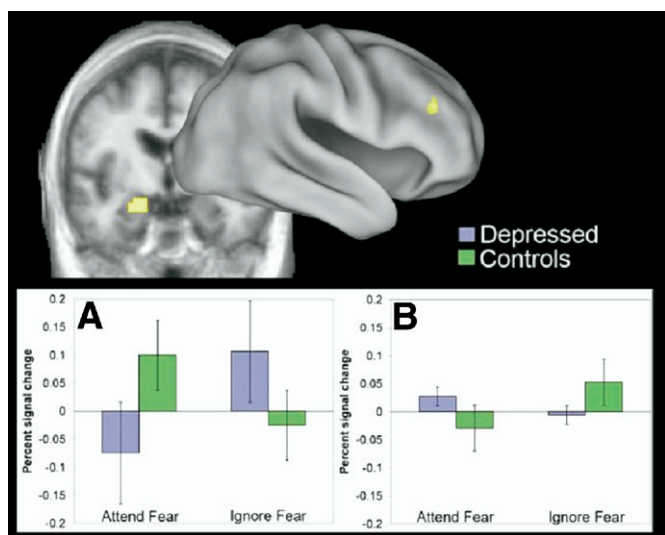

Figure 2. Areas in the left amygdala **(A)** and right dorsolateral prefrontal cortex **(B)** showing a significant three-way interaction of attention × emotion × group. Graphs show percent change in signal magnitude for the fear-minus-neutral contrast in each region. Error bars show standard errors of the mean.
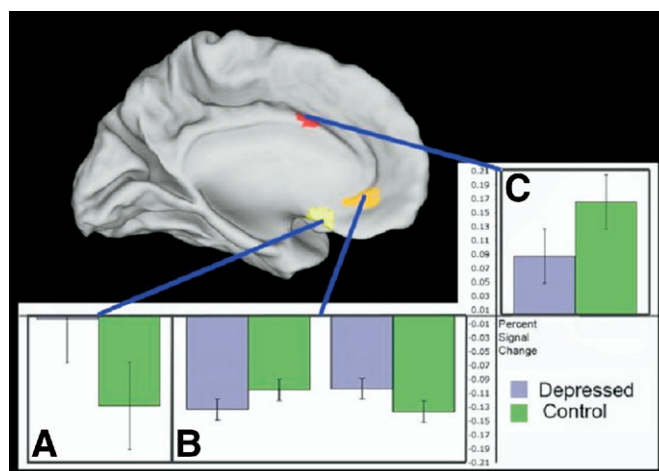
Figure 3. Areas in the subgenual anterior cingulate **(A)** and superior rostral anterior cingulate **(C)** show significant group differences across all conditions. Areas in pregenual cingulate **(B)** show significant differences in a group × attention interaction, where control subjects had less deactivation in the attend-to-faces conditions (left side of graph), while depressed patients had less deactivation in the ignore-faces conditions (right side of graph). Graphs show percent change in signal magnitude for each region. Error bars show standard errors of the mean.

Posterror Analysis. All correct trials were classified as either postcorrect (following a correct trial) or posterror (following an error trial). We found two areas in right and left DLPFC (Figure 4 and Table 3) that showed significant group differences in the contrast of postcorrect versus posterror processing. Both areas showed the same pattern. Both control subjects and depressed patients showed a modest deactivation on postcorrect trials. However, for the posterror trials, the control subjects increased activation significantly (into the positive range), consistent with recruiting stronger cognitive control, while the depressed patients did not change.

Correlational Analyses. We conducted correlational analyses to look for similarities in fear-related activation between right DLPFC and left amygdala. We found a significant negative correlation between activity in these regions only in the depressed patients and then only in the attend condition, not in the ignore condition, r = −.726, p = .000.
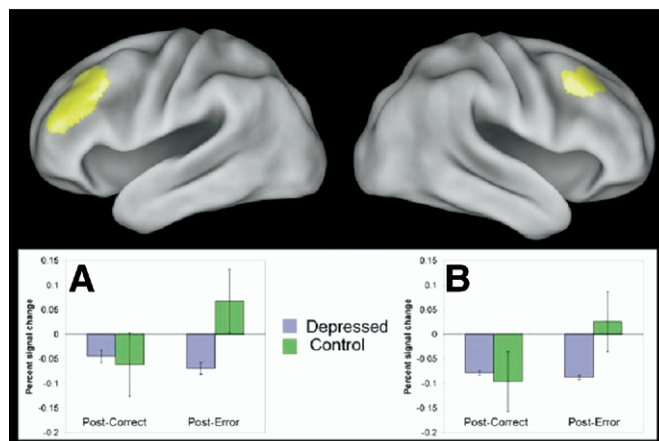
Figure 4. Areas in left **(A)** and right **(B)** dorsolateral prefrontal cortex showing significant group differences in the posterror effect: interaction of trial type (postcorrect versus posterror) × group. Graphs show percent change in signal magnitude for each region. Error bars show standard errors of the mean.

Table 3. Error-Related Effects in the Neuroimaging Data

Brain Region	BA	Voxels	Side	Talairach Coordinates			Z-Value	Effect
				x	y	z		
Correct Trials vs. Error Trials:								
Trial Type × Group								
Pregenual cingulate	11	36	L	−8	36	−12	2.55	Control: Error > Correct
								Depressed: Error >> Correct
Correct Trials vs. Error Trials:								
Effects of Trial Type								
Dorsal cingulate	32	287		0	13	40	5.29	Error > Correct
Pregenual cingulate	24	393	L	−1	36	6	3.85	Correct > Error
Middle frontal gyrus	9,46	126	R	42	26	26	3.95	Error > Correct
Middle frontal gyrus	9,46	77	L	−40	24	28	3.67	Error > Correct
Inferior frontal gyrus	10,46	39	L	−33	37	10	3.05	Correct > Error
Middle frontal gyrus	8,9	407	L	−23	35	38	4.69	Correct > Error
Middle/superior frontal gyrus	8	428	R	20	34	38	4.69	Correct > Error
Postcorrect vs. Posterror Trials:								
Trial Type × Group								
Middle frontal gyrus	9	198	L	−38	31	33	3.48	Depressed: Posterror = Postcorrect
								Control: Posterror > Postcorrect
Middle frontal gyrus	8,9	52	R	37	19	42	2.83	Depressed: Posterror = Postcorrect
								Control: Posterror > Postcorrect
Postcorrect vs. Posterror Trials:								
Effect of Trial Type								
Pregenual cingulate	24	32	L	−1	26	−2	2.56	Posterror > Postcorrect
Superior-rostral cingulate	9,32	27	L	−5	38	30	2.5	Posterror > Postcorrect
Inferior frontal gyrus	10,46	10	R	31	31	13	2.55	Posterror > Postcorrect
Middle/superior frontal gyrus	9	334	L	−26	34	32	3.65	Posterror > Postcorrect
Middle frontal gyrus	9	438	R	27	29	32	3.65	Posterror > Postcorrect

BA, Brodmann area; L, left; R, right.

Discussion

This study investigated the negativity bias in depression by asking whether this bias reflected dysfunction in emotional processing or impaired cognitive control over emotion. The main result was a depression-related difference in both the right DLPFC and the left amygdala in response to fearful versus neutral stimuli, an effect strongly modulated by attention. As predicted for the emotional interference condition, the depressed patients showed enhanced amygdala responses to unattended fear-related stimuli while the control subjects did not. In the same conditions, the control subjects recruited the DLPFC while the depressed patients did not. The enhanced amygdala activation seen in the depressed patients while ignoring fear-related stimuli, and their failure to recruit DLPFC, suggest that the patients did not suppress emotional responses to fear-related distracters. This is consistent with findings suggesting that depression entails a particular sensitivity to negative stimuli that are unattended (12). The control subjects' robust recruitment of right DLPFC in the same condition suggests that cognitive control recruitment is normally increased in response to fear distracters. Enhanced DLPFC activation could be recruited to increase selective attention, consistent with theories of attentional control. Increased attention to houses could decrease activation in face-processing areas, perhaps reducing amygdala activation as a side effect. Alternatively, DLPFC might be recruited to directly suppress amygdala activity, consistent with theories of emotion regulation (17,47,48).

An opposite and more surprising result was found in the attend condition. The control subjects showed no DLPFC increases in this condition (perhaps because emotional stimuli facilitated attention) but did increase amygdala activation. This suggests that amygdala responses are normally not suppressed when fear stimuli are directly attended. By contrast, the depressed patients in this condition showed a pattern normally associated with affect regulation: increased DLPFC and deactivated amygdala indicating they were able to suppress amygdala responses when directly attending to fear stimuli. A supposition of explicit affect regulation in the patients is supported by the strong negative correlation between fear-related activity in the right DLPFC and left amygdala in the attend conditions.

While amygdala and DLPFC activation depended on attention and facial expressions, other regions showed robust main effects. Subgenual ACC activation was increased in the depressed patients, consistent with findings of elevated resting metabolism in this region in depression (16). The dorsal and superior rostral cingulate showed decreased activation in the depressed patients. Given the proposed role for these areas in conflict monitoring and error processing (25,49,50), hypoactivity here could predispose depressed patients to deficits in cognitive control. Nevertheless, the dorsal cingulate increased activity on error trials in the depressed patients, consistent with unimpaired error processing. On the other hand, in the pregenual cingulate during error trials, the depressed patients failed to increase activation as the control subjects did. Moreover, on posterror trials, the patients failed to increase activity in DLPFC as the control subjects did, suggesting an impairment in recruiting posterror cognitive adjustments. This effect is consistent with their hypoactivity in superior rostral cingulate, a region where dysfunction has been linked to failure to increase cognitive control after committing errors (27).

A primary goal of this study was to determine whether abnormal function in depression implicates dysfunction in cognitive or emotional circuitry. In the depressed patients, reduced recruitment in right DLPFC was only present when the amygdala was overactive, arguing against a primary dysfunction in the DLPFC. This finding suggests that amygdala overactivity had a bottom-up influence on the level of activity in DLPFC. In contrast, the dorsal cingulate showed global deficits independent of emotional condition or level of amygdala activity. Importantly, however, the depressed participants showed enhanced amygdala activity only when ignoring fearful faces, not when attending to them. This suggests that when negative stimuli were explicitly attended, amygdala responsiveness could be modulated. Thus, depression may involve a primary dysfunction in both cognitive control and emotion areas, but the two systems may also modulate each other. Indeed, in the development of early depressive episodes, compromises in one system could lead to and lock in dysregulation of the other.

The design of this study involves some limitations. First, contrary to the findings of Vuilleumier *et al.* (30), our study did not find increased amygdala activation to unattended fear stimuli in control subjects. However, increased amygdala activation is not found consistently in healthy people (51) and may depend on other factors such as cognitive load (52) or anxiety level (31,53). Indeed, in the current study, removal of anxiety variance from our analyses (Supplement 1) weakened or abolished some of our depression effects, consistent with the known importance of anxiety in mood disorders. Future studies might pursue the separate contributions of anxiety and mood symptoms by comparing responses of depressed patients to sadness-related versus fear-related distracters.

Secondly, although the MDD participants were overall slower, we found no performance deficits related to task factors, despite clear evidence for functional brain changes that were specific to certain task conditions. Functional brain activity may have more sensitivity to detect cognitive or emotional processing changes in MDD than purely behavioral measures. In addition, we found no posterror slowing, even in the control subjects. This may have been an artifact of the rapid intertrial intervals used, which may have prevented participants from being able to slow down after errors. We believe that the nonsignificant tendency of the patients to speed up after errors is consistent with their failure to increase DLFPC activation in posterror trials. However, given the lack of performance effects, our brain activation findings, while suggesting a basis for the negativity bias in depression, must be interpreted with caution.

Conclusions

Depressed subjects exhibited a bottom-up impairment in emotional processing, as summarized above. In addition, depressed patients showed impaired top-down cognitive control over affective interference. When exposed to emotional distracters during a cognitive task, control participants were able to recruit dorsolateral PFC and suppress amygdala activation. By contrast, depressed individuals showed exaggerated amygdala response to such distracters and a failure to recruit DLPFC. Simultaneously, the patients in this study showed error-processing abnormalities that may reflect downstream effects of insufficient error monitoring in dorsal cingulate cortex.

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