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.

Key Words: Affective control, amygdala, cognitive control, depression, dorsolateral prefrontal cortex, emotion, emotional interference

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 hyperresponsive 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

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Received May 13, 2007; revised June 7, 2007; accepted June 7, 2007.

0006-3223/08/$34.00
doi:10.1016/j.biopsych.2007.06.012

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).