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# Neural correlates of emotional processing in depression: Changes with cognitive behavioral therapy and predictors of treatment response

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ABSTRACT

Major depressive disorder (MDD) is characterized by the presence of disturbances in emotional processing. However, the neural correlates of these alterations, and how they may be affected by therapeutic interventions, remain unclear. The present study addressed these issues in a preliminary investigation using functional magnetic resonance imaging (fMRI) to examine neural responses to positive, negative, and neutral pictures in unmedicated MDD patients ($N = 22$) versus controls ($N = 14$). After this initial scan, MDD patients were treated with cognitive behavioral therapy (CBT) and scanned again after treatment. Within regions that showed pre-treatment differences between patients and controls, we tested the association between pre-treatment activity and subsequent treatment response as well as activity changes from pre- to post-treatment. This study yielded three main findings. First, prior to treatment and relative to controls, patients exhibited overall reduced activity in the ventromedial prefrontal cortex (PFC), diminished discrimination between emotional and neutral items in the amygdala, caudate, and hippocampus, and enhanced responses to negative versus positive stimuli in the left anterior temporal lobe (ATL) and right dorsolateral PFC. Second, CBT-related symptom improvement in MDD patients was predicted by increased activity at baseline in ventromedial PFC as well as the valence effects in the ATL and dorsolateral PFC. Third, from pre- to post-treatment, MDD patients exhibited overall increases in ventromedial PFC activation, enhanced arousal responses in the amygdala, caudate, and hippocampus, and a reversal of valence effects in the ATL. The study was limited by the relatively small sample that was able to complete both scan sessions, as well as an inability to determine the influence of comorbid disorders within the current sample. Nevertheless, components of the neural networks corresponding to emotion processing disturbances in MDD appear to resolve following treatment and are predictive of treatment response, possibly reflecting improvements in emotion regulation processes in response to CBT.



## 1. Introduction

A key feature of major depressive disorder (MDD) is the presence of disturbances in emotional processing, which generally are expressed as a negative bias in processing emotional information (e.g., Gotlib et al., 2005; Koster et al., 2005; Siegle et al., 2002a). Specifically, patients with MDD tend to experience increased negative affect and reduced positive affect, and these mood disturbances are accompanied by negative affective biases during the perception and interpretation of emotional information. Patients with MDD show attentional biases toward cues for sadness or dysphoria (Gotlib et al., 2004) and tend to interpret neutral or positive information

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negatively compared to nondepressed individuals (Gollan et al., 2008; Gur et al., 1992). However, a number of questions remain about the mechanisms underlying these alterations in the way MDD patients process emotional information, and how such mechanisms may be affected by therapeutic interventions.

One avenue for understanding the neural substrates of MDD has been to explore how the brain instantiates the observed biases in emotional processing. There have been a wide variety of efforts to characterize neural differences between patients with MDD and healthy controls, interrogating either resting state or task-related differences between groups with an emphasis on established emotional processing networks. These approaches have revealed functional disturbances in specific brain regions, such as the medial prefrontal cortex (PFC; Price and Drevets, 2009), particularly the anterior cingulate cortex (ACC), as well as in the amygdala (AMY) and other limbic regions (see Drevets, 2001 for a review).

The medial PFC appears to serve at least two distinct purposes with regard to emotion processing (Bush et al., 2000). Ventromedial PFC (vmPFC) and ventral ACC (vACC), including subgenual and pregenual ACC, are thought to be part of an emotion-sensitive network that includes the AMY and increases activity following exposure to emotionally-salient stimuli (Bush et al., 2000; Phillips et al., 2003). Dorsomedial PFC (dmPFC) and dorsal ACC (dACC), including supragenual ACC, have been associated with cognitive control processes that, in the context of emotion processing, serve to regulate emotion-related responses in the ventral network (Phillips et al., 2003). In addition, pregenual ACC has been posited to facilitate communication between more ventral and dorsal sectors of the PFC (Mayberg, 1997). In general, patients with MDD tend to exhibit enhanced activity within vmPFC/vACC and reduced activity within dmPFC/dACC (Fitzgerald et al., 2008; Matthews et al., 2008; Mayberg, 1997). However, this pattern has not been entirely consistent across studies. Other evidence points to a decrease in vACC activity in patients with MDD (Drevets et al., 1997; Elliott et al., 2002; Lee et al., 2008), possibly due to a reduction in cortical volume in this area (Drevets, 2001; Drevets et al., 1997). Interpretation of these findings is further complicated by the wide variability in imaging methods, task designs, and patient characteristics (e.g., number of previous episodes, treatment history), as well as by the functional heterogeneity of the medial frontal regions.

Findings in the AMY also have been mixed. It has been shown that AMY metabolism during the resting state is elevated in depressed patients (Drevets et al., 1992), consistent with a pattern of AMY hyper-reactivity in patients with MDD. Also, in tasks involving presentation of negative and neutral material, patients tend to show exaggerated AMY responses to negative (relative to neutral or positive) material (Fales et al., 2008; Hamilton and Gotlib, 2008; Siegle et al., 2002b), consistent with a negativity bias. However, other reports indicate that AMY responses are elevated for both negative and neutral material (Almeida et al., 2010; Sheline et al., 2001), or not elevated at all relative to healthy controls (Davidson et al., 2003). Nevertheless, there appears to be some consensus concerning alterations in the AMY's functions associated with depression.

Recent investigations also have attempted to delineate the interaction of these neural differences with various forms of treatment. One important question is whether the neural differences between MDD patients and nondepressed controls persist after treatment, or whether successful treatment eliminates or reduces such differences. The vast majority of studies addressing this question have used pharmacological antidepressant treatments, and typically report normalization of pre-treatment activity differences in both cortical regions, including dmPFC/dACC and vmPFC/vACC (Fitzgerald et al., 2008; Mayberg et al., 1999), as well as subcortical structures, including AMY (Anand et al., 2007; Fales et al., 2009; Fu et al., 2004; Sheline et al., 2001).

It remains unclear, however, whether these changes in patterns of neural activation are specific to pharmacological treatments, which may suggest a specific mechanism of action, or whether similar changes are observed for non-pharmacological interventions. A handful of studies have compared groups of patients treated with antidepressants to those treated with brief, structured psychotherapies. In comparisons of antidepressant medication and interpersonal psychotherapy (IPT) (Brody et al., 2001; Martin et al., 2001), Brody et al. (2001) found that both forms of treatment yielded similar effects on the brain: increased resting-state metabolism in the insula and the inferior temporal regions and decreased metabolism in the lateral PFC, vACC, and caudate, with the effects moving in the direction of normalization. Similarly, Martin et al. (2001) found only limited differences between patients treated with medications versus IPT: the antidepressant-treated group exhibited increased resting-state metabolism in right lateral posterior temporal cortex, whereas the therapy group had increased metabolism in right posterior cingulate cortex. Neither study reported any treatment-related changes in the AMY (Brody et al., 2001; Martin et al., 2001).

Other studies have examined the effects of treatment with cognitive behavioral therapy (CBT), an approach that emphasizes challenging and restructuring depressed patients' negative cognitions (Hollon et al., 2002). Compared to pharmacological antidepressants, this form of therapy may reflect a more "top-down" approach to resolving depressive symptoms (Goldapple et al., 2004; Simons et al., 1984). In one study, depressed patients treated with CBT showed increased resting-state metabolism in hippocampus and dorsal mid-cingulate, but reduced metabolism in dorsolateral, ventrolateral, and medial PFC regions (Goldapple et al., 2004). However, this pattern was not found in patients treated with antidepressants, thus suggesting distinct mechanisms of change associated with CBT (Goldapple et al., 2004). Unlike the aforementioned studies of therapy effects on neural activity, which employed resting-state designs rather than emotion-related tasks, a recent study examined CBT influences on neural responses during an implicit facial affect processing task. Comparisons of pre- versus post-treatment activity revealed that task-related elevations in AMY activity were reduced post-CBT, and in contrast to the results of Goldapple et al., mid/dorsal ACC activity increased after treatment (Fu et al., 2008). Finally, there is additional evidence that CBT modulates brain activity in patients with anxiety disorders, which are frequently comorbid with MDD. For example, after CBT, phobic patients show reductions in hyperactivation of the dorsolateral PFC (Paquette et al., 2003) and the dorsal ACC (Straube et al., 2006) in response to fear-relevant stimuli.

Despite progress in elucidating treatment-related changes in brain activity, a number of important questions concerning the effect of treatment on the neural correlates of emotion processing in MDD remain. For instance, the influence of CBT on neural activity associated with recovery from depression remains largely unspecified, mainly due to the paucity of research on this issue and the lack of consistency in available findings. Furthermore, these investigations have only rarely incorporated an assessment of neural differences between depressives and controls associated with emotion processing, which may help to elucidate some of the core features of MDD. Another unresolved issue is whether baseline neural responsivity, particularly to emotionally-salient stimuli, may predict subsequent treatment outcome. Improving the prediction of subsequent treatment response is an important goal of research on MDD (Kemp et al., 2008), and neuroimaging data may provide useful measures for these assessments. To the extent that neural