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Prefrontal mechanisms for executive control over emotional distraction are altered in major depression

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Abstract

A dysfunction in the interaction between executive function and mood regulation has been proposed as the pathophysiology of depression. However, few studies have investigated the alteration in brain systems related to executive control over emotional distraction in depression. To address this issue, 19 patients with major depressive disorder (MDD) and 20 healthy controls were scanned using functional magnetic resonance imaging. Participants performed an *emotional oddball task* in which infrequently presented circle targets required detection while sad and neutral pictures were irrelevant novel distractors. Hemodynamic responses were compared for targets, sad distractors, and for targets that followed sad or neutral distractors (Target-after-Sad and Target-after-Neutral). Patients with MDD revealed attenuated activation overall to targets in executive brain regions. Behaviorally, MDD patients were slower in response to Target-after-Sad than Target-after-Neutra stimuli. Patients also revealed a reversed activation pattern from controls in response to this contrast in the left anterior cingulate, insula, right inferior frontal gyrus (IFG), and bilateral middle frontal gyrus. Those patients who engaged the right IFG more during Target-after-Neutral stimuli responded faster to targets, confirming a role of this region in coping with emotional distraction. The results provide direct evidence of an alteration in the neural systems that interplay cognition with mood in MDD.

Keywords: Event-related fMRI; Interaction of executive function and emotion; Anterior cingulate cortex; Inferior frontal cortex

1. Introduction

Emotional distraction often interferes with cognitive processing (Johnson et al., 2005; Dolcos and McCarthy, 2006). One of the cardinal features of major depressive disorder (MDD) is an inability to disengage from negative thoughts, memories and events in order to sustain attention towards on-going cognitive tasks (Lyubomirsky et al., 1998; Wenzlaff and Bates, 1998; Ellenbogen et al., 2002; Siegle et al., 2002). In turn, susceptibility to emotional distraction adversely affects the capabilities of patient to cope with the demands of daily living (Ottowitz et al., 2002; Rogers et al., 2004). Despite the established

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clinical importance of executive dysregulation of emotional processing in MDD, alterations in neural functioning associated specifically with this aspect of the disorder are not yet clear.

An influential neurobiological model proposed for mood regulation posits a failure of coordination in dorsal and ventral brain systems subserving executive control and emotional processing, respectively (Mayberg, 1997). Mayberg and colleagues propose that the rostral anterior cingulate (ACC) and related areas in the inferior and medial prefrontal cortex (PFC) may serve critical roles in balancing the relative influence of these brain systems to guide goal-directed behavior and maintain healthy mood. In healthy populations, emotional Stroop and emotional Go/NoGo tasks have been employed to investigate inhibitory cognitive control over emotional distraction by presenting task-irrelevant emotional information simultaneously with task-relevant stimulus features. The ACC, particularly its rostral and ventral aspects, is consistently activated by emotional interference in these tasks (Whalen et al., 1998; Elliott et al., 2000; Bishop et al., 2004; Etkin et al., 2006; Shafritz et al., 2006). This region has been associated with mediating conflict between competing responses (Carter et al., 1998; Botvinick et al., 2001), monitoring for the occurrence of response conflict in information processing (Carter et al., 1998, 2000; Botvinick et al., 1999; Barch et al., 2000; Botvinick et al., 2001), and error monitoring and detection (Rubia et al., 2003). In addition, a number of studies using the Stroop, Go/No Go and other attention-demanding tasks suggest a role of the right inferior frontal gyrus (IFG) in inhibitory processes relevant for successful cognitive performance and executive function (Jonides et al., 1998; Konishi et al., 1998; D'Esposito et al., 1999; Smith and Jonides, 1999; Liddle et al., 2001; Rubia et al., 2003; Aron et al., 2004).

Of particular relevance to the present study, Dolcos and McCarthy (Johnson et al., 2005; Dolcos and McCarthy, 2006) revealed a role of the IFG in inhibiting emotional distraction in healthy adults. While subjects performed a working memory task, activation in the IFG was enhanced when the subject was distracted by negative emotional pictures relative to distracting neutral or scrambled pictures. Subjects with great activity to emotional distracters in the IFG tended to rate emotional distracters as less distracting, suggesting that activity in the IFG indexed successful inhibition of emotional distraction. It is unknown, however, whether recruitment of this region during emotional distraction is altered in clinical populations, such as MDD, and whether dysregulation of IFG activity has behavioral consequences on task performance.

Functional neuroimaging of MDD patients during emotional tasks has implicated dysfunction in frontolimbic regions, providing initial support for Mayberg's neuroanatomical model of mood regulation. For instance, a sustained emotional response in the amygdala during a personal relevance rating task and decreased dorsolateral PFC activity on a digit-sorting task has been reported in MDD relative to controls (Siegle et al., 2002, 2006). Siegle and colleagues also reported a decreased correlation of amygdala and dorsolateral PFC activity in the MDD group (Siegle et al., 2006); however, this study did not address how emotional responses affected subsequent brain activity associated with executive control. George et al. (1997) reported decreased activity in the ACC in MDD patients who performed an emotional Stroop task while undergoing positron emission tomography (PET) scanning. Elliott et al. (2002) reported attenuated neural responses to emotional relative to neutral targets in the ventral ACC and the posterior orbitofrontal cortex during an emotional Go/No Go task in MDD. However, because the latter attentional studies used blocked designs, it is not possible to disambiguate responses to different stimulus events and time epochs during the task.

In the present event-related functional magnetic resonance imaging (fMRI) study, we extended these initial neuroimaging findings in MDD to investigate alterations in executive and emotional processing systems during an attentionally demanding visual oddball task with intermittent emotional distraction by presentation of sad pictures (Wang et al., 2005, 2006). This task more closely models the disruption of on-going task-relevant cognitive processes by sporadic mood-congruent thoughts in MDD than Stroop or Go/No Go tasks in which the emotional stimuli are themselves task-irrelevant. Furthermore, because the emotional distractors are temporally separated from presentation of the attentional targets, we can evaluate whether emotional dysregulation in MDD leads to performance decrements and differential brain activation to task-relevant attentional targets that follow emotional distractors close in time.

Our previous studies using this paradigm in healthy adults have consistently shown that the attentional targets activate dorsal frontoparietal structures and the sad distractors activate ventral frontolimbic structures, including the amygdala (Wang et al., 2005, 2006). In the present study, we first compared brain activation patterns in MDD and controls to attentional targets and sad distractors separately in order to address the main effect of depression on executive and emotional processing, respectively. Next, to probe the lingering impact of the sad distractors on executive function, we isolated activity to attentional