Poster

Neural signatures of cognitive and emotional biases in depression

Functional brain imaging studies suggest that depression is a system-level disorder affecting discrete but functionally linked cortical and limbic structures, with abnormalities in the anterior cingulate, lateral, and medial prefrontal cortex, amygdala, and hippocampus. Within this circuitry, abnormal corticolimbic interactions underlie cognitive deficits and emotional impairment in depression. Depression involves biases toward processing negative emotional information and abnormal self-focus in response to emotional stimuli. These biases in depression could reflect excessive analytical self-focus in depression, as well as impaired cognitive control of emotional response to negative stimuli. By combining structural and functional investigations, brain imaging studies may help to generate novel antidepressant treatments that regulate structural and functional plasticity within the neural network regulating mood and affective behavior.

Functional and structural neuroimaging studies have assumed a unique position in defining the neuroanatomy of depression. Studies of cerebral blood flow and glucose metabolism with positron emission tomography (PET) scans in primary depression and depression associated with brain lesions have consistently revealed that major depressive disorder is a system-level disorder.[1,2]

Resting state studies

The majority of neuroimaging studies assessing resting state neural response have involved ventral and dorsal prefrontal cortex, anterior cingulate, basal ganglia, amygdala, and hippocampal regions in depression. The best-replicated behavioral correlate of a resting state abnormality in depression is that of an inverse relationship between prefrontal activity and depression severity.[3] Changes in specific neural networks have also been associated with symptomatic dimensions of depression. Dimensions of depression can be categorized into behavioral subsystems—mood and affect, circadian-somatic, cognitive, and motor—where mechanisms mediating variations within a normal behavior domain might be more easily evaluated. Dorsolateral prefrontal (DLPF) activity has been linked to psychomotor speed and executive functions,[4] a set of cognitive processes engaged in the generation of multiple response alternatives, error monitoring, and self-evaluation. Parietal and parahippocampal activity has been associated with anxiety[5]; medial frontal and cingulate activity with emotional bias.[6] Finally, a more complex ventral-dorsal segregation of frontal-lobe functions has also been described, with anxiety/tension positively correlated with ventral prefrontal activity, and psychomotor and cognitive slowing negatively correlated with DLPF activity.[7]

Neural correlates of cognitive and emotional biases in depression

Few studies have examined dynamic responses of depressed patients to cognitive and/or emotional stimuli with PET scanning or functional magnetic resonance imaging (fMRI).

Emotional processing in depression is characterized by two biases. The first bias reflects the tendency of depressed patients to prioritize the processing of negative stimuli.[8] Mood disorders may be associated with abnormalities in the way emotional stimuli are perceived, interpreted, and stored in memory. It has long been suggested that depressed patients have no attentional or identification bias for negative stimuli. However, recent studies using a dot-probe task showed that depressed patients allocate more attention to sad faces than happy faces.[9] This bias was not observed in depressed patients for other negative

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stimuli (ie, angry faces), suggesting that depressed patients do not have a general problem with negative emotional stimuli per se. Consistent with this explanation, depressed patients interpret emotionally neutral faces as sad.[10] On the other hand, depressed patients have better memory for negative stimuli, including words and pictures. Finally, depression is also associated with diminished responsiveness to positive stimuli.

Several fMRI studies have evaluated the neural correlates of this emotional bias in depression, with special focus on the amygdala. Presentation of sad faces to depressed patients is associated with exaggerated activity in the amygdala and ventral striatum. This increased response to sad faces attenuated after 8 weeks of antidepressant treatment with a selective serotonin reuptake inhibitor (SSRI).[11] Using emotional words, Siegle et al[12] have reported abnormally sustained amygdala responses to negative words in depressed patients compared with normal controls. This amygdala sustained response in the context of negative information processing is postulated to be an important neural correlate of rumination—a common clinical feature of a major depressive episode. Other fMRI studies in depression using emotional words showed reduced activation in frontotemporal and limbic regions in responses to positive stimuli.[13,14]

More recently, Keedwell et al[15] examined neural responses to happy and sad provocation in depressed patients and
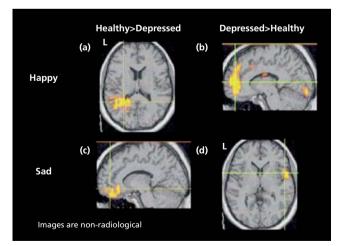

Figure 1. Double dissociation in medial prefrontal activation during processing of happy and sad stimuli in depressed patients and controls.
Adapted from ref 15: Keedwell PA, Andrew C, Williams SCR, Brammer MJ, Philipps ML. A double dissociation of ventro-medial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. *Biol Psychiatry.* 2005;58:495-503. Copyright © Elsevier 2005

controls. Keedwell et al used personally relevant stimuli, positive and negative autobiographical memories, to prompt mood changes. They observed that depressed patients showed an increased response in the ventromedial prefrontal cortex (VMPFC) to happy stimuli, whereas the controls showed a decreased response *(Figure 1)*. The pattern was reversed for sad stimuli in healthy controls and depressed patients. The VMPFC, in relation with the orbitofrontal cortex and the ventral striatum, was involved in reward processing. According to Keedwell et al, their findings indicate abnormal reward processing in major depression. Indeed, the increased response to happy stimuli in the VMPFC was associated with a reduction in the general autonomic reactivity in depressed patients. Overall, this suggests that during happy provocation, depressed patients may have paid more attention to the abstract representation of the positive stimuli rather than to an increased autonomic response per se to these stimuli.

Both ventral and dorsal medial prefrontal cortex have been associated with self-referential processing in healthy controls (*Figure 2*, see ref 16). Abnormal self-focus is a second emotional bias in major depression. Usually, depressed patients tend to engage in self-reflection and self-evaluation spontaneously or after emotional perception. This persistent, increased self-focus in depression may maintain negative mood and reinforce the activation of negative self-schema in depression.

In a recent study (Lemogne et al, unpublished data) we used a self-referential memory task combined with fMRI to study self-focus in acutely depressed patients and healthy controls. Subjects made evaluative judgments of emotional words describing positive and negative personality traits. In the self-condition subjects answered the question: "Does the word describe you?" In the general condition they answered the question: "Does the word describe a socially desirable trait?" Fifteen acutely depressed inpatients and 15 matched healthy subjects were included in the study. We observed a greater activation of the dorsal medial prefrontal cortex in the "self" vs the "general" condition that was unique to patients. Additionally, patients displayed a greater activation of the left inferior frontal gyrus in the "self" condition, and an increased functional connectivity between the self-network, the right inferior frontal gyrus and the dorsal anterior cingulate cortex. These results are consistent with the idea that depressed are more engaged in an analytical self-focus in depression rather than an experiential self-focus.
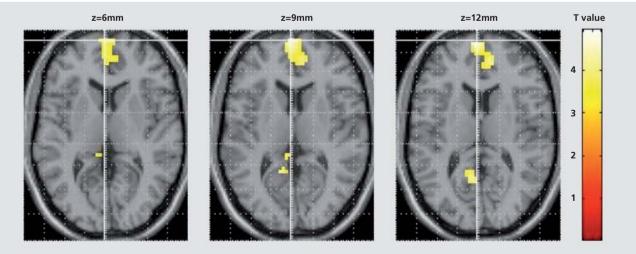
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The analytical self-focus describes the internally orientated attention toward the causes and consequences of emotional response. One example of such self-analytical self-focus is rumination. Unlike analytical self-focus, subjects in an experiential self-focus mode pay attention to their feeling and emotional experience, regardless of the causes or consequences of that experience.
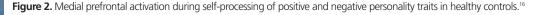
Depression and cognitive homeostasis

Mayberg and Fossati[2] further postulate that depression is not simply the result of selective regional or pathway dysfunction, but also involves failure of the remaining systems to maintain homeostatic emotional control in times of increased cognitive demands. From this point of view, normal individuals have limited cognitive resources (or limited capacity to process information) and mental operations may differ in the amount of attention or cognitive resources they require.

Depression interferes with effortful cognitive processes—processes accomplished in sequence and restricted by the short-term memory capacity—leaving intact automatic processes in several domains such as learning, memory, problem-solving, reading, and speed processing (for review see ref 17). The effortful-deficit hypothesis in depression predicts impairment in the actions requiring attentional and executive resources such as complex goal-directed behaviors. We suggest that deficits of depressed patients on effortful tasks are preceded by increasing efforts to maintain a high level of perfor-

mance. The progressive exhaustion of cognitive resources preceding the deficits of depressed patients and the reduction of cognitive resources is a final by-product of the failure of depressed patients to constantly adapt to cognitive and emotional demands. Recent fMRI data support this hypothesis.

In a recent fMRI study,[18] we compared 10 depressed subjects and 10 normal controls on a verbal n-back task. The n-back task is a working memory task that requires both maintenance of the n-stimuli and updating of these stimuli each time a new stimulus occurs. The working memory load was manipulated across the experiment (1,2,3-back) to increase the cognitive demands. We selected, a priori, depressed patients with normal performance on the n-back task, and no difference between groups was found for both performance and reaction times for each levels of complexity of the n-back task. Both groups, depressed patients and controls, showed bilateral activation of DLPFC (BA 9/46), premotor and SMA (BA 6/8), Broca's area, dorsal anterior cingulate cortex (ACC), and parietal cortex during n-back tasks. Activation of these regions was modulated by the complexity of the task. Within this n-back neural network, depressed patients showed greater activation of the DLPFC and dorsal ACC than normal controls. Since this seminal work, three fMRI studies have used an n-back task or a working memory task in depressed patients. Two of these three studies replicated our original findings, and showed a hyperactivation in the left DLPFC in depressed patients as compared with normal controls (see refs 19-21).

Figure 2. Medial prefrontal activation during self-processing of positive and negative personality traits in healthy controls.[16]

The aberrant activation of the DLPFC and anterior cingulate associated with normal performance in depressed subjects may reflect several problems: (i) inefficiency of a task-related neural network reflecting difficulty organizing neural activity and abnormal signal-to-noise ratio that indicates dopaminergic dysfunction; (ii) structural brain abnormalities within the working memory network; (iii) excess of subjective effort (volition) or subject's task engagement; (iv) difficulties in inhibiting activation in limbic structures during the cognitive task reflecting an inability to allocate resources to the external world; (v) depressed patients have a greater need to monitor the putative errors and conflict than controls, reflected by a greater activation of the ACC. Recent fMRI experiments in healthy subjects have indicated that increasing cognitive demand engages a pattern of brain activation characterized by a balance between increasing activity in cortical cognitive areas and decreasing activity in the limbic and paralimbic structures such as ventromedial prefrontal regions.[22] The deactivation in limbic areas may represent an emotional gating function aimed at inhibiting emotional interference. In our n-back study, depressed patients had more difficulty than normal controls in deactivating the medial prefrontal cortex activity, which may be associated with abnormal self-evaluation during cognitive effort[18] (see also ref 19).

Summary and future directions

To summarize, abnormal corticolimbic balances and connectivity may subserve cognitive deficits and emotional bias in acutely depressed patients. Antidepressants, by improving functional connectivity in these dysfunctional cortical-limbic pathways, may help the brain to restore a homeostatic cognitive and emotional balance.

Cognitive and emotional studies in remitted depressed patients, or patients with high risk for depression, are needed to elucidate the neural correlates of vulnerability to depression.

Finally, further clinical and experimental in vivo and in vitro studies are needed to determine genetic and environmental factors that regulate structural and functional plasticity within the neural network regulating mood and affective behavior, and to prepare the ground for the development of novel antidepressant treatments. ❏

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