Neurocognitive Mechanisms in Depression: Implications for Treatment

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mood, depressive, mania, bipolar, affect, cognition, neuroimaging

Abstract

Mood disorders collectively account for a substantial proportion of disease burden across the globe and have a devastating impact on quality of life and occupational function. Here we evaluate recent progress in understanding the neurocognitive mechanisms involved in the manifestation of mood disorders. We focus on four domains of cognitive function that are altered in patients with depression: executive control, memory, affective processing, and feedback sensitivity. These alterations implicate a distributed neural circuit composed of multiple sectors of the prefrontal cortex in interaction with subcortical regions (striatum, thalamus) and temporal lobe structures (amygdala, hippocampus). Affective processing and feedback sensitivity are highly sensitive to serotonergic manipulation and are targeted by antidepressant treatments. By drawing together cognitive, neuroanatomical, and pharmacological tiers of research, we identify treatment targets and directions for future investigation to identify people at risk, minimize relapse, and maximize long-term beneficial outcomes for those suffering from depression.

Contents

INTRODUCTION

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are prevalent neuropsychiatric conditions that represent a leading cause of disability across the globe. Patients with MDD experience depressive episodes of at least two weeks duration that are accompanied by a number of characteristic subjective, behavioral, and physiological symptoms (Am. Psychiatr. Assoc. 2000). Patients with BD experience episodes of depression as well as manic episodes during which they are typically elated, agitated, and socially inappropriate. Lifetime prevalence of these two conditions has been estimated at up to 19% and 1.5%, respectively, depending on the country (Weissman et al. 1996). Approximately 60% of completed suicides occur in patients with a mood disorder (Shaffer et al. 1996). Depressive and manic symptoms functionally impact sufferers and their families, and mood disorders are costly to the economy. For example, the economic cost of depression was estimated at $44 billion in the United States in 2000 (Greenberg et al. 2003) and £7.5 billion in England in 2007 (McCrone et al. 2008). Consequently, it is important to understand the neurobiology of mood disorders and the brain mechanisms by which treatments for depression exert their beneficial effects. The application of neuroscience techniques can facilitate early detection, optimize treatment, and reduce the risk of subsequent relapse.

Mood disorders are unlikely to stem from aberrant function of a specific gene, brain region, or cognitive process. Rather, the clinical phenotype (the symptoms) should be seen as the end point of underlying dysregulation of distributed neural networks and cognitive-emotional control processes (Mayberg 2007). This selective review aims to summarize the recent advances in understanding neurocognitive mechanisms in mood disorders and their underlying neurobiological substrates. We begin by considering the cognitive symptoms that are described in the diagnostic criteria for mood disorders and the key brain systems implicated in their development. We then review the core findings in mood disorders across four domains of psychological function: executive control, memory, affective processing, and response to negative feedback. In considering their underlying substrates, we focus on functional neuroimaging research that has examined the neural correlates of these processing deficits, as well as the neurochemical mechanisms identified by challenge studies and radioligand positron emission tomography (PET) imaging. We conclude by discussing the first-line treatments for mood disorders, along with recent experimental approaches to the treatment of depression, which are derived largely from improved understanding of its neural substrates.

PET: positron emission tomography

Cognitive Abnormalities in Mood Disorders: Diagnostic Criteria and Psychological Models

Cognitive problems are included in the diagnostic criteria for depressive and manic episodes, according to the Diagnostic and Statistical Manual (Am. Psychiatr. Assoc. 2000). The criteria for depression include a reduced ability to concentrate and indecisiveness.

Criteria for mania include distractibility and excessive involvement in pleasurable activities that are likely to result in damaging outcomes (i.e., risk-taking). The emotional states of patients with depression and mania can be considered to represent two polar extremes on a mood spectrum (see **Figure 1**). Although we all experience mood fluctuations in day-to-day life, the states manifested in depression and mania are pathological in that they are extreme, disrupt quality of life, and are persistent and often recurrent (Chamberlain & Sahakian 2004).

Aberrant cognition is also emphasized in psychological models of mood disorders. Two classic formulations that continue to influence current theory are the learned helplessness model (Seligman 1972) and Beck's cognitive model of depression (Beck et al. 1979). According to the learned helplessness model, patients grow to accept that stressful circumstances cannot be altered through their own actions, which leads to disruption of learning and stagnant, anhedonic behavior (Seligman 1972). In Beck's cognitive model, dysfunctional negative schemata formed early in life are activated by stressful life events and lead to a characteristic triad of negative thoughts directed at the self, the world, and the future. Systematic errors of logic then perpetuate the low mood; for example, patients with depression engage in maximization and minimization, where criticism or minor errors are overemphasized and major achievements are ignored. Maladaptive belief systems and negative schemata have been objectively identified in patients (Hollon et al. 1986, Scott et al. 2000) and are challenged in psychotherapies such as cognitive behavior therapy (CBT) (Beck et al. 1979), which aims to train patients to recognize and modify their dysfunctional beliefs and negative automatic thoughts.

Figure 1

Mood states in patients with depression and mania can be considered to occupy extreme poles on an affective spectrum. Although healthy mood fluctuates in response to life events, the extreme mood states are pathological in that they are persistent and impede everyday functioning and quality of life.

Implicated Neural Circuitry

The frontal lobes and basal ganglia have been consistently implicated in the pathophysiology of mood disorders since seminal work was completed in patients with secondary mood disturbance as a result of acquired brain injury. Post-stroke depression was reported to have higher prevalence following lesions that involved the prefrontal cortex (PFC) or the basal ganglia, particularly on the left side of the brain (Robinson et al. 1983, Starkstein et al. 1987). Although a systematic review has questioned this association (Carson et al. 2000), a subsequent study in 275 cases of ischemic stroke corroborated the link to infarcts affecting the PFC and subcortical regions in the left hemisphere (Vataja et al. 2001). It is also notable that rare cases of secondary mania are often associated with right-lateralized damage to the same regions (Robinson et al. 1988). Neurological conditions affecting the basal ganglia (namely, Parkinson's disease and Huntington's disease) are also associated with elevated levels of depression (McDonald et al. 2003). These clinical observations have been confirmed subsequently using MRI in patients with primary (i.e., nonorganic) mood disorders (e.g., Sheline 2003; see also below).

The frontal lobes and basal ganglia are in fact richly interconnected via a series of functionally segregated loops or circuits that link discrete stations in the frontal cortex, striatum, and thalamus (Alexander et al. 1986). Although some cross-talk likely occurs between these circuits (e.g., Haber et al. 2000), this basic conceptualization has been extremely fruitful within neuropsychiatry because diagnoses may be linked to differential degrees of dysfunction

CBT: cognitive behavior therapy

PFC: prefrontal cortex

across these fronto-striatal loops (Mega & Cummings 1994). Several tiers of evidence implicate dysregulation of a medial/orbitofrontal circuit in depression, comprising the orbitofrontal cortex and anterior cingulate cortex, the ventral striatum (including the nucleus accumbens), the ventral pallidum, and the medial thalamus (Drevets 2000, Mayberg 2003). Components of this circuit are reciprocally connected with the amygdala, another locus that is widely implicated in emotional processing in the healthy brain (Phillips et al. 2003) and dysregulated in mood disorders (Phillips et al. 2008). The neurobiology of mania has been less well characterized compared with MDD, but similar regions are implicated in functional imaging studies (Blumberg et al. 2003), and patients with lesions to the ventromedial PFC display risk-seeking and socially disinhibited behavior that is reminiscent of mania (Clark & Sahakian 2006).

Modern imaging techniques offer the precision to localize structural abnormalities within fronto-striatal circuitry. One pivotal observation by Drevets and colleagues (1997) was of volume reduction in a specific sector of the anterior cingulate cortex, lying ventral to the genu of the corpus callosum (hence subgenual cingulate). This reduction was observed in patients with BD and MDD diagnoses, with high familial loading for mood disorder (Drevets et al. 1997). These volume reductions have since been replicated in early-onset mood disorders (Botteron et al. 2002, Hirayasu et al. 1999) with some specificity to mood disorders (Coryell et al. 2005). Moreover, the subgenual cingulate region was shown to be functionally dysregulated in the depressed state. Although the initial study indicated reduced glucose metabolism (Drevets et al. 1997), this effect was partly confounded by the volumetric differences (Drevets 2000). Later studies identified functional hyperactivity in the subgenual cingulate (Mayberg 2003), which predicted a positive treatment response (Mayberg et al. 1997, Saxena et al. 2003) and normalized upon recovery from depression (Kennedy et al. 2001; Mayberg et al. 1999, 2005).

Brain imaging techniques have also given insight into the underlying neurochemistry of mood disorders by using PET imaging with receptor-selective tracers. The status of the serotonin system has been probed using the 5-HT_{1A} antagonist, [11C] WAY100635, and the serotonin transporter ligand, [11C] DASB (3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile). A WAY100635 study comparing unmedicated MDD patients against healthy controls reported a 41% reduction in 5-HT_{1A} binding potential (BP) in the raphe nucleus, the source of the ascending serotonin projection, coupled with a 27% reduction in BP in the medial temporal lobe (i.e., hippocampus and amygdala) (Drevets et al. 1999; see also Sargent et al. 2000). Using the [11C]DASB ligand, serotonin transporter BP was increased in several areas receiving serotonergic innervation (prefrontal cortex, anterior cingulate, putamen) in a subset of MDD cases with severe negative beliefs, and BP in these regions was correlated significantly with a measure of Beckian dysfunctional attitudes (Meyer et al. 2004). These BP increases are thought to occur as a reaction to low levels of extracellular serotonin in these patients. In considering the changes in affective processing and feedback sensitivity in patients with depression, it will become clear that serotonin has a fundamental role in modulating emotional behavior and that these changes in serotonin transmission may represent an important cause of cognitive dysfunction in depression.

COGNITION IN MOOD DISORDERS

Neuropsychological assessment provides a framework for objectively investigating cognitive functions in patients with depression and mania. Investigators have developed computerized tests to measure specific components of cognitive function. These tests offer many advantages over conventional pencil-and-paper testing because they standardize aspects of administration and automate data collection and analysis. The neuroanatomical and

neurochemical substrates of these measures may be elucidated using a variety of methods: studies in humans with focal neurosurgical damage, functional neuroimaging in patients and controls, and neurochemical probes. The ecological validity of these tests in mood disorders is supported by studies using cognitive measures to predict poorer functional outcomes, for example, in terms of return to employment or quality of life (Jaeger et al. 2006, Martinez-Aran et al. 2007). In the following section, we focus on four domains of psychological function that have been studied most extensively in relation to mood disorders.

Executive Control

Executive function is a collective term that refers to higher-level processes involved in the flexible organization of behavior, including working memory, forward planning, and the inhibition of dominant responses. Functional imaging and human lesion studies have localized executive processes to the dorsal and lateral aspects of the PFC, albeit in interaction with subcortical structures and posterior cortical regions (Robbins 1998). Executive function is significantly compromised across a range of paradigms in MDD (Elliott et al. 1996, Rogers et al. 2004). These deficits were present in unmedicated MDD patients (Taylor Tavares et al. 2007) and exacerbated in bipolar depression compared with MDD (Borkowska & Rybakowski 2001). Although executive function improves substantially as depressive episodes subside, some impairments persist in remitted cases (Clark et al. 2005), particularly in older adults (Beats et al. 1996).

Consistent with these neuropsychological findings, functional imaging studies have indicated dysregulation of dorsal and lateral PFC in depressed patients performing executive tasks. The direction of this effect appears to depend on the level of performance in the clinical group. In studies where MDD cases were behaviorally impaired relative to controls, for example on tests of forward planning (Elliott et al. 1997a) or verbal fluency (Okada et al. 2003), prefrontal activation was attenuated in the MDD group. However, prefrontal activation was reported to be greater in MDD during working memory (Harvey et al. 2005), mental arithmetic (Hugdahl et al. 2004), and the Stroop task (Wagner et al. 2006), in studies where there were no performance differences between patient and control groups. While these inconsistencies may be related to differences in patient characteristics or the precise tasks employed, a parsimonious explanation is that the overactivations reflect diminished cortical efficiency; in short, depressed patients may need a greater degree of frontal lobe activation to maintain the same level of task performance as healthy individuals.

Memory

Memory impairment is a second domain of impairment in patients with depression and can be captured with a range of paradigms including a virtual reality spatial navigation task (Gould et al. 2007) or paragraph recall (remembering the details of a complex story after a 10-min delay) (Gorwood et al. 2008). Mnemonic impairment is highly predictive of functional outcome (Martinez-Aran et al. 2007) and correlates with indices of illness chronicity. For example, a recent study in a primary care cohort (n = 8229) estimated a 2%-3% decline in delayed paragraph recall with each depressive episode up to the fourth episode (Gorwood et al. 2008). Data such as these highlight the importance of early detection and intervention in the clinical management of depressed patients to minimize these cumulative effects.

Hippocampal pathology is thought to underlie this pronounced memory deficit. Hippocampal function is impaired in patients with MDD and BD during memory encoding tasks (Bremner et al. 2004, Deckersbach et al. 2006), and reduced hippocampal volume is arguably the most robust neuropathological finding reported in MDD, as supported by meta-analyses of MRI data (Campbell et al. 2004, Videbech & Ravnkilde 2004) as well as postmortem evidence (Stockmeier et al. 2004). For example,

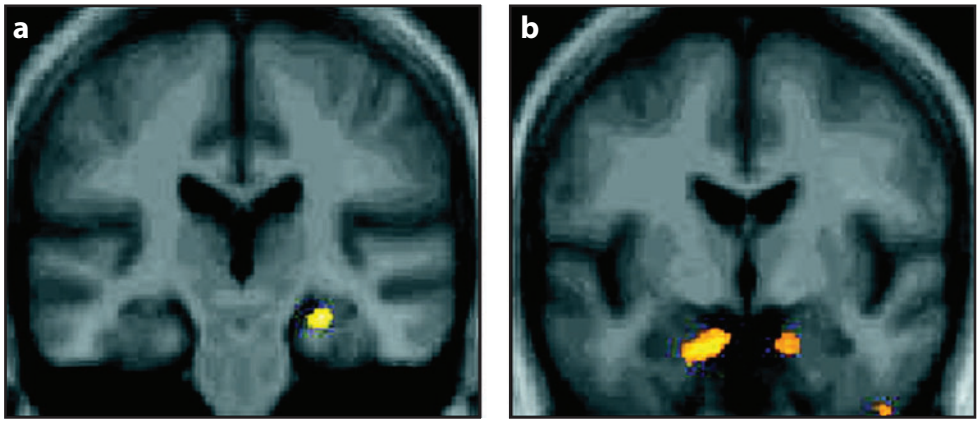

Figure 2

(*a*) Using voxel-based morphometry of magnetic resonance imaging data, elderly depressed patients showed reduced gray matter volume in the right hippocampus compared with controls. The yellow region represents voxels of reduced gray matter volume at the $p < 0.001$ threshold, after controlling for age. (*b*) A negative correlation (also $p < 0.001$ controlling for age) was found between gray matter volume in the perihippocampal region (comprising the right and left anterior hippocampal gyrus and entorhinal cortex) and the number of years since the first onset of depression. Reprinted with permission from Bell-McGinty et al. 2002. Reprinted with permission from the American Journal of Psychiatry (copyright 2002).

a structural MRI study in elderly depressed subjects reported hippocampal volume reductions that were correlated with the duration of illness (Bell-McGinty et al. 2002) (see **Figure 2**). In young adult cases with MDD, hippocampal volume did not differ from controls in untreated first-episode cases but was reduced in patients who had experienced multiple episodes (MacQueen et al. 2003), and recent work has shown decreases in hippocampal gray matter over a three-year period in MDD (Frodl et al. 2008).

Which mechanisms contribute to this progressive deterioration in the hippocampus? One hypothesis proposes that the increased cortisol levels that are evident during depressive episodes (Carroll et al. 1976) have a toxic effect in the hippocampus (Sapolsky et al. 1985); for example, the hippocampus is also highly sensitive to hypoxic injury. Certain classes of medication may be capable of stalling these deteriorations. For example, hippocampal volume was inversely correlated with the duration of untreated depressive illness but was not associated with the duration of depressed mood under antidepressant medication (Sheline et al. 2003). Preclinical research has suggested that the clinical efficacy of antidepressant drugs may depend on their capacity to stimulate hippocampal neurogenesis (Sahay & Hen 2007). When hippocampal neurogenesis was disrupted in mice, two antidepressant drugs, the tricyclic imipramine and the SSRI fluoxetine, were rendered behaviorally ineffective (Santarelli et al. 2003). Similarly, anticonvulsant drugs that are widely used in treating BD may exert neuroprotective effects in the hippocampus (Manji et al. 2000): Lithium treatment in rodents prevented the effect of chronic stress to reduce dendritic length in the hippocampus (Wood et al. 2004). Further clinical studies are now needed to support these translational approaches because the relative roles of cell death, cell shrinkage, and a failure of neurogenesis in causing the evident hippocampal pathology in depression remains unclear.

Affective Processing Bias

The symptomatology of depression suggests a processing bias toward negative aspects of the environment. Within memory, for example,

patients with depression are more likely to recall negative autobiographical memories, and when they do recall positive experiences, they are overgeneral, that is, lacking in detail (Brittlebank et al. 1993). By contrast, the mood typical of mania is grandiose, suggestive of a positive processing bias. Depressed patients are impaired at recognizing happy facial expressions, whereas manic patients are impaired at recognizing negative (including sad) facial expressions (Lembke & Ketter 2002, Rubinow & Post 1992). Much of the recent neurocognitive work on affective processing in mood disorders has employed tasks of emotional facial recognition, or tasks that present emotional words or pictures, because these tasks can be easily adapted for use in functional imaging.

Another procedure used to study these biases is the affective go/no-go test (**http://www.camcog.com**), which requires the processing of affect in the context of an inhibitory control task. Volunteers observe a series of emotional words (e.g., "HAPPY", "FAILURE") and are instructed to make rapid responses to words of one valence and to ignore words of the other valence. Target valence changes across blocks of the task. Affective bias is indicated by a difference in reaction time to respond to happy versus sad targets. Using this test, Murphy et al. (1999) showed that depressed patients responded more rapidly to sad versus happy word targets, whereas manic patients displayed the opposite bias, responding faster to happy words (see **Figure 3**). Manic patients also made more impulsive commission errors to nontargets. The effect in MDD was replicated in unmedicated patients who were faster to respond to sad words and also made more omission errors to happy targets (Erickson et al. 2005). Healthy controls in that study were significantly faster to respond to happy than sad targets, albeit with a smaller effect size compared with manic patients in the Murphy et al. (1999) study. The investigators suggested that this positive bias in healthy subjects may confer resilience during times of stress (Erickson et al. 2005; see also McCabe & Gotlib 1995).

Using a functional magnetic resonance imaging (fMRI) variant of the affective go/no-go task, increased activation was observed in the subgenual cingulate when healthy controls viewed emotional versus neutral words (Elliott et al. 2002). Depressed patients showed abnormally increased neural responses to sad targets in this region and a distinct response to sad distractors in the right orbitofrontal cortex

(f)MRI: functional magnetic resonance imaging

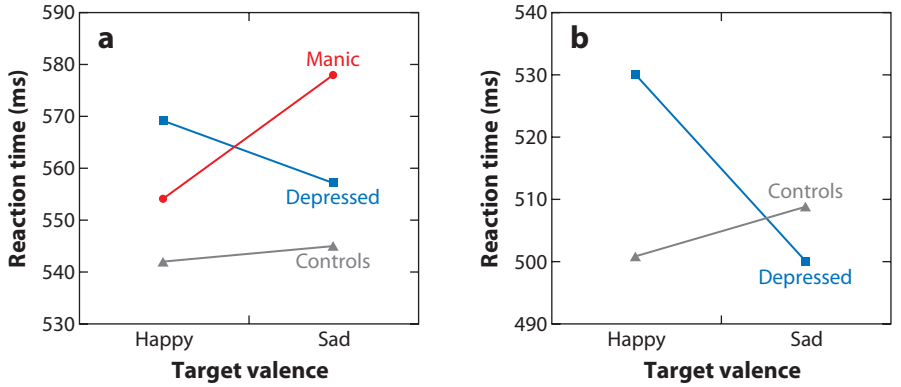

Figure 3

Affective bias in mood disorders. (*a*) On the affective go/no-go task, patients with depression are faster to respond to negative words than positive target words, whereas patients with bipolar disorder tested during mania are faster to respond to positive words than negative words. Data redrawn from Murphy et al. (1999). (*b*) This negative bias in depressed patients was later replicated in an unmedicated sample with major depressive disorder. Healthy controls in that study were significantly faster to positive words than negative words, which may be associated with resilience against low mood. Data from Erickson et al. 2005.

SSRI: selective serotonin reuptake inhibitor

NRI: noradrenaline reuptake inhibitor

(Elliott et al. 2002). Dysregulation of the orbital and medial PFC has also been revealed by inducing low mood through autobiographical scripts in remitted MDD patients (Liotti et al. 2002). Other key nodes for affective processing are disrupted in depressive states. In particular, increased amygdala response has been reported in a number of studies of MDD groups; for example, in response to negative emotional faces (Fales et al. 2008, Sheline et al. 2001). This amygdala hyperreactivity is sustained into affectively neutral blocks that follow the emotional task (Siegle et al. 2002) and is attenuated through chronic SSRI treatment (Fu et al. 2004, Sheline et al. 2001).

The amygdala is extensively interconnected with the multiple regions within the PFC, and these interactions may allow top-down control of emotional behavior (e.g., Johnstone et al. 2007). Several recent findings have indicated that these patterns of connectivity may be compromised during depressive states (Chen et al. 2008, Johnstone et al. 2007, Siegle et al. 2007). For example, Johnstone et al. (2007) scanned healthy controls and unmedicated MDD cases on an emotional reappraisal task, where, on some trials, subjects were asked to enhance or suppress their emotional responses to affective pictures. Controls displayed a negative association between amygdala and ventrolateral PFC activity, which was mediated by the ventromedial PFC. These correlations were absent or reversed in the MDD cases. The degree of coupling between the amygdala, and the prefrontal and anterior cingulate cortex also increased with eight weeks of selective serotonin reuptake inhibitor (SSRI) treatment (Chen et al. 2008).

Other evidence supports the regulatory role of serotonin in affective processing. Much of this work has used the acute tryptophan depletion (ATD) procedure in healthy subjects, which entails the ingestion of an amino-acid mixture that selectively lacks tryptophan, the precursor of serotonin. ATD robustly depletes serotonin availability in the brain over a six-to-eight-hour period (Carpenter et al. 1998, Williams et al. 1999). The finding that ATD administration to remitted MDD cases can cause a temporary relapse of low mood (Smith et al. 1997) remains one of the few direct pieces of evidence for a causal (rather than correlative) relationship between depression and reduced serotonin function, although it is an enduring puzzle that healthy volunteers rarely show ATD induction of negative mood (Robinson & Sahakian 2008). Nonetheless, healthy subjects do show some of the cognitive sequelae of depression following ATD: On the affective go/no-go task, ATD slowed reaction times to happy stimuli (Murphy et al. 2002) and abolished the normal tendency to improve accuracy on nonshift trials (Rubinsztein et al. 2001), suggesting a role for serotonin in the ability to maintain an affective set. Recent studies have also begun to explore the subchronic effects of antidepressant administration in healthy volunteers. Harmer et al. (2004) investigated the effects of seven-day treatment with citalopram (an SSRI) or reboxetine (an NRI) in healthy volunteers. Both classes of antidepressant significantly reduced the recognition of negative facial expressions (anger and fear) and increased recall of positive emotional material. Thus, antidepressant treatments may share an early effect of mediating negative affective biases that characterize the depressive state.

Feedback Sensitivity

Depressed patients frequently ruminate over perceived failures and criticism. Neuropsychological evidence shows that patients with depression also have an exaggerated response to negative feedback during laboratory testing. An early study using two tests of working memory (delayed matching to sample) and forward planning (one-touch tower of London) found that if MDD cases responded incorrectly on a given trial (trial N), they were disproportionately likely to fail the subsequent trial (N+1) (Elliott et al. 1997b). This catastrophic response to perceived failure occurred across both tasks and could impact upon cognitive ability on any tasks that deliver performance-contingent feedback. Moreover, the effect appeared specific to depression because it was not seen in

other neuropsychiatric conditions that showed overall task impairments, such as Parkinson's disease.

The deleterious effect of negative feedback was also identified on a probabilistic reversal learning task, during which subjects attempted to learn from feedback which of two stimuli is correct. The trial-by-trial feedback ("CORRECT" or "INCORRECT") is probabilistic, such that misleading feedback is provided on 20% of trials; for example, a correct response may yield incorrect feedback. At some point during the task, the rule reverses so that the other stimulus becomes correct. To acquire and reverse the rule successfully, subjects must be able to disregard the misleading feedback. Depressed patients were more likely to reverse their responding repeatedly on trials that followed misleading false feedback (Murphy et al. 2003) (see **Figure 4**). This effect was recently replicated in unmedicated MDD cases, but Taylor Tavares et al. (2008) showed it to be absent in similarly depressed BD patients. The symptom profile of bipolar depression may be subtly distinct from MDD, with fewer cognitive symptoms (e.g., guilt) and more physiological/behavioral symptoms (e.g., psychomotor slowing) (Mitchell et al. 2001).

Taylor Tavares et al. (2008) also examined the neural correlates of the abnormal response to false feedback in MDD using fMRI. The healthy controls and BD group recruited ventrolateral and dorsomedial PFC during reversal rule shifts, and these frontal responses were attenuated in the MDD group, consistent with evidence for the hypofrontality during executive control. In addition, the controls and BD subjects show reduced amygdala activity in response to negative feedback, compared with trials given correct feedback. These signal reductions likely reflect the task requirement to ignore misleading negative feedback because the amygdala reduction correlated with the ability to ignore this feedback. The MDD group failed to show this amygdala decrease. This combination of reversal-related hypofrontality and failure to regulate the amygdala is highly consistent with the aforementioned findings of attenuated frontolimbic connectivity leading to reduced top-down control of the amygdala (Chen et al. 2008, Johnstone et al. 2007, Siegle et al. 2007).

In addition to abnormal processing of negative feedback in depression, the anhedonic symptoms of depression, where patients fail to derive enjoyment from pleasurable activities, suggest that there may also be altered processing of positively valenced information in MDD. Recent fMRI studies have indicated reductions in ventral striatal activity in MDD in response to happy facial expressions (Surguladze et al. 2005) and positive words (Epstein et al. 2006), which correlate inversely with anhedonic symptoms (Epstein et al. 2006). An elegant study by Steele et al. (2007) used a gambling task during which correct or incorrect feedback was provided to card guesses. Reaction times were used to assess the impact of feedback: Healthy controls sped up after positive feedback and slowed down on trials after negative feedback. In the healthy controls, receipt of correct feedback yielded ventral striatal activity, and receipt of negative feedback yielded anterior cingulate activity; both effects correlated with the associated change in reaction time. Both neural effects were attenuated in the MDD cases, and the changes in reaction time associated with both positive and negative feedback were correlated with a measure of anhedonia. Similarly, we have also found that hypersensitivity to loss on a gambling task was correlated with anhedonia ratings (Taylor Tavares et al. 2007). As such, anhedonia appears to reflect both a blunting of positive reinforcement processing, as well as an inability to use negative feedback to improve task performance.

As with affective processing, the effects of negative feedback are also sensitive to serotonin manipulation. A recent study from our group compared the effects of citalopram, an SSRI, and atomoxetine, an NRI, in healthy volunteers using a single-dose, placebo-controlled design (Chamberlain et al. 2006). Citalopram treatment (but not the NRI) increased the tendency to reverse responding following misleading negative feedback, mimicking the effect

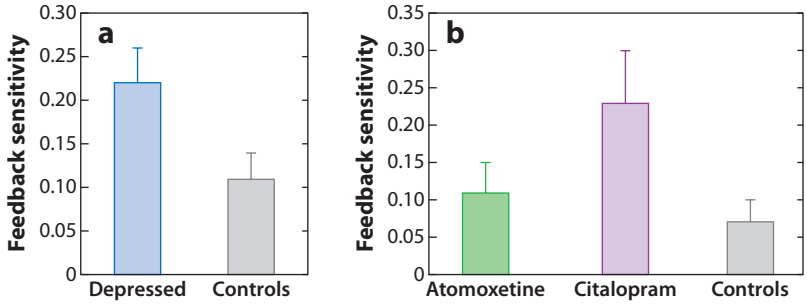

Figure 4

Abnormal response to negative feedback on the probabilistic reversal learning task. (*a*) Subjects with MDD were more likely to switch responding following misleading negative feedback. Feedback sensitivity score is the proportion of misleading negative feedback trials during which the subject inappropriately switched on the next trial. Data from Murphy et al. 2003. (*b*) The tendency to switch following misleading negative feedback was induced in healthy volunteers through single-dose administration of the selective serotonin reuptake inhibitor citalopram, but not by the noradrenaline reuptake inhibitor atomoxetine, compared with placebo. Data redrawn from Chamberlain et al. 2006.

observed in depression (Murphy et al. 2003) (see **Figure 4**). In single doses, SSRIs may differentially affect presynaptic 5-HT autoreceptors, acting to temporarily downregulate serotonin transmission. Future work is needed to explore the subchronic effects of citalopram on these measures and to examine antidepressant effects in patients with depression. Recent work has used an adapted reversal learning task to separate reversal shifts triggered by reward from reversal shifts triggered by punishment. Using the ATD procedure, serotonin depletion selectively enhanced reversal learning from punishment cues (Cools et al. 2008), consistent with theoretical notions that serotonin may signal punishment-related prediction errors (Daw et al. 2002). Collectively, these studies implicate serotonin in the modulation of affective processing and feedback sensitivity, putatively associated with the medial and ventral frontostriatal circuitry.

TREATMENTS FOR MOOD DISORDERS

First Line Interventions

Current pharmacological treatment algorithms for depression are directed at drugs that block the reuptake of serotonin (the SSRIs) and/or noradrenaline (the NRIs) from the synapse, which is thought to enhance transmission within these systems over time. Although researchers traditionally thought that the beneficial effects of these drugs occurred with prolonged (~3 weeks) treatment, recent analysis showed that beneficial effects were evident in the first week (Taylor et al. 2006), suggesting that the response is gradual and cumulative. Antidepressants likely exert early effects on emotional processing (e.g., Harmer et al. 2004), but it is likely that further time is required for patients to relearn patterns of behavior and implement them (Robinson & Sahakian 2008). Pharmacotherapy has limitations in terms of side effects and lack of response in some patients. For example, in the large STAR*D trial ($n = 2876$), only 33% of depressed patients remitted following 14 weeks of citalopram treatment, and less than half (47%) showed a beneficial response (defined as a reduction of $\geq$50% of the baseline depression rating) (Trivedi et al. 2006). Thus, other interventions (stand-alone or augmentation) need to be considered.

Psychotherapies, especially CBT, show efficacy in the treatment of depression and increasingly represent a first-line option (Butler et al. 2006). A course of CBT would typically entail 10–20 sessions, would aim to identify and challenge the dysfunctional beliefs that perpetuate

negative thinking patterns, and would provide patients with alternative ways of coping with stressful life events. Functional imaging studies have recently begun to compare the brain changes associated with recovery from depression via CBT or pharmacotherapy (Goldapple et al. 2004, Kennedy et al. 2007). For example, Kennedy et al. (2007) demonstrated a common effect of CBT and venlafaxine treatment to reduce metabolism in the orbitofrontal cortex and medial prefrontal cortex in treatment responders. In addition to these shared effects, unique effects of either modality were also apparent in the subgenual cingulate region (adjacent decreases following venlafaxine and increases following CBT) (Kennedy et al. 2007).

SSRIs are used more cautiously in BD because there is limited evidence for their efficacy in treating bipolar depression (Ghaemi et al. 2003, Sachs et al. 2007), and they can elicit manic upswings (Howland 1996). Mood stabilizers (e.g., lithium, valproate) are widely used in the treatment of BD, and psychotherapy can also be effective (Miklowitz et al. 2007), helping patients recognize early signs of relapse, improving interpersonal function, and stabilizing social routines (Frank et al. 2005).

Experimental Approaches

There is an ongoing need to explore and validate new treatments capable of targeting fronto-striatal circuitry, especially for treatment-resistant cases. Cognitive enhancing agents could augment the beneficial mood effects of traditional treatments and may also ameliorate cognitive deficits, some of which can persist into remission (e.g., Clark et al. 2002, 2005). Modafinil is one example of a cognitive enhancer that could be useful because it is already licensed for the treatment of daytime sleepiness and has a good side-effect profile (Minzenberg & Carter 2008, Sahakian & Morein-Zamir 2007). The utility of modafinil as an augmentation strategy in bipolar patients maintained on mood stabilizers was demonstrated in a six-week trial and showed significant improvements in response and remission compared with placebo (Frye et al. 2007). Future studies will be required to assess the effects of such agents on the cognitive profile in BD.

Electroconvulsive therapy (ECT) has a contentious history within psychiatry, in part given its side effects on cognitive function (Sackeim et al. 2007). In mood disorders, its efficacy is undisputed, particularly in medication-resistant cases (Geddes 2003). However, there remains a search for more targeted stimulation methods to minimize the risk of side effects such as amnesia. Transcranial magnetic stimulation (TMS) is a noninvasive intervention that involves the rapid alternation of magnetic field pulses over the scalp to trigger electrical changes in the underlying cortex. TMS to the left PFC shows medium-term antidepressant effects compared with sham stimulation (Gershon et al. 2003, Pascual-Leone et al. 1996) and is efficacious in medication-resistant cases (Avery et al. 2006). However, clinical benefits have been found at varying stimulation frequencies that are known to both excite (high-frequency TMS) and suppress (low-frequency TMS) cortical excitability. This occurrence seems paradoxical, although the effectiveness of different protocols may depend on baseline activity, such that patients with frontal hypometabolism may respond to a high-frequency protocol and vice versa (Kimbrell et al. 1999). Other aspects of the mechanism of action also remain unclear, such as the optimal location for stimulation and the dependency on distal changes elsewhere in the brain (Gershon et al. 2003).

Deep brain stimulation (DBS) is an invasive, neurosurgical alternative to TMS that also holds promise for treatment-refractory patients. In the first study of its kind, Mayberg et al. (2005) implanted DBS electrodes into the white matter tracts of subgenual cingulate region (Brodmann Area 25) bilaterally in six patients with treatment-resistant depression. Striking mood improvement was observed in the short term, and sustained remission over a six-month course of stimulation was seen in four of the six patients. Subsequent work using MRI tractography in 9 DBS responders

suggested that these benefits may be mediated by the connectivity of the subgenual region with limbic and visceromotor areas including the nucleus accumbens, amygdala, hypothalamus, and orbitofrontal cortex (Johansen-Berg et al. 2008). Clinical benefits were also reported following DBS in the nucleus accumbens (Schlaepfer et al. 2008). Although caution is warranted given the small sample sizes and lack of placebo or sham controls, DBS may provide a valuable alternative for patients with treatment-resistant depression. It is also encouraging that the rationale for this treatment was derived from functional imaging data that identified these neurobiological markers of the depressive state.

CONCLUSION

Mood disorders are associated with prominent cognitive symptoms that can be quantified with computerized neuropsychological testing. We have reviewed the extensive evidence for impairments within four domains: executive control, memory, affective processing, and feedback sensitivity. These disruptions implicate pathophysiology across a distributed neural network that includes multiple sectors of the PFC and cingulate gyrus, subcortical regions in the striatum and thalamus, and temporal lobe structures including the amygdala and hippocampus. Functional changes within this circuitry occur in depressive and manic states and can persist into periods of remission. Key components of this circuitry, including the subgenual cingulate region and hippocampus, may also display structural alterations. This circuitry represents the target of established treatments for depression, including both pharmacotherapies (e.g., SSRIs) and psychotherapies (e.g., CBT). Currently available treatments are not effective in all cases, and the continuing search for novel treatments will be aided by further understanding of the cognitive deficits and neural markers that characterize the depressive state. For severe or treatment-resistant patients, novel techniques including TMS and DBS have potential. We hope that the clinical application of biological markers rooted in the neurosciences (including genetics and neuropsychological measures) will facilitate improved disease detection, monitoring of recovery and relapse, and novel treatment directions for mood disorders (Beddington et al. 2008).

SUMMARY POINTS

1. Deficits in executive control in depression have been associated with pathophysiology in lateral aspects of the PFC.
2. Memory impairment is a robust finding that is associated with volumetric reductions in the hippocampus and may arise as a progressive consequence of depression, putatively via neurotoxic effects of increased cortisol.
3. Biases are seen in affective processing: Patients with depression show preferential processing of negative material and impaired processing of positive material.
4. Depressed patients also showed altered responses to task feedback, including an exaggerated response to negative feedback.
5. The changes in affective processing and feedback sensitivity are associated with dysregulation of limbic brain circuitry comprising the medial and orbital PFC, striatum, and amygdala. These processes are sensitive to serotonergic manipulations and may be targeted early in the course of antidepressant treatment.

FUTURE ISSUES

1. Changes in neural connectivity in depression may be particularly important in emotional regulation. Investigation of the neurochemical modulation of these interactions will carry fundamental implications for treatment.
2. Cognitive and neurobiological biomarkers can facilitate early detection and predict treatment response to prevent MDD from having a chronic relapsing course. Ultimately, it may be possible to predict which variety of treatment (e.g., SSRI versus CBT) will be most appropriate for a given patient.
3. Understanding the neural basis of resilience should help prevent depression in vulnerable groups.
4. A more thorough understanding of pharmacogenomics holds promise for the development of safe and more effective pharmacological treatments for mood disorders.

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L.C., S.R.C., and B.J.S. consult for Cambridge Cognition.

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LITERATURE CITED

Alexander GE, DeLong MR, Strick PL. 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* 9:357–81

Am. Psychiatr. Assoc. 2000. *Diagnostic and Statistical Manual of Mental Disorders—Text Revision*. Washington, DC: Am. Psychiatr. Assoc. 5th ed.

Avery DH, Holtzheimer PE 3rd, Fawaz W, Russo J, Neumaier J, et al. 2006. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol. Psychiatry* 59:187–94

Beats BC, Sahakian BJ, Levy R. 1996. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol. Med.* 26:591–603

Beck AT, Rush AJ, Shaw AF, Emery G. 1979. *Cognitive Therapy of Depression*. New York: Guilford

Beddington J, Cooper CL, Field J, Goswami U, Huppert FA, et al. 2008. The mental wealth of nations. *Nature* 455:1057–60

Bell-McGinty S, Butters MA, Meltzer CC, Greer PJ, Reynolds CF 3rd, Becker JT. 2002. Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. *Am. J. Psychiatry* 159:1424–27

Blumberg HP, Leung HC, Skudlarski P, Lacadie CM, Fredericks CA, et al. 2003. A functional magnetic resonance imaging study of bipolar disorder: state- and trait-related dysfunction in ventral prefrontal cortices. *Arch. Gen. Psychiatry* 60:601–9

Borkowska A, Rybakowski JK. 2001. Neuropsychological frontal lobe tests indicate that bipolar depressed patients are more impaired than unipolar. *Bipolar. Disord.* 3:88–94

Botteron KN, Raichle ME, Drevets WC, Heath AC, Todd RD. 2002. Volumetric reduction in left subgenual prefrontal cortex in early onset depression. *Biol. Psychiatry* 51:342–44

Bremner JD, Vythilingam M, Vermetten E, Vaccarino V, Charney DS. 2004. Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. *Am. J. Psychiatry* 161:637–45

Brittlebank AD, Scott J, Williams JM, Ferrier IN. 1993. Autobiographical memory in depression: state or trait marker? *Br. J. Psychiatry* 162:118–21

Butler AC, Chapman JE, Forman EM, Beck AT. 2006. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin. Psychol. Rev.* 26:17–31

Campbell S, Marriott M, Nahmias C, MacQueen GM. 2004. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am. J. Psychiatry* 161:598–607

Carpenter LL, Anderson GM, Pelton GH, Gudin JA, Kirwin PD, et al. 1998. Tryptophan depletion during continuous CSF sampling in healthy human subjects. *Neuropsychopharmacology* 19:26–35

Carroll BJ, Curtis GC, Mendels J. 1976. Neuroendocrine regulation in depression. II. Discrimination of depressed from nondepressed patients. *Arch. Gen. Psychiatry* 33:1051–58

Carson AJ, MacHale S, Allen K, Lawrie SM, Dennis M, et al. 2000. Depression after stroke and lesion location: a systematic review. *Lancet* 356:122–26

Chamberlain SR, Muller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. 2006. Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science* 311:861–63

Chamberlain SR, Sahakian BJ. 2004. Cognition in mania and depression: psychological models and clinical implications. *Curr. Psychiatry Rep.* 6:451–58

Chen CH, Suckling J, Ooi C, Fu CH, Williams SC, et al. 2008. Functional coupling of the amygdala in depressed patients treated with antidepressant medication. *Neuropsychopharmacology* 33:1909–18

Clark L, Iversen SD, Goodwin GM. 2002. Sustained attention deficit in bipolar disorder. *Br. J. Psychiatry* 180:313–19

Clark L, Sahakian BJ. 2006. Neuropsychological and biological approaches to understanding bipolar disorder. In *The Psychology of Bipolar Disorder*, ed. S Jones, RP Bentall, pp. 139–78. Oxford, UK: Oxford Univ. Press

Clark L, Scarna A, Goodwin GM. 2005. Impairment of executive function but not memory in first-degree relatives of patients with bipolar I disorder and in euthymic patients with unipolar depression. *Am. J. Psychiatry* 162:1980–82

Cools R, Robinson OJ, Sahakian B. 2008. Acute tryptophan depletion in healthy volunteers enhances punishment prediction but does not affect reward prediction. *Neuropsychopharmacology* 33:2291–99

Coryell W, Nopoulos P, Drevets W, Wilson T, Andreasen NC. 2005. Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. *Am. J. Psychiatry* 162:1706–12

Daw ND, Kakade S, Dayan P. 2002. Opponent interactions between serotonin and dopamine. *Neural Netw.* 15:603–16

Deckersbach T, Dougherty DD, Savage C, McMurrich S, Fischman AJ, et al. 2006. Impaired recruitment of the dorsolateral prefrontal cortex and hippocampus during encoding in bipolar disorder. *Biol. Psychiatry* 59:138–46

Drevets WC. 2000. Neuroimaging studies of mood disorders. *Biol. Psychiatry* 48:813–29

Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, et al. 1999. PET imaging of serotonin 1A receptor binding in depression. *Biol. Psychiatry* 46:1375–87

Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, et al. 1997. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386:824–27

Elliott R, Baker SC, Rogers RD, O'Leary DA, Paykel ES, et al. 1997a. Prefrontal dysfunction in depressed patients performing a complex planning task: a study using positron emission tomography. *Psychol. Med.* 27:931–42

Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ. 2002. The neural basis of mood-congruent processing biases in depression. *Arch. Gen. Psychiatry* 59:597–604

Elliott R, Sahakian BJ, Herrod JJ, Robbins TW, Paykel ES. 1997b. Abnormal response to negative feedback in unipolar depression: evidence for a diagnosis specific impairment. *J. Neurol. Neurosurg. Psychiatry* 63:74–82

Elliott R, Sahakian BJ, McKay AP, Herrod JJ, Robbins TW, Paykel ES. 1996. Neuropsychological impairments in unipolar depression: the influence of perceived failure on subsequent performance. *Psychol. Med.* 26:975–89

Epstein J, Pan H, Kocsis JH, Yang Y, Butler T, et al. 2006. Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. *Am. J. Psychiatry* 163:1784–90

Erickson K, Drevets WC, Clark L, Cannon DM, Bain EE, et al. 2005. Mood-congruent bias in affective go/no-go performance of unmedicated patients with major depressive disorder. *Am. J. Psychiatry* 162:2171–73

Fales CL, Barch DM, Rundle MM, Mintun MA, Snyder AZ, et al. 2008. Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. *Biol. Psychiatry* 63:377–84

Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, et al. 2005. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Arch. Gen. Psychiatry* 62:996–1004

Frodl TS, Koutsouleris N, Bottlender R, Born C, Jäger M, et al. 2008. Depression-related variation in brain morphology over 3 years: effects of stress? *Arch. Gen. Psychiatry* 65:1156–65

Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE Jr, et al. 2007. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am. J. Psychiatry* 164:1242–49

Fu CH, Williams SC, Cleare AJ, Brammer MJ, Walsh ND, et al. 2004. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Arch. Gen. Psychiatry* 61:877–89

Geddes J. 2003. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* 361:799–808

Gershon AA, Dannon PN, Grunhaus L. 2003. Transcranial magnetic stimulation in the treatment of depression. *Am. J. Psychiatry* 160:835–45

Ghaemi SN, Hsu DJ, Soldani F, Goodwin FK. 2003. Antidepressants in bipolar disorder: the case for caution. *Bipolar Disord.* 5:421–33

Goldapple K, Segal Z, Garson C, Lau M, Bieling P, et al. 2004. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. *Arch. Gen. Psychiatry* 61:34–41

Gorwood P, Corruble E, Falissard B, Goodwin GM. 2008. Toxic effects of depression on brain function: impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. *Am. J. Psychiatry* 165:731–39

Gould NF, Holmes MK, Fantie BD, Luckenbaugh DA, Pine DS, et al. 2007. Performance on a virtual reality spatial memory navigation task in depressed patients. *Am. J. Psychiatry* 164:516–19

Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, et al. 2003. The economic burden of depression in the United States: How did it change between 1990 and 2000? *J. Clin. Psychiatry* 64:1465–75

Haber SN, Fudge JL, McFarland NR. 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J. Neurosci.* 20:2369–82

Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM. 2004. Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *Am. J. Psychiatry* 161:1256–63

Harvey PO, Fossati P, Pochon JB, Levy R, Lebastard G, et al. 2005. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *NeuroImage* 26:860–69

Hirayasu Y, Shenton ME, Salisbury DF, Kwon JS, Wible CG, et al. 1999. Subgenual cingulate cortex volume in first-episode psychosis. *Am. J. Psychiatry* 156:1091–93

Hollon SD, Kendall PC, Lumry A. 1986. Specificity of depressotypic cognitions in clinical depression. *J. Abnorm. Psychol.* 95:52–59

Howland RH. 1996. Induction of mania with serotonin reuptake inhibitors. *J. Clin. Psychopharmacol.* 16:425–27

Hugdahl K, Rund BR, Lund A, Asbjornsen A, Egeland J, et al. 2004. Brain activation measured with fMRI during a mental arithmetic task in schizophrenia and major depression. *Am. J. Psychiatry* 161:286–93

Jaeger J, Berns S, Uzelac S, Davis-Conway S. 2006. Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Res.* 145:39–48

Johansen-Berg H, Gutman DA, Behrens TE, Matthews PM, Rushworth MF, et al. 2008. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cereb. Cortex* 18:1374–83

Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ. 2007. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *J. Neurosci.* 27:8877–84

Kennedy SH, Evans KR, Kruger S, Mayberg HS, Meyer JH, et al. 2001. Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. *Am. J. Psychiatry* 158:899–905

Kennedy SH, Konarski JZ, Segal ZV, Lau MA, Bieling PJ, et al. 2007. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. *Am. J. Psychiatry* 164:778–88

Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, et al. 1999. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biol. Psychiatry* 46:1603–13

Lembke A, Ketter TA. 2002. Impaired recognition of facial emotion in mania. *Am. J. Psychiatry* 159:302–4

Liotti M, Mayberg HS, McGinnis S, Brannan SL, Jerabek P. 2002. Unmasking disease-specific cerebral blood flow abnormalities: mood challenge in patients with remitted unipolar depression. *Am. J. Psychiatry* 159:1830–40

MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, et al. 2003. Course of illness, hippocampal function, and hippocampal volume in major depression. *Proc. Natl. Acad. Sci. USA* 100:1387–92

Manji HK, Moore GJ, Chen G. 2000. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. *Biol. Psychiatry* 48:740–54

Martinez-Aran A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea JM, et al. 2007. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord.* 9:103–13

Mayberg HS. 2003. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *Br. Med. Bull.* 65:193–207

Mayberg HS. 2007. Defining the neural circuitry of depression: toward a new nosology with therapeutic implications. *Biol. Psychiatry* 61:729–30

Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, et al. 1997. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 8:1057–61

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, et al. 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am. J. Psychiatry* 156:675–82

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, et al. 2005. Deep brain stimulation for treatment-resistant depression. *Neuron* 45:651–60

McCabe SB, Gotlib IH. 1995. Selective attention and clinical depression: performance on a deployment-of-attention task. *J. Abnorm. Psychol.* 104:241–45

McCrone P, Dhanasiri S, Patel A, Knapp M, Lawton-Smith S. 2008. *Paying the Price: The Cost of Mental Health Care in England to 2026*. London: King's Fund. **http://www.kingsfund.org.uk/publications/the_kings_fund_publications/paying_the_price.html**

McDonald WM, Richard IH, DeLong MR. 2003. Prevalence, etiology, and treatment of depression in Parkinson's disease. *Biol. Psychiatry* 54:363–75

Mega MS, Cummings JL. 1994. Frontal-subcortical circuits and neuropsychiatric disorders. *J. Neuropsychiatry Clin. Neurosci.* 6:358–70

Meyer JH, Houle S, Sagrati S, Carella A, Hussey DF, et al. 2004. Brain serotonin transporter binding potential measured with carbon 11-labeled DASB positron emission tomography: effects of major depressive episodes and severity of dysfunctional attitudes. *Arch. Gen. Psychiatry* 61:1271–79

Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Kogan JN, et al. 2007. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: results from a 9-month randomized controlled trial. *Am. J. Psychiatry* 164:1340–47

Minzenberg MJ, Carter CS. 2008. Modafinil: a review of neurochemical actions and effects on cognition. *Neuropsychopharmacology* 33:1477–502

Mitchell PB, Wilhelm K, Parker G, Austin MP, Rutgers P, Malhi GS. 2001. The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. *J. Clin. Psychiatry* 62:212–16

Murphy FC, Michael A, Robbins TW, Sahakian BJ. 2003. Neuropsychological impairment in patients with major depressive disorder: the effects of feedback on task performance. *Psychol. Med.* 33:455–67

Murphy FC, Sahakian BJ, Rubinsztein JS, Michael A, Rogers RD, et al. 1999. Emotional bias and inhibitory control processes in mania and depression. *Psychol. Med.* 29:1307–21

Okada G, Okamoto Y, Morinobu S, Yamawaki S, Yokota N. 2003. Attenuated left prefrontal activation during a verbal fluency task in patients with depression. *Neuropsychobiology* 47:21–26

Pascual-Leone A, Rubio B, Pallardo F, Catala MD. 1996. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 348:233–37

Phillips ML, Clark L, Sahakian BJ, Frank E, Kupfer DJ. 2008. Neurocognition and neuroimaging in major depressive disorder and bipolar depression: implications for treatment and functional outcome. *UK Government Foresight Project: Mental Capital and Mental Wellbeing*. **http://www.foresight.gov.uk**

Phillips ML, Drevets WC, Rauch SL, Lane R. 2003. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol. Psychiatry* 54:504–14

Robbins TW. 1998. Dissociating executive functions of the prefrontal cortex. In *The Prefrontal Cortex: Executive and Cognitive Functions*, ed. AC Roberts, TW Robbins, L Weiskrantz, pp. 117–30. Oxford: Oxford Univ. Press

Robinson OJ, Sahakian BJ. 2008. Recurrence in major depressive disorder: a neurocognitive perspective. *Psychol. Med.* 38:315–18

Robinson RG, Boston JD, Starkstein SE, Price TR. 1988. Comparison of mania and depression after brain injury: causal factors. *Am. J. Psychiatry* 145:172–78

Robinson RG, Kubos KL, Starr LB, Rao K, Price TR. 1983. Mood changes in stroke patients: relationship to lesion location. *Compr. Psychiatry* 24:555–66

Rogers MA, Kasai K, Koji M, Fukuda R, Iwanami A, et al. 2004. Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neurosci. Res.* 50:1–11

Rubinow DR, Post RM. 1992. Impaired recognition of affect in facial expression in depressed patients. *Biol. Psychiatry* 31:947–53

Rubinsztein JS, Rogers RD, Riedel WJ, Mehta MA, Robbins TW, Sahakian BJ. 2001. Acute dietary tryptophan depletion impairs maintenance of "affective set" and delayed visual recognition in healthy volunteers. *Psychopharmacology (Berlin)* 154:319–26

Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, et al. 2007. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N. Engl. J. Med.* 356:1711–22

Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. 2007. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology* 32:244–54

Sahakian B, Morein-Zamir S. 2007. Professor's little helper. *Nature* 450:1157–59

Sahay A, Hen R. 2007. Adult hippocampal neurogenesis in depression. *Nat. Neurosci.* 10:1110–15

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, et al. 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301:805–9

Sapolsky RM, Krey LC, McEwen BS. 1985. Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. *J. Neurosci.* 5:1222–27

Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, et al. 2000. Brain serotonin1A receptor binding measured by positron emission tomography with [11C]WAY-100635: effects of depression and antidepressant treatment. *Arch. Gen. Psychiatry* 57:174–80

Saxena S, Brody AL, Ho ML, Zohrabi N, Maidment KM, Baxter LR Jr. 2003. Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. *Am. J. Psychiatry* 160:522–32

Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, et al. 2008. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 33:368–77

Scott J, Stanton B, Garland A, Ferrier IN. 2000. Cognitive vulnerability in patients with bipolar disorder. *Psychol. Med.* 30:467–72

Seligman ME. 1972. Learned helplessness. *Annu. Rev. Med.* 23:407–12

Shaffer D, Gould MS, Fisher P, Trautman P, Moreau D, et al. 1996. Psychiatric diagnosis in child and adolescent suicide. *Arch. Gen. Psychiatry* 53:339–48

Sheline YI. 2003. Neuroimaging studies of mood disorder effects on the brain. *Biol. Psychiatry* 54:338–52

Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. 2001. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol. Psychiatry* 50:651–58

Sheline YI, Gado MH, Kraemer HC. 2003. Untreated depression and hippocampal volume loss. *Am. J. Psychiatry* 160:1516–18

Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. 2002. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol. Psychiatry* 51:693–707

Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME. 2007. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biol. Psychiatry* 61:198–209

Smith KA, Fairburn CG, Cowen PJ. 1997. Relapse of depression after rapid depletion of tryptophan. *Lancet* 349:915–19

Starkstein SE, Robinson RG, Price TR. 1987. Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. *Brain* 110:1045–59

Steele JD, Kumar P, Ebmeier KP. 2007. Blunted response to feedback information in depressive illness. *Brain* 130:2367–74

Stockmeier CA, Mahajan GJ, Konick LC, Overholser JC, Jurjus GJ, et al. 2004. Cellular changes in the postmortem hippocampus in major depression. *Biol. Psychiatry* 56:640–50

Surguladze S, Brammer MJ, Keedwell P, Giampietro V, Young AW, et al. 2005. A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biol. Psychiatry* 57:201–9

Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. 2006. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch. Gen. Psychiatry* 63:1217–23

Taylor Tavares JV, Clark L, Cannon DM, Erickson K, Drevets WC, Sahakian BJ. 2007. Distinct profiles of neurocognitive function in unmedicated unipolar depression and bipolar II depression. *Biol. Psychiatry* 62:917–24

Taylor Tavares JV, Clark L, Furey M, Williams GB, Sahakian BJ, Drevets W. 2008. Neural basis of abnormal response to negative feedback in mood disorders. *NeuroImage* 42:1118–26

Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, et al., STAR*D Study Team. 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am. J. Psychiatry* 163:28–40

Vataja R, Pohjasvaara T, Leppavuori A, Mantyla R, Aronen HJ, et al. 2001. Magnetic resonance imaging correlates of depression after ischemic stroke. *Arch. Gen. Psychiatry* 58:925–31

Videbech P, Ravnkilde B. 2004. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am. J. Psychiatry* 161:1957–66

Wagner G, Sinsel E, Sobanski T, Kohler S, Marinou V, et al. 2006. Cortical inefficiency in patients with unipolar depression: an event-related FMRI study with the Stroop task. *Biol. Psychiatry* 59:958–65

Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, et al. 1996. Cross-national epidemiology of major depression and bipolar disorder. *JAMA* 276:293–99

Williams WA, Shoaf SE, Hommer D, Rawlings R, Linnoila M. 1999. Effects of acute tryptophan depletion on plasma and cerebrospinal fluid tryptophan and 5-hydroxyindoleacetic acid in normal volunteers. *J. Neurochem.* 72:1641–47

Wood GE, Young LT, Reagan LP, Chen B, McEwen BS. 2004. Stress-induced structural remodeling in hippocampus: prevention by lithium treatment. *Proc. Natl. Acad. Sci. USA* 101:3973–78

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