

# Cognition in Mania and Depression: Psychological Models and Clinical Implications

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Affective disorders, including bipolar disorder and major depressive disorder, are highly prevalent throughout the world and are extremely disabling. Diagnostic and Statistical Manual criteria and psychological models strongly implicate cognitive dysfunctions as being integral to our understanding of these disorders. We review the findings from studies that have used neurocognitive tests and functional imaging techniques to explore abnormal cognition in affective disorders. In particular, we highlight the evidence for cognitive dysfunctions that persist into full clinical remission, and the recent trend toward the use of “hot” processing tasks, involving emotionally charged stimuli, as a means of differentiating between the cognitive underpinnings of mania and depression. The clinical relevance of these developments is discussed.

## Introduction

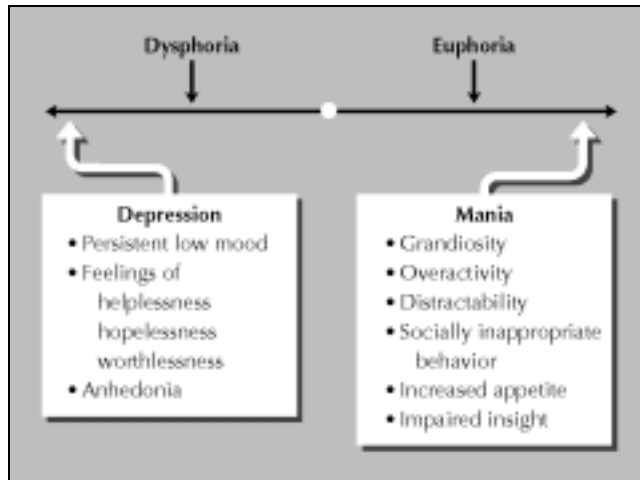
Affective disorders are prevalent psychiatric conditions collectively accounting for more disability than any other cause worldwide, according to World Health Organization Years Lived with Disability measures [1]. The economic burden of depression is estimated at \$44 billion per year in the United States [2], and the treatment of depression currently costs the taxpayers in the United Kingdom at least £370 million per year [3]. Cognitive abnormalities are central to the diagnosis of these disorders according to the Diagnostic and Statistical Manual IV (DSM-IV) [4]. Distractibility and excessive involvement in pleasurable activities that have a high potential for painful consequences are included in the diagnostic criteria for manic episodes, and diminished ability to concentrate and indecisiveness are included in the criteria for major depressive disorder (MDD). This commentary aims to bring the reader up-to-

date with recent neurocognitive findings in affective disorders, with particular reference to exciting future research directions and treatment implications.

## Psychological Models: Affect and Cognitive Dysfunction

The emotional states of people with mania and depression can be considered as being at two extremes of an affective spectrum (Fig. 1). The position of an individual on this spectrum can fluctuate in response to life events. We may tend toward euphoria in response to good news such as being promoted at work, or toward sadness in response to relationship break-ups. However, the key differences between the variations in mood that we all experience and the two extremes of mania and depression are that these states are more persistent and are severely debilitating. The incidence of depression is considerably higher in women than men, and this disparity between the genders manifests from adolescence onward [5]. The underlying etiology of psychiatric disorders often is difficult to model, and it is necessary to “fractionate out” the role of genetic variations and mutations, gene-gene interactions, environmental factors, and the interaction of genes with the environment [6,7]. Though some studies have attempted to identify sociodemographic factors contributing to the differing incidence rates between males and females, no clear factors have been identified [8]. It has been suggested that social attitudes toward women and the effects of estrogen on the hypothalamo-pituitary-adrenal (HPA) axis may be important [9,10].

Even before the development of sophisticated cognitive testing batteries and neuroimaging tools, cognitive dysfunction was held to be integral to our understanding of affective disorders according to psychological approaches, including the Learned Helplessness [11] and Learned Hopelessness (attributional) [12] models. According to Beck's Cognitive Model [13,14], negative automatic schema develop during early life and are activated by stressful negative events, leading to the triad of negative beliefs toward self, world, and future, and systematic errors in logic (or cognition). Psychological models have contributed to the development of cognitive therapies [13,14]. These typically focus on the interplay between cognitions,



**Figure 1.** The affective spectrum. An individual's position on the affective spectrum is determined by genetic, social, and other factors and can fluctuate in response to life events. True depression and mania are seen as polar ends of the spectrum.

affect, and behavior, examine evidence for and against key beliefs, and encourage patients to try alternative conceptualizations. Various incarnations of cognitive therapy are used in the modern treatment setting [15,16].

### Neurocognitive Testing

Given the centrality of cognitive dysfunction to psychological models of depression and DSM-IV diagnosis, it is logical to ask whether cognitive dysfunction can be shown in “laboratory-based” cognitive tasks. Investigations in the 1980s identified deficits in the retrieval of word lists from memory in people with depression [17–20], and the classic Wisconsin Card Sorting Test [21] showed cognitive inflexibility in these patients [22–24]. However, these measures are difficult to interpret as they confound multiple cognitive domains, and so there is an ongoing need to develop more specific diagnostic tools [25••]. The development of theoretically based cognitive tests, such as those in the Cambridge Neuropsychological Test Automated Battery [26], has clarified our understanding and allowed for a more cohesive approach. It has been possible to make comparisons with other psychiatric groups and patients with focal neurosurgical lesions. Studies have identified deficits across a range of cognitive functions in mania [27,28•,29,30] and depression [31–33] on measures of attention, executive functioning, memory, and psychomotor speed. These findings are reviewed elsewhere [34••]. Attentional deficits can be contrasted with DSM-IV “reduced ability to think or concentrate” in a depressive episode, and the “flight of ideas” and “distractibility” in a manic episode. Likewise, psychomotor speed problems shown during cognitive tasks may relate to the “psychomo-

tor agitation or retardation” during depressive episodes. Affective disorders are somewhat heterogenous in presentation, and DSM-IV allows for some flexibility within the diagnostic criteria. In the future it may be possible to subclassify these disorders on the basis of neurocognitive dysfunctions found in particular patients.

### Functional and Structural Brain Abnormalities

Brain imaging techniques have been used to identify neurobiological substrates underlying affective disorders. Abnormal baseline metabolism and regional blood flow in depressive patients has been identified in medial and orbital prefrontal cortex, mesiotemporal cortex, striatum, amygdala, and thalamus [35,36••,37–39,40•]. The neurobiological substrates of mania have been less thoroughly explored to date, but similar brain regions are implicated [41–43]. Cortical and subcortical neural structures form distinct anatomical and functional loops that can be considered to have different specializations [44]. Successful psychotherapeutic interventions seem to normalize activity within these aberrant circuits [45,46].

Traumatic brain injury and stroke (ischemic brain damage) are associated with the onset of a diverse range of neurological dysfunctions, particularly depression [47,48]. Additionally, depression is a common comorbidity in Parkinson's disease [49] and Huntington's disease [50]. All of these disorders involve brain damage, and depression may arise because of the psychosocial effects of these disabling conditions and neuropathological changes to structures within relevant basal ganglia-thalamocortical loops [51]. The mechanisms are elusive, but represent important potential therapeutic targets, especially in elderly patients in whom cognitive impairment may exacerbate deficits in functional outcome. For example, there is increasing evidence that cognitive dysfunction in depression is disproportionately worse in older patients [52,53], and white matter lesions in cortical regions, including anterior cingulate and orbitofrontal cortex, are associated with late-onset depression and depression in the elderly [54–59,60•]. It is unclear whether these white matter lesions are attributable to cerebrovascular disease or some other mechanism [61,62], but they appear to be associated with a poorer prognosis [56,63,64]. Structural imaging is important in elderly patients with new-onset affective disorder because depression is more likely to be secondary to other medical conditions (cerebrovascular disease or tumor) for which non-psychiatric interventions may be available to limit further neurological damage. More severe brain dysfunction in elderly patients with depression may necessitate the careful augmentation of the usual pharmacological treatments with agents such as methylphenidate or modafinil [65–67].

## Modulation of Cognition by Cortisol: is Hypothalamo-Pituitary-Adrenal Axis Dysfunction Important?

The HPA axis is implicated in chronic stress responses in animals and humans [68,69], and often is dysfunctional in patients with affective disorders [70–77] in whom it seems to be associated with increased rates of relapse and risk of suicide [78–80]. Frequent findings include raised baseline plasma cortisol and corticotrophin-releasing hormone, blunted adrenocorticotrophic hormone response to corticotrophin-releasing hormone, and a failure of the HPA axis to respond appropriately to administration of dexamethasone [79,81–86]. There is evidence for altered volumes of pituitary and adrenal glands in some cases [87–90], and these findings may relate to cellular hypertrophy and excessive hormone secretion. The administration of glucocorticoids in animals exacerbates ischemic neuronal damage in the hippocampus [91–93], and HPA axis function has been shown to modulate serotonin (5-HT 1A) receptor expression in the same brain region [94–98]. Acute administration of cortisol induces memory and recall impairments in healthy volunteers that in many ways mimic some of the changes found in depression [99–101], and it is likely that cortisol mediates some of the cognitive characteristics of mania and depression. It is tempting to speculate that repeated brain exposure to high cortisol levels may contribute to neuronal damage in humans. Consistent with neuronal loss, there is evidence for reduced hippocampal and cortical matter volumes in affective disorder versus control subjects [102,103]. Pharmacological intervention may be protective against such volume reductions [104]. HPA axis dysregulation worsens with increasing age in depressed patients and controls, as assessed by clinical and functional imaging measures [105].

Many researchers have proposed that HPA-axis-modifying pharmacological agents may have a role to play in the treatment of affective disorder [79,106–111], but the application has been limited clinically by the significant side-effect profiles [110]. Some antidepressant medications have been found to exert HPA-modulating effects indirectly [112–114], and there are complex interrelationships between the HPA axis and serotonergic transmitter system [115]. Identifying HPA axis effects of acute and chronic antidepressive administration and relating these to cognitive characteristics should be a focal area for research: it may be that some medications serve to worsen dysregulation, whereas others are capable of normalizing the axis. Greater understanding of these effects may contribute to the development of more advanced treatment algorithms, and a fuller understanding of physiological factors involved in poor prognostic outcome. This is of particular importance because HPA axis abnormalities have been implicated in developmental models of mood disorders [116–122].

## Differentiating Cognitive Characteristics in Mania and Depression: Hot Processing

Various studies have been done to compare the cognitive abnormalities found in mania with those found in depres-

sion. Early studies assessed cognitive performance during acute episodes on various measures including attention, memory, visuospatial function, the Wisconsin Card Sorting Test [21], and the Wechsler Adult Intelligence Scale [123]. Though impairments were found in depression and mania on many of these measures, no differential pattern of cognitive characteristics was identified. By considering how mania and depression differ on a syndromic behavioral level, there are clues as to where we may expect differential cognitive characteristics to manifest. Both disorders are debilitating and characterized by diverse deficits in daily functioning [124,125], but mania and depression are considered to be at opposite ends of the affective (mood) spectrum. Multiple empirical studies have shown mood-dependent biases in information processing in depression. For example, when patients are asked to recall pleasant or unpleasant experiences from their past in response to cue words, they recall unpleasant memories more readily and rapidly than pleasant memories and the extent of this difference is dependent on clinical disease severity [126]. Therefore, it seems logical that differential cognitive characteristics should manifest on cognitive tasks that are affectively colored or emotionally “hot” [127••]. This has been found to be true for neurocognitive tasks exploring attentional processing bias, abnormal response to negative feedback, and altered decision making [28•,29,31,33,128–130,131•]. It is important to objectively measure the core cognitive deficits in depression, including dysfunctional attitudes, negative automatic thoughts, and ruminations. Much of our research work is geared toward developing objective tests so that we can detect disease onset, monitor recovery and relapse, and assess the efficacy of established and novel psychological and pharmacological treatments. This is especially important because failure to achieve full recovery and protection against future episodes still is common in the treatment of affective disorders [25••].

### Attentional processing bias

In Go/No-Go Tasks, subjects are asked to give a motor response as quickly as possible to words that fit into a particular category (target words), and to withhold a motor response to words in other categories (distractor words). Using a “hot” version of this task, with “happy” and “sad” sets of words, differential processing bias between mania and depression has been shown [28•]. Patients with depression respond more rapidly to sad versus happy words, and manic patients respond more rapidly to happy versus sad words. These findings fit within the affective spectrum framework discussed previously. Additionally, manic patients cannot withhold their responses on this task. This result may relate to decision making impairments found on other tasks. The Affective Go/No-Go Task has been coupled with concurrent brain imaging to identify the neural substrates of processing in different target word conditions [130,132••]. In healthy control subjects, responding to emotional “hot” words compared with neu-

tral words leads to differential neural responses in the subgenual cingulate region [130]. This region is known to function abnormally in depression and mania [37,38,133], and is involved in the directing of attention in situations of emotional significance [134,135]. Patients with depression when compared with control subjects show elevated neural responses to sad targets in the rostral anterior cingulate extending to anterior medial prefrontal cortex [132••], reaffirming the importance of medial prefrontal cortical regions in emotional processing [37,40•]. Patients with depression also show a differential neural response to sad distractors in the right lateral orbitofrontal cortex [132••], a region known to be important in behavioral inhibition processes. Collectively, these findings are consistent with attentional bias toward sad stimuli, and the grabbing of attention by sad distractor words, in patients with depression. Such dysfunctions can be linked to the underlying neural substrates discussed previously.

### Abnormal response to negative feedback

Novel cognitive tasks have shed light on abnormal responses to negative feedback in affective disorders, including the Delayed Matching-To-Sample Test of Recognition Memory (DMTS) and New Tower of London test of planning (NTOL) [26]. Although both are dependent on a distributed neural network, NTOL seems dependent on more frontal cortical regions, whereas DMTS seems more dependent on more posterior cortical regions [128,136]. Given the cognitive distortions central to Beck's Cognitive model [13,14], it is interesting to consider whether the performance of depressed patients on cognitive tasks is affected when they are informed that their response on a previous trial was wrong (when they are given negative feedback). Indeed, the performance of patients with depression is impaired on NTOL and DMTS trials when negative feedback is given, relative to control subjects [128,129]. An abnormal response to negative feedback also has been identified in geriatric depression using a different task [137•]. Although patients with depression, schizophrenia, and Parkinson's disease all are similarly impaired in the percentage of problems correct in NTOL, only patients with depression show a significantly increased risk of failing a problem if they have failed the previous problem. False negative feedback (feedback that a subject was wrong when they responded correctly on a previous trial) on a visual discrimination and reversal task [33] also selectively impairs depressed patients' performance on the subsequent trial.

### Altered decision making

Patients with mania often have excessive involvement in pleasurable activities carrying a high potential for harmful consequences, such as erratic shopping sprees or making unwise business decisions. They show poor decision making similar to patients with brain lesions in regions including the orbitofrontal and/or ventromedial prefrontal

cortex, secondary to trauma or possibly drug abuse [138–144]. Patients with brain damage in these regions often show normal performance on cognitive tasks of learning, memory, and executive function, but deficits on cognitive gambling tasks [139–141,145]. In the Cambridge Decision Making Task, subjects are asked to win as many points as possible by placing bets based on variably-weighted probabilities. A study in healthy control subjects has shown that this task is dependent on right orbitofrontal and inferior prefrontal convexity cortex activation [131•]. When the performance of manic patients, depressed patients, and control subjects is contrasted, it is found that manic patients make suboptimal decisions dependent on the clinical severity of mania according to Young's mania score [29,146,147]. An imaging study has shown that manic patients performing this task show different neural activities in regions including dorsal anterior cingulate, frontal polar, and right inferior frontal cortex, compared with control subjects [131•].

### Residual Cognitive Deficits

Patients with a history of affective disorder have been found to have residual cognitive deficits that persist even when they are considered to be fully recovered clinically [52,148–154]. Core residual cognitive dysfunctions seem to include psychomotor slowing, impaired visual recognition memory, and impaired sustained attention. Residual cognitive deficits in psychiatric patients with affective disorders may prove to be the greatest barrier to rehabilitation, as has been found in schizophrenia [27,34••,124]. In contrast to the broad and variable cognitive deficits found during episodes of mania and depression, deficits in remission seem to be more specific in nature. By identifying the neural substrates responsible for these residual impairments [155], it will be possible to seek out novel pharmacological agents capable of reversing these residual deficits, thereby helping to overcome rehabilitation barriers.

### Conclusions

Affective disorders are prevalent, debilitating, and socioeconomically costly. Cognitive dysfunction is central to our understanding of these disorders on many levels: in terms of behavioral symptomatology, DSM-IV diagnosis, and psychological approaches. Imaging techniques have been used to identify structural and metabolic abnormalities in specific brain regions in the resting state. With the development of theoretically based neurocognitive testing, cognitive traits have been identified that are common to mania and depression, capable of differentiating between mania and depression, and found in remission. These findings have been coupled with functional neuroimaging to identify important neural substrates of task performance. Macroscopic "structural" lesions may contribute to these cognitive dysfunctions in older patients (in whom white

matter lesions often are seen) and in patients with basal ganglia disorders and comorbid depression (including Parkinson's disease and Huntington's disease). Augmentation of the usual pharmacological intervention with agents such as modafinil may be appropriate in these cases. Cortisol is involved in the modulation of aspects of cognition, and HPA axis dysfunction is a frequent finding in affective disorders. Medications acting directly on this axis often have significant side effects, though increasingly selective HPA axis modifying medications may become available in the near future. Mania and depression are considered to be at two polar ends of an affective spectrum, and cognitive characteristics differentiating between them are found on "hot" processing tasks examining attentional processing bias, effects of negative feedback, and decision making. Residual persisting cognitive deficits are found in euthymic and recovered depressive patients, and represent an important barrier in the rehabilitation process that may be susceptible to treatment with novel pharmacological agents. Collectively, the findings are suggestive of exciting potential therapeutic directions, and ultimately may contribute toward the development of advanced treatment algorithms capable of selecting psychotherapeutic interventions on the basis of cognitive dysfunction in individual patients.

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