The Neuropsychology of Mood Disorders

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Cognitive dysfunction is central to our understanding of mood disorders in terms of patient experiences, *Diagnostic and Statistical Manual of Mental Disorders* criteria, and psychological models. In this article, we highlight key findings from studies that have used neuropsychological tests and functional neuroimaging techniques to explore cognitive dysfunction in patients with depression and mania. In particular, we focus on affective processing bias, abnormal response to negative feedback, and decision making. Results are discussed in the context of current conceptualizations of dysfunctional neural circuitry, and in relation to important clinical and research implications.

Introduction

Mood disorders, including major depressive disorder and mania, are prevalent and debilitating conditions that are expected to account for greater burden of disease in developed countries than any other cause by 2020, including ischemic heart disease [1,2]. There are significant economic and social costs to these conditions. The annual economic cost of manic-depressive illnesses has been estimated to be at least $45 billion in the United States and £2 billion in the United Kingdom [3,4]. This commentary aims to bring the reader up to date with underlying neuropsychological abnormalities that have been identified in patients with mood disorders. We begin by discussing the centrality of cognitive dysfunction to our understanding of mood disorders, and then move on to provide an overview of current conceptualizations of dysfunctional brain circuitry. Within this framework, we discuss neuropsychological findings with a focus on affective processing bias, abnormal response to negative feedback, and decision making. We finish by summarizing the clinical and research implications of these important developments.

Diagnostic Criteria and Psychological Models

Cognitive abnormalities are suggested by the daily life experiences of patients with mood disorders, and are integral to the diagnostic criteria for depressive and manic episodes according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*). The criteria for depression include diminished ability to concentrate and indecisiveness, and criteria for mania include distractibility and excessive involvement in pleasurable activities that have a high potential for painful consequences. When one considers the various psychological models that have been put forth to describe depression, cognitive distortions or abnormalities also are evident. In the Learned Helplessness model, life experiences lead to patients accepting that their actions cannot influence outcomes (a state of helplessness), which retards motivation and cognitive learning processes [5]. In the Attribution Model of Seligman et al. [6], patients with depression attribute the causes of perceived failures inappropriately to internal, global, and stable factors. For example, a depressed patient may think, "I failed that exam because I am useless at all exams and will always be" rather than "I failed that one exam because it was tough, other people failed it, too, and I can work harder in the future." According to Beck's Cognitive model, adverse events during childhood lead to the formation of negative automatic cognitive schemata, which are activated by stressors later in life [7]. In turn, Beck suggests that these negative schemata drive cognitive distortions such as selective abstraction, which is the tendency to disregard positive comments and place great emphasis on criticisms. Cognitive distortions, in turn, contribute to the maintenance of negativity directed at the self, world, and future. Psychological approaches such as these have led to the development of cognitive therapies that train patients to focus on the interplay among cognitions, affect (mood), and behavior; to examine evidence for and against key beliefs; and to try alternative conceptualizations [8].

Neural Circuitry

Given that cognitive abnormalities are evident in patients with mood disorders, it is necessary to question whether there are underlying brain abnormalities that may contribute to these findings. The clarification of overlapping and distinct neural involvement between psychiatric conditions may shed light on etiologic contributions, novel treatment directions, and more appropriate diagnostic classification systems [9••]. Furthermore, an understanding of neural involvement in mood disorders is relevant to selecting appropriately sensitive neuropsychological tests, and to interpreting findings from such tests [10••].

Functional neuroimaging studies in depressed patients have shown abnormalities in regions including medial and orbital prefrontal cortex, mesiotemporal cortex, striatum, amygdala, and thalamus [11,12,13••]. The neurobiological substrates of mania have been less thoroughly explored, but similar brain regions are implicated [14,15]. Cortical and subcortical neural structures form circuits that can be considered to have distinct functional specializations [16]. To date, the focus in people with mood disorders has been on the "affective" orbitofrontal loop connecting structures such as anterior cingulate and orbitofrontal cortices to basal ganglia (Fig. 1). Pretreatment metabolic activity in this circuit has been found to be predictive of likely pharmacologic treatment response, and to normalize in response to successful drug intervention [18,19]. Psychological therapy also seems to normalize these neural dysfunctions in a similar fashion [20].

There is additional evidence implicating these neural regions in the manifestation of mood disorder symptomatology. Direct damage to structures within the affective loop, such as from trauma or stroke, can lead to depressive or manic symptoms developing de novo in people without a history of psychiatric illness. Although there is a reactive contribution, the frequency of depression after brain injury is higher than anticipated, and damage specific to the orbitofrontal cortex can lead to the "disinhibition" syndrome, which is a persistent manic-like state [21]. Additionally, white matter signal hyperintensities often are reported within orbitofrontal loop structures in older depressed patients, and these are associated with poorer prognostic outcome [22]. Neuropsychiatric conditions with established involvement of orbitofrontal loop circuitry, such as obsessive-compulsive disorder and Huntington's disease, show unexpectedly high comorbidity with depression [9••,23].

The hypothalamic-pituitary-adrenal (HPA) axis is implicated in chronic stress responses in animals and humans [24], and often is functionally abnormal in patients with mood disorders [25–27]. HPA abnormalities may precede the development of mood episodes and thereby act as a developmental "risk factor" for the later development of disorders [28]. Frequent findings in patients with mood disorders include raised baseline plasma cortisol and corticotrophin-releasing hormone, blunted adrenocorticotropic hormone response to corticotrophin-releasing hormone, and a failure of the HPA axis to respond appropriately to administration of dexamethasone. There is evidence for altered volumes of pituitary and adrenal glands in some cases. These findings may relate to cellular hypertrophy and excessive hormone secretion [29–31]. The administration of glucocorticoids in animals exacerbates ischemic neuronal damage in the hippocampus [32], and HPA axis function has been shown to modulate serotonin (5-HT 1A) receptor expression in the same brain region [33–37]. Acute administration of cortisol induces memory and recall impairments in healthy volunteers that in many ways mimic some of the changes found in depression [38,39], and it is likely that the HPA axis is implicated in some of the cognitive characteristics of mania and depression. Classic drugs capable of specifically targeting the HPA axis are associated with unacceptable side effects [40,41]. However, this axis represents a key target for novel drugs, and it is noteworthy that selective serotonin reuptake inhibitors exert effects on this axis indirectly [42].

Neuropsychological testing

Early neuropsychological investigations in the 1980s showed deficits in cognitive flexibility and the retrieval of word lists in patients with mood disorders [43,44], but more recently, it has been possible to develop computerized diagnostic tools that hold advantages over pen-and-paper approaches. Theoretically based cognitive tests, such as those in the Cambridge Neuropsychological Test Automated Battery [45], allow for the dissection of different domains of cognition and are sensitive to neural dysfunction in the affective loop circuit. Many studies using such tasks have identified deficits across a broad range of cognitive functions in mania and depression, especially on measures of attention, executive planning, memory, and psychomotor speed [46]. Attentional deficits can be linked with the *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 "psychomotor agitation or retardation" during depressive episodes. However, it is important to question whether the cognitive deficits reported can be explained by more fundamental impairment in cognition such as affective processing bias, abnormal response to feedback, or impulsivity. Much of our research work is geared toward developing objective tests so that we can better detect disease onset, monitor recovery and relapse, and assess the efficacy of established and novel psychological and pharmacologic treatments. This is especially important because failure to achieve full recovery and protection against future episodes still is common in the treatment of mood disorders [47].

Affective processing bias

Depression and mania are associated with significant impairments in social and occupational functioning, but they differ fundamentally in terms of affect. The emotional states of people with depression and mania can be considered to represent two poles of an affective spectrum [23]. 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 extreme polarities on this spectrum are pathologic: They tend to be persistent, debilitating, and recurring. Depressed patients show the triad of negativity toward self, world, and future, whereas manic patients are grandiose and display positive, and often unrealistic, expectations and socially inappropriate behavior. Consistent with affective processing biases existing in mood disorders, people with depression show excessive recall of negative autobiographical material [48,49] and impaired recognition of happy facial expressions, whereas manic patients are impaired in recognizing negative facial expressions (including sad faces) [50].

Objective neuropsychological tests have been used to explore affective processing biases in patients with mood disorders. 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 version of this task with "happy" and "sad" sets of words (the Affective Go/No-Go test), differential processing bias between mania and depression has been shown [51]. In a seminal study, patients with depression responded more rapidly to sad versus happy words, and manic patients responded more rapidly to happy versus sad words. These findings fit within the affective spectrum framework discussed previously. In addition to this positive reaction time bias on the task, manic patients made increased numbers of commission errors (inappropriate responses to distractor words) consistent with additional problems with impulsivity.

The Affective Go/No-Go test has been used in neuroimaging studies to clarify the involvement of specific brain regions. In healthy control subjects, responding to emotional words compared with neutral words leads to differential neural responses in the subgenual cingulate region [52]. This region is critically implicated in mood-cognition interactions, and is functionally hypoactive in familial depressive patients [53]. In comparison to control subjects, depressed patients undertaking the Affective Go/No-Go test show elevated neural responses to sad targets in the rostral anterior cingulate extending to the anterior medial prefrontal cortex [54], reaffirming the importance of these regions in emotional processing. Patients with depression also show a differential neural response to sad distractors in the right lateral orbitofrontal cortex, a region known to be important in behavioral inhibition processes. In another study, manic patients also have been found to show abnormal activation in these neural regions implicated in mood-cognition interactions [55].

Abnormal response to negative feedback

Depressed patients are unduly negative about perceived failures in life, and tend to ruminate over these perceived failures rather than dismiss them as most people would do. This is consistent with the cognitive distortions and triad of negativity directed toward the self, world, and future discussed previously in the context of Beck's cognitive model. It is important to question whether catastrophic responses to perceived failures [56] contribute to impaired performance on neuropsychological tests in depressed patients.

Two tests that have been found to be sensitive to catastrophic responses to failure in depression include the New Tower of London test of planning and Delayed Matching to Sample test of memory from the Cambridge Neuropsychological Test Automated Battery [45]. Both are dependent on distributed neural networks, but the New Tower of London test seems dependent on more frontal regions compared with the Delayed Matching to Sample test [56]. In terms of the proportion of problems solved correctly at the first attempt, patients with depression are similarly impaired to patients with other conditions such as schizophrenia and Parkinson's disease on both of these tests. However, only depressed patients show a catastrophic response to failure: The probability of failing a problem (problem N) given that the previous problem (N-1) was failed has been found to be significantly raised in depression only [57]. An abnormal response to negative feedback also has been identified in geriatric patients with depression using a different task [58]. False negative feedback (ie, being informed by the computer that the previous response was incorrect when it was correct) also impairs depressed patients' performance, as exemplified by findings on a visual discrimination and reversal task known to be dependent on affective loop circuitry [59,60]. This pathologic response to perceived failures may contribute to the state of hopelessness and loss of interest in day-to-day activities experienced by patients with depression.

Decision making

Patients with mania often show excessive involvement in pleasurable activities carrying a high potential for harmful consequences, such as erratic shopping sprees or making unwise business decisions. They show impulsive decision making similar to that found in patients with orbitofrontal cortex lesions (the "disinhibition" syndrome) [61]. Patients with brain damage in this region often show normal performance on cognitive tasks of learning, memory, and executive function, but deficits on cognitive gambling tasks [62–64]. In the Cambridge Decision Making test, subjects are asked to win as many points as possible by placing bets based on variably weighted probabilities. This test activates right orbitofrontal and inferior prefrontal cortices in healthy volunteers [65]. Depressed and manic patients show suboptimal gambling strategies on this task in that they collect fewer points than control subjects. However, only manic patients show an impulsive response style: They make abnormally high numbers of irrational choices, whereas depressed patients do not [66]. The extent of this impulsive response style has been found to correlate with the severity of mania according to Young's rating scale. In a neuroimaging study using an adapted version of this task, manic patients showed different neural activities in regions including dorsal anterior cingulate, frontal polar, and right inferior frontal cortex compared with control subjects [67]. The extent of

abnormal cingulate activation was found to correlate with manic symptom severity, again supporting a critical link between impulsive decision making and manic symptom expression.

Residual cognitive deficits

Patients with a history of depression or mania have been found to have residual cognitive deficits that persist even when they are considered to be fully recovered clinically, including psychomotor slowing, impaired memory, and impaired sustained attention [68–71]. By examining the cumulative effects of recurrent mood episodes on cognition (eg, by comparing with first-episode cases), it may soon be possible to clarify the etiologic contributions [72], and to seek out novel pharmacologic agents capable of preventing or reversing these residual deficits. This is important because persisting deficits are likely to interfere with ability of patients to make full functional recoveries, as has been found to be the case in the treatment of schizophrenia.

Conclusions

Mood disorders are prevalent, debilitating, and costly. Cognitive dysfunction is central to our understanding of these disorders on many levels: in terms of patient experiences, *DSM-IV* diagnoses, psychological approaches, and findings on objective tests. Several tiers of evidence implicate dysfunction within the affective orbitofrontal loop circuit, and abnormalities are found on cognitive tests dependent on this neurocircuitry. Patients with depression show an attentional bias toward sad stimuli, and manic patients show a bias toward happy stimuli plus additional problems with motor impulsivity on the Affective Go/No-Go test. Depressed patients show an abnormal response to negative feedback on various tests consistent with catastrophic responses to perceived failures. Manic patients show impulsive decision making on the Cambridge gamble test, the extent of which has been found to correlate with symptom severity. 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 pharmacologic agents. Key focal areas for ongoing research include 1) the search for intermediate "brain-based" markers of disease (endophenotypes) that may help elucidate the etiology and optimize disease assessment and tracking [9••]; 2) clarify cognitive effects of psychiatric medications and relationship with symptom amelioration; and 3) compare neuropsychological profiles between conditions to aid development of disease classification systems and understanding of neuropathology.

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Figure 1. The affective orbitofrontal loop. Abnormalities in this circuit are implicated in depression, mania, and other neuropsychiatric conditions such as obsessive-compulsive disorder [16,17}.