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Cognitive and neurological impairment in mood disorders

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Mood disorders are common psychiatric illnesses that represent a major cause of disability and mortality worldwide. It is estimated that 8% to 20% of the population will experience a depressive episode at some point in their lives [1]. Of those individuals with symptoms so severe as to require hospitalization, 15% will go on to commit suicide.

Mood disorders are characterized by conspicuous disturbances in emotional disposition (ie, extreme lows [depression] or highs [mania]). The lack of inability to enjoy what once was pleasurable (anhedonia) is also a primary symptom and may occur during major depression in place of depressed mood. Expansive mood can present in bipolar disorder, often accompanied or replaced by irritability. Boxes 1 and 2 show Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [2] diagnostic criteria for these two disorders. Patients with major depression need to experience symptoms for 2 or more weeks to meet criteria; remission may be obtained spontaneously or with antidepressant medication often combined with psychotherapy. Some patients, however, develop a chronic course despite medication treatment. Patients with bipolar disorder type I experience periods of heightened energy, elevated mood, or irritability for a period of at least 1 week (or shorter if hospitalized during this time). Treatment is often somatic, consisting of neuroleptics, mood stabilizers, or electroconvulsive therapy.

Other symptoms accompany these mood disturbances, such as disruptions in normal sleep, appetite, and psychomotor functions. Delusions and hallucinations may be present, especially in relation to depressive thoughts (eg, pertaining to worthlessness or excessive guilt). Neurocognitive changes also occur. Measurable decreases in attention, executive function, and recall memory have been observed in patients with mood disorders. In major depression, cognitive impairment can be severe and global, sometimes meeting criteria for dementia [3]. In the acute phase of bipolar disorder, impairment of cognition may progress to a stuporous state. Other symptoms include motor impairments, which cover a wide range of symptoms. They can manifest themselves as abnormal involuntary disturbances that interrupt a patient's daily activities. They can escalate to a level of extreme psychomotor retardation (retarded catatonia) or, alternatively, agitation (agitated catatonia). The latter can be life-threatening if not treated in time because of elevated creatinine levels (secondary to muscle breakdown) and subsequent acute renal failure. Within these broad descriptions of deficits, symptoms of mood disorders can be divided into three primary domains: psychological and vegetative signs and symptoms, neurocognitive deficits, and neurological abnormalities.

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*Depressed mood or anhedonia must be one of the five symptoms. In addition to these criteria, symptoms include a significant drop in social or occupational function, and they are not better accounted for by other factors, such as substance abuse or a general medical condition.
Data from Diagnostic and Statistical Manual for Mental Disorders, 4th edition.

Research has shown that the relationships between mood and cognition, as that between mood and movement, are dynamic ones, with components that are trait-dependent and others that are state-dependent. This article discusses state- and trait-related changes in cognitive and neurological function that have been associated with depressed, manic, and euthymic phases of mood disorders. Because of their relatively static nature, trait characteristics of cognitive and neurological manifestations may provide insights into core brain abnormalities that give rise to severe mood disorders. The article also reviews evidence from brain imaging studies that point to specific neural systems that may underlie cognitive deficits seen in unipolar and bipolar disorders.

Cognitive deficits

Cognitive deficits within mood disorders have been studied extensively. Although results have not always been consistent, an overall pattern of specific impairments has become evident. In general, unipolar and bipolar patients have shown impaired performance in tests of attention, executive function, and memory. Increased cognitive dysfunction often is associated with greater symptom severity. Nevertheless, cognitive deficits persist during the euthymic/remitted states, indicating that some types of cognitive processing deficits represent fundamental trait characteristics. Examining deficits during remission allows researchers to better characterize the nature and course of nonaffective symptoms associated with mood disorders.

The study of the relation between impaired cognition and mood is complicated by the subset of patients who present for the first time to a practitioner with complaints of mood (often depression) and then go on to develop Alzheimer's Disease (AD) [3]. Evidence that cognitive decline might develop in conjunction with mood disorders recently has been confirmed. A 7-year study followed more than 600 healthy elderly (greater than 64 years old) clergy on measures of mood and cognition [4]. Participants with no depressive symptoms at study intake presented mild, yet progressive, cognitive decline annually, presumably due to the natural effects of aging. With each additional depressive symptom presented at intake, however, the annual rate of cognitive decline increased by 24%. Thus, the number of depressive symptoms at baseline was associated with increased risk of developing AD.

Attention and working memory

An impairment in attention or immediate memory can interfere with almost every facet of daily life. Sustained attention, vigilance, and impulse control has often been assessed using Continuous Performance Tests (CPTs) [5]. These tests require a participant to respond to a specified target when it is presented spontaneously within a stream of interfering visual stimuli. In such tests, euthymic patients do not show significant impairment [6]. In contrast, depressed and manic patients in the acute phase of their illness produce more errors of attention compared with matched controls [7–8], and performance deficits worsen with severity of illness [7].

Performance of patient groups across mood states in a variety of tasks has been summarized in Table 1. As can be seen in the table, other tests of attention show a slightly different pattern of results. The Trail Making Test, Part A (TMT-A) [9] and the Digit Symbol Substitution Test (DSST) [10] involve attentional and working memory components. Unipolar depressed patients when acutely ill or when euthymic show deficits in both of these tasks [11–13]. In contrast, bipolar patients are unimpaired on the TMT-A [14–15]. As with the CPT, performance on these measures of attention correlates to symptom severity [13]. Taken together, these reports indicate that patients with mood disorders can experience measurable deficits of attention during euthymic and disturbed mood states. Because attention and working memory are cognitive functions that are integral to many types of neuropsychological tests, the interpretation of studies showing deficits in a broad range of cognitive abilities should take into account the role of poor attentional/working memory capacity in these patients.

Executive function

Executive function describes a broad range of cognitive processes that contribute to decision-making and higher-level thinking, such as initiation, planning, execution, and flexibility in response to changing contingencies. Researchers typically have used tests such as the Wisconsin Card Sorting Test (WCST) [16], Stroop Test [17], or the Trail Making Test, Part B (TMT-B) to assess executive abilities. Each test requires the suppression of a prepotent response to respond in accordance with an imposed task rule. To examine the stability of executive function in bipolar mood disorder, patients were tested on the WCST during their acute manic phase and then again when symptoms had attenuated [14]. Compared with healthy controls, bipolar patients were impaired while acutely ill, but they showed improvements beyond normal practice when tested again during the subacute phase of their illness, suggesting that some degree of improvement was related to the alleviation of mood symptoms. Still, a separate study showed that patients with a history of bipolar disorder who were euthymic when tested on the WCST committed more errors than did healthy controls [6]. Similarly, patients in either acute manic or euthymic mood states have demonstrated significant impairments on the Stroop Test [6,12,14]. Austin et al [13] showed that performance on the TMT-B was impaired for depressed patients and worsened with a patient's level of depression.

Memory

Subjective complaints of memory loss are often reported by patients with mood disorders and have been confirmed during neuropsychological assessment of declarative memory. Impairments have been reported during the depressed, manic, and euthymic phases of illness in tests of verbal memory, such as story recitation [6] and word list recall [12–13,15,18]. One study comparing depressed and euthymic patients versus healthy controls found an additional impairment for nonverbal memory, but only in acutely depressed patients, whereas the nonverbal memory performance for euthymic patients was comparable to that of controls [19]. As with other cognitive processes, memory function worsens with mood severity [13].

In contrast to recall deficits, performance on implicit (ie, non-declarative) memory tasks, such as primed word stem completion, has been found to be normal for depressed patients compared with that of matched controls [11]. Preserved implicit memory in the presence of impaired recall memory is consistent with a similar performance dissociation in other psychiatric and neurologic disorders, such as schizophrenia and amnesia [20,21].

Structural and functional abnormalities of the brain in mood disorders

Combined with cognitive assessment, more recent advances in neuropathological and neuroimaging studies have begun to delineate the neural substrates of mood disorders. Neuroanatomical findings help to not only gain insight into the underlying neural systems of mood regulation, but also to provide a basis for understanding the cognitive features associated with mood disorders. Neuroanatomical abnormalities have been found in limbic regions associated with identification of emotion, social cognition, and homeostatic regulation [22, 23]. Specific limbic and paralimbic regions include the subgenual and rostral cingulate gyrus, orbital frontal cortex, entorhinal cortex, anterior insula, ventral striatum, and amygdala [24–28]. The general findings in functional neuroimaging studies have reported increased activity in ventral limbic regions (the genu of the cingulate gyrus, the amygdala, and the ventral striatum). Functional abnormalities in these limbic regions are thought to reflect the emotional and autonomic symptoms of mood disorders [29].

Studies have found abnormalities in other regions that also are thought to be important for the regulation of emotional behavior, such as in the prefrontal cortices, hippocampus, and caudate/putamen nuclei [30]. Reductions in brain volume and blood flow in the dorsal medial and dorsal

lateral prefrontal cortices in unipolar and bipolar disorders have been among the most consistent findings [31–37]. In both disorders, reductions in the size of the hippocampus also have been reported [38–44], whereas reductions in the caudate/putamen volumes have been found only in unipolar depression [45,46].

Localized structural and functional abnormalities in the mood-disordered brain are consistent with the kind of cognitive deficits that would be expected based on putative functions of the affected neuroanatomical regions. Specifically, disruptions in the dorsal lateral prefrontal cortex (DLPFC), striatum, and hippocampus potentially can impair several cognitive domains that often are symptomatic in mood disorders, namely, attention/working memory, executive function, and recall memory.

Tables 2 and 3 summarize the neural systems that have been implicated in mood disorders and may underlie certain types of mood-associated cognitive deficits. As shown in the tables, one brain area named across cognitive domains is the DLPFC, and it appears to play a role in unipolar depression and bipolar disorder [47]. The pattern of cognitive impairment in these two disorders is similar, perhaps differing only in severity [12,48]. Therefore, it makes sense that these two disorders might share a common substrate in neurocognition, even though the two populations otherwise present very different clinical profiles. The two disorders differentially affect the hippocampus. Unipolar patients often show reduced hippocampal volume, but results have been mixed in bipolar patients, who show volumetric reductions, no difference, or increases compared with controls [30]. Differences across studies related to the patients' duration of illness, age, and stress may be responsible for these discrepancies.

Correlations between regional blood flow and cognition

Evidence from structural neuroimaging studies has been helpful in providing indirect evidence for neural disturbances that may underlie cognitive deficits. In contrast, some functional neuroimaging studies have more directly examined the link between the integrity of particular brain areas at rest and during cognitive performance. Dolan et al [49] compared estimated regional resting cerebral blood flow in cognitively impaired (Mini-Mental State Examination (MMSE) less than 26) and noncognitively impaired (MMSE higher than 28) depressed patients. They found reduced activity in the left medial prefrontal gyrus (Brodmann's area 10) and increased activity in the cerebellar vermis in the cognitively impaired patients relative to the noncognitively impaired patients. Another study of depressed patients found that decline in global cognitive function was correlated with decreased regional cerebral blood flow in the medial prefrontal cortex (PFC) [50]. In another study, memory and attention factors were derived from a principal component analysis of scores obtained from a neuropsychological battery given to 29 patients with major depression [51]; both memory and attention were found to be correlated to medial prefrontal activity (eg, the greater the impairment, the lower the blood flow). In addition, the memory factor was uniquely associated with blood flow in the anterior cingulate cortex (ACC).

Functional neuroimaging studies using cognitive challenges

Some neuroimaging studies of patients with mood disorders were conducted while patients performed cognitive tasks. In contrast to studies in which blood flow is measured during a resting baseline state, studies that involve cognitive challenges help to reduce variability in blood flow by minimizing random mental activity during test. These types of studies also help identify which brain areas become engaged while performing specific cognitive functions.

Unipolar depression

Positron emission tomography (PET) was used to test spatial working memory in medication-resistant patients with major depression and healthy controls [52]. Relative to healthy controls,

depressed patients showed increased left and right posterior temporal lobe activity, even though behaviorally, both groups showed similar levels of performance. Unlike controls, depressed patients failed to activate the left medial PFC. Another PET study used the Tower of London task to examine executive function in currently depressed patients and healthy controls [53]. Patients showed less activity in the frontal and posterior cortical regions compared with that of controls. When task demands increased, patients failed to show a normal increase in activation of the ACC and caudate. Frontal and ACC abnormalities in depression have been replicated in other neuroimaging studies of verbal fluency [54] and of executive function using the Stroop Test [55].

Bipolar disorder

Neuroimaging studies that have examined bipolar disorder directly have reported similar findings of reduced frontal lobe function. Studies of word generation [56], decision making [57], and executive function (Stroop Test) [58] were used to probe frontal circuits in mania. Abnormalities consistently were found in the ventral PFC. Moreover, deficits of the left PFC appeared to be related to trait, as opposed to state, aspects of the disorder.

Summary

Findings from functional neuroimaging studies support the notion that cognitive impairments of attention/working memory and executive function in mood disorders are associated with disturbances of the PFC, ACC, and hippocampus. These data are consistent with converging evidence from structural and resting baseline studies of cerebral blood flow, showing correlations between these specific regional brain abnormalities (especially in the PFC) and impaired cognition. Functional neuroimaging studies of cognition also suggest that patients engage compensatory brain regions when they perform a task normally; blood flow differences between groups under these circumstances may reflect the additional recruitment of brain structures by patients in order for them to stay on task.

Neurological deficits

There has been a renewed interest in the motor component of neurological deficits that often accompany mood disorders. Some neurological signs are evident in nonmedicated patients, while other signs have been associated primarily with medication treatment. Neurological symptoms add to the global burden of mood disorders and often constitute a major therapeutic challenge. This section, summarized in Table 4, provides a general description of motor deficits that have been observed in unipolar and bipolar disorders, and comments on the associated mood state and responsible drug agents that have been linked to each type of neurological sign.

Psychomotor retardation

Psychomotor retardation, or slowed response time, is a prominent feature of mood disorders, although it is not present in every patient [59]. Increased time to initiate movement, accompanied by increased time to complete movement, may represent impairment in cognitive and motor processing. Researchers have tried to tease apart the cognitive and motor components of psychomotor retardation and have suggested that both domains play an integral role in motor speed. There may be differences, however, in how each factor influences movement according to the specific mood disorder. Psychomotor deficits associated with unipolar depression may be tied closely to cognitive–motor impairments (eg, time to initiate response), whereas psychomotor deficits associated with bipolar depression may be linked more closely to neuromotor dysfunction (eg, peak movement velocity) [60]. In either case, however, it has been shown that general motor retardation decreases with attenuation of mood disturbance [60,61].

Psychomotor agitation

Patients with psychomotor agitation, by comparison, frequently present with symptoms of restlessness [1]. From a behavioral perspective, patients may seem nervous, demonstrating such behaviors as wringing their hands or pulling their hair. Speech may be pressured and rapid, and patients may show feelings of irritability, rather than of depressed mood. They have a hard time sitting through an interview, instead standing up to pace about the room.

Researchers have examined whether psychomotor agitation is more closely tied to mania or depression. A recent study compared three groups of patients, many of whom were diagnosed with mixed state depression (ie, the presentation of rapidly fluctuating depressive and manic symptoms) [62]. The three groups included: patients currently experiencing a mixed state, patients with a history of mixed state but currently having a major depressive episode, and patients with a diagnosis of bipolar disorder who were currently depressed. Symptom assessment was performed, which included measures of agitation derived from the Hamilton Rating Scale for Depression [63]. The authors found that psychomotor agitation, in particular, was more prevalent in both mixed state groups compared with the bipolar depressed group. Another study examined patients with unipolar depression and bipolar disorder with a seasonal pattern (ie, seasonal affective disorder) [64]. Bipolar patients had more severe agitation than did unipolar patients. These and other studies suggest that psychomotor agitation is associated more closely with signs of mania than with melancholy.

Catatonia

As many as 20% of depressed patients have been reported to show signs of catatonia [65]. Symptoms of retarded catatonia may be characterized by profound disorders of movement, such as akinesia (lack of movement), bradykinesia (slowed movement), Parkinsonism, stupor, and tics. There may be pathological posturing in which the individual maintains a position for long periods of time, known as waxy flexibility. Agitated catatonia is marked by excessive and purposeless motor activity and mimicry. Mutism, stuttering, and echolalia (repetition of what has just been said by another) represent speech and language problems associated with catatonia [66].

In a comparison study of a consecutive series of catatonic depressed patients, noncatatonic depressed patients, and nondepressed patients with Parkinson's Disease (PD), catatonic depressed patients were found to be older, have a higher degree of cognitive impairment, and present more signs of depression compared with either of the other two patient groups [65]. Twenty-one percent of the noncatatonic depressed group consisted of patients with dysthymia (prolonged depressed mood without a full-fledged major depressive episode), while there were no dysthymic patients included in the catatonic group. These findings suggest that severely depressed, cognitively impaired aging patients may be particularly vulnerable to developing catatonia.

Myoclonus

Although some neurological deficits might be related to mood, others may be tied more directly to antidepressant medications given to treat affective symptoms. These medications alter the brain's neurochemistry, which inadvertently can influence the regulation of motor behavior.[1] Myoclonus is one example of an adverse neurological reaction to anti-depressants. Myoclonic twitches and jerks can occur in any part of the body, but they have been reported, in decreasing order of frequency, in the lower extremities, upper extremities, trunk, neck, and face [67]. They

[1]There are several adverse cognitive effects related to medications used to treat mood disorders. Tricyclic antidepressants may be associated with delirium in the elderly, lithium with subjective cognitive dullness, and benzodiazepines with reduced memory. This very broad topic goes beyond the intent of this article.

can precipitate with sensory stimulation and worsen with volitional movements. Although myoclonus develops in isolated muscle groups, it can become generalized to a shiver throughout the patient's body.

The emergence of myoclonus in depression may stem from drug-induced elevated levels of serotonin [67].[2] One class of antidepressants works through monoamine oxidase inhibitors (MAOIs) by binding to the enzyme (monoamine oxidase) that degrades monoamines, including serotonin and dopamine. A number of studies of MAOI-induced myoclonus have reported involuntary muscle contractions in patients who received clinical doses of MAOI or MAOI augmented with the serotonin precursor L-tryptophan [67].

Heterocyclic antidepressants (HCAs) work by blocking the reuptake of serotonin and norepinephrine in the synapse. This increases the availability of these neurochemicals for transmission. HCA-induced myoclonus has been reported often in high doses but relatively infrequently at therapeutic doses [67]. One study, however, showed that careful inspection of adverse effects detected myoclonus in 39 of 98 (40%) patients who were taking tricyclic antidepressants [69].

Exposure to lithium also has been linked to myoclonus [31]. The precise mechanism of action of lithium is unknown [70], although it may work through the facilitation of serotonin release [71]. While studying myoclonus in unipolar and bipolar patients, Caviness et al [71] found that lithium-induced myoclonus rarely occurred at rest, unlike the myoclonus induced by traditional antidepressants. Lithium at therapeutic levels may be associated with tremor, which can be an early sign of toxicity.

There does not appear to be a specific vulnerability for myoclonus to develop in unipolar or bipolar disorders. Regardless of severity, antide-pressant-induced myoclonus usually can be reversed by removing the responsible agent [67,71].

Tardive dyskinesia

Tardive dyskinesia (TD) is characterized by repetitive and stereotypic movements that can result from protracted dopamine-blocking neuroleptic treatments. Symptoms of TD typically present in the face and mouth region, but they also can appear in the neck, trunk, and extremities. Mood disorders may present a risk factor for developing TD [72]. For example, the incidence of TD in mood disorders is higher than that seen in schizophrenia, a patient population routinely placed on neuroleptic medications [73]. Moreover, there appears to be a direct relation between affective state and TD. Increased severity of depressed symptoms often is coupled with worsening TD. In contrast, signs of TD often diminish with mania, usually several days before the elevation in mood [74,75]. TD, however, is sometimes irreversible.

Parkinsonism

Parkinsonism is another adverse effect associated with neuroleptic treatment, although it is often reversible upon medication discontinuation. Parkinsonian symptoms include fine tremor and bradykinesia or akinesia. Parallels have been drawn between the state-dependent motor abnormalities observed in bipolar disorder and the on (dyskinetic) and off (akinetic) phenomena of Parkinson 's disease [76]. For bipolar disorder, the on phase of Parkinsonism accompanies mania, whereas the off phase coincides with depression.

[2]Myoclonus can be a symptom of serotonin syndrome, a severe and sometimes fatal clinical entity associated with a hyperserotonergic state [68]. This disorder, brought on by simultaneous use of multiple serotonergic agents, is difficult to distinguish from the neuroleptic malignant syndrome. Ascertaining prior use of neuroleptics is paramount in the differential diagnosis. Symptoms of the serotonin syndrome are: hyper-reflexia, clumsiness, myoclonus, rigidity, elevated temperature, drowsiness, sweating, shivering, diarrhea, and mental status changes, including hypomania and loss of consciousness. Death may ensue.

One study examined depressed patients with signs of Parkinsonism (D-P) versus depressed patients without signs of Parkinsonism (D) [77]. Measures of interest were predominantly motor signs assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) [78]. The D-P group had higher UPDRS scores, reflecting greater neurological impairment, than did the D group. A group of PD patients without depression also was tested on the UPDRS and was compared with the D-P group. They differed on two categories. The PD group showed a greater amount of tremor at rest; the D-P group showed more body bradykinesia. A subset of the D-P patients was re-evaluated from 1 to 89 months later. Of those who had become euthymic, their UPDRS dropped more than 40%, whereas those who remained depressed showed a 60% increase in overall UPDRS motor scores. These findings suggest that patients with lasting depression are more likely to develop symptoms consistent with parkinsonism. Neurological symptoms, however, can remit with mood improvement. Parkinsonism, like PD, has been associated with decreased dopaminergic activity in the basal ganglia [79]. The reversibility of motor dysfunction in conjunction with mood improvement, however, suggests that abnormalities of the basal ganglia circuit are functional rather than structural [77].

Relationships among mood, cognition, and movement

This article characterizes the relations of mood state to cognition, brain structure/function, and abnormal movements. An intriguing question is whether there is a predictable association among various domain deficits, including mood disturbance, cognitive deficit, and movement abnormality. Few studies have addressed this question directly. Gilleard and Vaddadi [80] compared TD and mood symptoms to memory function in patients with bipolar disorder. They found that increased TD was correlated to impaired memory and depressed mood. Another study related abnormal movements with cognitive impairment and clinical history in bipolar patients [81]. Those patients with noticeable involuntary movements had lower cognitive function but fewer depressive episodes (but not fewer manic episodes) than did a comparable group of bipolar patients with no neurologic signs.

Given what has been shown, there appears to be a relation among mood, movement, and cognition. This association, however, is just beginning to be explored. Future studies might address a number of contributing factors, including specific mood diagnosis, number of recurrent episodes, age, gender, type of motor abnormality, and domain of cognitive impairment. Any simple consideration of multiple variables, however, quickly progresses to a complex investigation. For example, it has been reported that cognition declines with the presence of TD [82], and that TD improves with developing mania [74,75]. Therefore, one might expect that cognition (like TD) would improve with mania, yet this is not the case. The question remains: is there a pattern of cognitive deficits that are tied more closely to changes in mood, or to changes in movement? If so, could serotonin or dopamine modulate these interactions? Future research will need to incorporate a variety of symptom domains with clinical variables to answer these questions.

Summary

Disorders of mood are accompanied by a range of cognitive and neurological impairments. Similar types of cognitive deficits are shared by patients with unipolar depression and bipolar disorder. Given the disparate clinical nature of these two disorders, it is interesting and informative to understand that they share common impairments in cognition. Neuroimaging studies indicate that these impairments in both patient populations may be subserved by disruptions of the dorsal lateral and ventral medial PFC. An important problem that remains for clinicians is that some neurological symptoms are linked specifically to the adverse pharmacological effects of antidepressant agents, mood stabilizers, and neuroleptic agents.

Research has shown a relation between mood and cognitive ability. Studies also have shown an association between mood and specific types of neurological dysfunction. Although few studies have examined all three symptom domains within one investigation, preliminary reports indicate that mood, cognition, and motor function may be linked to one another by complex mechanisms. Moreover, either type of abnormality that persists in the euthymic state suggests that a fundamental neural dysfunction is unaffected by treatment with existing means. Understanding the neural mechanisms that underlie mood, cognition, and movements may help to devise better treatments that do not influence cognitive or neurological functions, yet treat mood successfully.

Box 1. Symptom criteria for major depressive disorder (unipolar depression)

At least five of the following symptoms must be present within a 2-week period*

Depressed mood most of the day

Diminished interest or loss of pleasure (anhedonia)

Significant weight loss or weight gain

Insomnia or hypersomnia

Psychomotor retardation or agitation

Loss of energy

Feelings of worthlessness or excessive guilt

Difficulty in thinking or concentrating

Suicidal ideation or attempt

Box 2. Symptom criteria for bipolar disorder type I

Abnormally expansive and elevated mood or irritability that lasts longer than 1 week, less if hospitalized, and three or more of the following symptoms:

Inflated self-esteem or grandiosity

Diminished need for sleep (eg, up for several consecutive nights without feeling tired)

Pressured need to keep talking

Racing thoughts

Distracted attention

Increase in goal-directed activity (eg, socially, professionally, or sexually)

Indulgence in pleasurable activities to the detriment of the patient's welfare

In addition to these criteria, symptoms include a significant drop in social or occupational function. They may be associated with psychosis and may lead to hospitalization to prevent harm to self or others. Symptoms are not better accounted for by other factors, such as substance abuse or a general medical condition.

Data from Diagnostic and Statistical Manual for Mental Disorders, 4th edition.

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Table 1

Cognitive deficits across mood states

Cognitive domain	Cognitive task	Euthymic state	Depressed state	Manic state	Deficits increase with symptom severity
Attention	Continuous Performance Test (CPT)	X	Yes	Yes	Yes
	Trails Making Test Part A (TMT-A)	Yes	Yes	X	
	Digit Symbol Substitution (DSST)	Yes	Yes	?	
Executive function	Wisconsin Card Sort Test (WCST)	Yes	?	Yes	Yes
	Stroop test	Yes	?	Yes	
	Trail Making Test, Part B (TMT-B)	Yes	Yes	?	
Memory	Verbal recall	Yes	Yes	Yes	Yes
	Non verbal recall	X	Yes	?	?
	Implicit memory	?	X	?	?

Table 2

Reduction of structural and functional integrity of brain regions that are putatively associated with cognitive impairment in unipolar depression

Cognitive domain	Structural abnormalities	Functional abnormalities	Postmortem findings
Attention/working memory	DLPFC [31,32]	DLPFC [34–37,50]	DLPFC (glia [24], neuron density [83])
Executive function	DLPFC [31,32]	DLPFC [34–37,50] ACC [53–55]	DLPFC (glia [24], neuron density [83])
Memory	Hippocampus [38–41] DLPFC [31,32]	DLPFC [34–37,50]	—

Abbreviation: DLPFC, dorsal lateral prefrontal cortex; ACC, anterior cingulate cortex.

Table 3

Reduction of structural and functional integrity of brain regions that are putatively associated with cognitive impairment in bipolar disorder

Cognitive domain	Structural abnormalities	Functional abnormalities	Postmortem findings
Attention/working memory	DLPFC [44,85]	DLPFC [36,37,86–88]	DLPFC (glia [24], neuron density [83])
Executive function	DLPFC [17,18]	DLPFC [36,37,86–88]	DLPFC (glia [24], neuron density [83])
Memory	Hippocampus (not all studies show reduced size) [42–44] DLPFC [44,85]	DLPFC [36,37,86–88]	Hippocampus, entorhinal cortex [84]

Abbreviation: DLPFC, dorsal lateral prefrontal cortex.

Table 4

Neurological deficits across mood states

Neurological deficit	Commonly associated with depressed state	Commonly associated with manic state	Deficits primarily related to mood	Deficits primarily related to medications
Psychomotor retardation	Yes	X	Yes	X
Psychomotor agitation	X	Yes	Yes	X
Catatonia	Yes	X	Yes	X
Myoclonus	Yes	Yes	X	Yes
Tardive dyskinesia	Yes	X	Yes	Yes
Parkinsonism	Yes	Yes	Yes	Yes