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Distinguishing between Unipolar Depression and Bipolar Depression: Current and Future Clinical and Neuroimaging Perspectives

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Abstract

Differentiating bipolar disorder (BD) from recurrent unipolar depression (UD) is a major clinical challenge. Main reasons for this include the higher prevalence of depressive relative to hypo/manic symptoms during the course of BD illness and the high prevalence of subthreshold manic symptoms in both BD and UD depression. Identifying objective markers of BD might help improve accuracy in differentiating between BD and UD depression, to ultimately optimize clinical and functional outcome for all depressed individuals. Yet, only eight neuroimaging studies to date directly compared UD and BD depressed individuals. Findings from these studies suggest more widespread abnormalities in white matter connectivity and white matter hyperintensities in BD than UD depression, habenula volume reductions in BD but not UD depression, and differential patterns of functional abnormalities in emotion regulation and attentional control neural circuitry in the two depression types. These findings suggest different pathophysiologic processes, especially in emotion regulation, reward and attentional control neural circuitry in BD versus UD depression. This review thereby serves as a “call to action” to highlight the pressing need for more neuroimaging studies, using larger samples sizes, comparing BD and UD depressed individuals. These future studies should also include dimensional approaches, studies of at risk individuals, and more novel neuroimaging approaches, such as, connectivity analysis and machine learning. Ultimately, these approaches might provide biomarkers to identify individuals at future risk for BD versus UD, and biological targets for more personalized treatment and new treatment developments for BD and UD depression.

Keywords

Bipolar Disorder; Major Depressive Disorder; Major Depressive Episode; Magnetic Resonance Imaging; Neuroimaging; Mood Disorder; Functional Imaging; Structural Imaging

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Introduction

Bipolar disorder (BD) is one of the top ten most debilitating of all illnesses (1, 2). Yet, the absence of biologically-relevant diagnostic markers of BD results in misdiagnosis of the illness as major depressive disorder, or recurrent unipolar disorder (UD) depression, in 60% of bipolar individuals seeking treatment for depression (1, 3, 4). In this manuscript, we will review the current neuroimaging literature directly comparing individuals with UD with individuals with BD in depressive episode. First, we discuss the reasons why misdiagnosis of BD is so common using current DSM-IV criteria. We then highlight the limitations of current clinical strategies for early diagnosis of BD, and focus on the potential utility of neuroimaging studies to identify biomarkers to aid in the differential diagnosis of BD versus UD depression. We then discuss future research strategies to study BD, including dimensional approaches such as the Research Domain Criteria (RDoC) initiative, in combination with neuroimaging, and discuss the necessity of prospective studies of individuals at risk for BD. Finally, we describe the potential of the combination of neuroimaging and machine learning to help identify individuals with, and those at future risk for, BD.

The difficulty in differentiating between BD and UD depression

Only 20% of BD individuals during a depressive episode receive the correct diagnoses of BD within the first year of seeking treatment,(4) and latency from onset to diagnosis and appropriate treatment averages 5–10 years (5, 6). Close to 60% of BD individuals are initially diagnosed as having UD depression (3, 4). Furthermore, despite notions that BD depression may be associated with more psychosis than UD depression, it remains extremely difficult to distinguish depressed patients with BD from those with UD (3). Unfortunately, misdiagnosing BD as UD depression has many potentially deleterious consequences, including, inappropriate medication, which in turn might lead to poor prognosis, increased suicidal and switching to mania, and greater health care costs (4, 7–11). An obvious benefit of making an early diagnosis of BD is thus in relation to making the diagnosis in young people before the onset of elevated mood, where a past history of hypomania is ambiguous or cannot be elicited, and in those depressed patients with a family history of BD. Given that antidepressant use may be associated with higher rates of switching to mania in BD youth in particular, optimizing treatment in this population is especially important (7, 8).

Two main reasons for the difficulty in distinguishing between BD and UD depression are the higher prevalence of depressive relative to hypo/manic symptoms during the course of BD, and the presence of subthreshold manic symptoms during a depressive episode (12). Two reports from the NIMH Collaborative Depression Study demonstrated that individuals with BD experience depression much more frequently than hypomania (13) or mania (14). Specifically, in these studies the hallmark symptoms of bipolar disorder (i.e. hypomanic or manic symptoms) occurred only during 9% of the time in individuals with BD-I (14), and in only 1% of the time in individuals with BD-II (13).

In parallel, studies show that subthreshold symptoms of hypomania may be more common than previously thought, being present in 30%-55% of individuals during a depressive episode (12, 15–20). This has prompted arguments that current DSM-IV criteria for BD may be too strict, not empirically-based (21), and that a substantial proportion of individuals currently diagnosed with recurrent UD may qualify for a BD diagnosis.

It is therefore crucial to identify objective markers of BD to distinguish BD from UD, especially in early stages of the disease, to ensure optimal clinical and functional outcome for all individuals suffering from BD.

Strategies to identify BD in depressed individuals

Clinical strategies have been developed to help detect subthreshold hypomanic symptoms in depressed individuals. These include self- and clinician-administered rating scales, including Bipolar Inventory Symptoms Scale (22), Mood Disorder Questionnaire (23), Screening Assessment of Depression Polarity (24), Hypomania Checklist (25), Bipolar Spectrum Diagnostic Scale (26), and Probabilistic Approach for Bipolar Depression (27). These rating scales vary somewhat, but most include items believed to be associated with BD, such as recurrence of mood episodes, early age of onset, psychotic symptoms and positive family history of mania.

While these rating scales might detect subthreshold hypomanic symptoms that may otherwise have been undetected, they are unable to identify biomarkers that reflect underlying pathophysiologic mechanisms to guide treatment choice. Despite the controversy surrounding the risks versus benefits of antidepressant prescription for bipolar depression, type-I (6–8, 28–33), it remains very difficult, if not impossible, for a treating physician to decide whether to prescribe a mood stabilizing or antidepressant medication to a depressed patient without a clear history of mania. The identification of objective biomarkers reflecting pathophysiologic processes that may differ between BD and UD depression might provide biologically-based measures to inform diagnosis of BD in the context of a depressive episode and biological targets for personalized treatment and development of novel interventions for BD depression. Moreover, the combination of different biomarkers cutting across different levels of disease complexity may lead to specific depression profiles that better characterize depressed individuals across BD and UD (Figure 1, panels A–D).

A promising research area with potential to identify pathophysiologic processes that may differ between BD and UD depression is neuroimaging examination of structural and functional measures of neural circuitry supporting emotion and reward processing and emotion regulation, key processes known to be abnormal in affective disorders. These neural circuitries include subcortical systems involved in emotion and reward processing (e.g. amygdala, ventral striatum); medial prefrontal and anterior cingulate cortical regions involved in processing emotion and automatic or implicit regulation of emotion; and lateral prefrontal cortical systems (e.g. ventrolateral prefrontal cortex (VLPFC) and dorsolateral prefrontal cortex) involved in cognitive control and voluntary or effortful regulation of emotion (34, 35). Several studies used neuroimaging techniques to examine key neural structures and circuitries underlying the above processes in mood disordered individuals, with convergent findings indicating abnormally elevated subcortical and reduced prefrontal cortical activity during emotion processing paradigms in BD and UD depressed individuals (see (34, 36–43)). In parallel, recent reviews compared findings from studies examining neural circuitry abnormalities in individuals with UD depression versus healthy volunteers (HI) with findings from studies examining abnormalities in neural circuitry in individuals with BD depression versus HI (44–50). Very few neuroimaging studies directly compared individuals with BD depression and those with UD depression. The latter approach is critical to determine whether patterns of abnormal function and structure in neural circuitry supporting emotion processing, reward and emotion regulation may help distinguish BD from UD depression.

We next describe findings from neuroimaging studies that directly compared individuals with BD and those with UD depression. These studies almost exclusively focused on depressed individuals with bipolar I disorder.

Neuroimaging studies directly comparing individuals with BD depression versus UD depression

Original research studies directly comparing individuals with BD depression with individuals with UD depression were identified through a comprehensive MEDLINE, EMBASE and PsycINFO search of the English-language literature covering publications between January 2000 and February 2012. The search keywords were “bipolar disorder”, “major depressive disorder” and “magnetic resonance imaging”. Additional articles were identified through the reference lists of these papers.

Studies were included if they a) reported direct comparisons of individuals with BD, currently in depressive episode, with individuals with recurrent UD, currently in depressive episode; and b) employed MRI as the main acquisition method. The current strategy resulted in eight neuroimaging original research articles (Table 1). Four studies used functional neuroimaging techniques, and four, structural neuroimaging techniques. All but one of these studies were conducted in adults.

Structural neuroimaging studies directly comparing unipolar and bipolar depression

One study (51) used diffusion tensor imaging (DTI) to examine wholebrain fractional anisotropy (FA) in fifteen BD-I depressed, sixteen UD depressed and twenty four healthy adults. Decreased FA in the left superior longitudinal fasciculus was found in BD versus UD depressed and healthy individuals. Decreased FA was also found in the right uncinate fasciculus in BD depressed versus healthy individuals. Decreased FA was found in the left inferior longitudinal fasciculus in UD depressed versus healthy individuals. These findings indicated abnormal bilateral white-matter connectivity between regions supporting emotion regulation and sensory processing in BD, but not UD, depression. The bilateral findings in BD, but not UD, depression suggest more widespread white matter connectivity abnormalities in BD relative to UD depression.

A second study (52) examined periventricular and deep white matter hyperintensities (DWMH) in thirteen BD-I depressed, eleven UD depressed, and nineteen healthy individuals. Here, increased DWMH were observed in BD versus UD depressed individuals, and in BD versus healthy adults. White matter hyperintensities have been associated with cardiovascular disease and are observed more commonly in those BD and UD individuals who have coexisting hypertension and/or diabetes (53). The authors therefore interpreted these findings as suggesting that BD may be more consistently associated with general medical comorbid illnesses (54).

A third study (55) examined habenula volume in twenty two unmedicated BD (I and II) depressed, fifteen medicated BD (I and II) depressed, twenty eight UD depression, thirty two UD remitted, and seventy four healthy individuals. The authors found significant volume reduction in the left habenula in unmedicated individuals with BD depression relative to UD depressed and healthy individuals. The habenula serves as a point of convergence for striatal and limbic input and provides forebrain control over serotonergic and dopaminergic transmission from the midbrain (56, 57). Thus, it has a role in adaptation to stressful events and negative feedback during reward processing which are abnormal in mood disorder (58, 59). The authors interpreted these findings as a possible dendritic atrophy due elevated adrenal steroid secretion associated with repeated stress.

A fourth study found no significant differences in gray matter in BD and UD depressed individuals (60). This study measured pituitary gland volume using high-resolution images

in ten adolescents with BD-I depression, ten adolescents with UD depression, and ten age-matched healthy adolescents. Both depressed groups had larger pituitary gland volumes than healthy individuals, but were not different from each other. The authors interpreted these findings as a possible reflection of neuroendocrine dysfunction in children and adolescents with UD and BD depression.

Functional neuroimaging studies directly comparing unipolar and bipolar depression

Two studies (61, 62) employed a well-validated emotional facial labeling paradigm to examine the functional integrity of emotion processing neural circuitry. The paradigm involved displaying negative (fear and sad) and positive (happy) facial expressions as important signals of external threat (fear), internal distress (sad) and social approval (happy) of both prototypical (intense) and mild intensities of each emotion, together with neutral expressions. Fifteen BD-I depressed, fifteen BD-I remitted, sixteen UD depressed and sixteen age/gender matched HI (61, 62) were recruited. Key findings from these studies were: 1. abnormally elevated left amygdala activity to mild sad and neutral faces in the sad experiment in BD-I depression relative to BD-I remission, UD depression and HI; 2. abnormally reduced left-sided top down ventromedial prefrontal cortical (vmPFC)-amygdala effective connectivity to happy faces in BD-I depression relative to HI, and 3. abnormally reduced right-sided bottom up amygdala-vmPFC effective connectivity to happy faces in BD-I depression relative to UD depression and HI. In contrast, UD depressed individuals demonstrated abnormal inverse left-sided top down vmPFC-amygdala effective connectivity relative to HI to happy faces (61, 62).

A third study (63) investigated emotion processing and regulation circuits in twelve BD depressed (type not described), thirteen UD depressed and fifteen healthy individuals employing a reversal learning paradigm that estimates the ability to modify behavior when reinforcement change (i.e. positive or negative feedback). A key finding was that UD, but not BD, depressed were more likely to reverse response following misleading negative feedback, and that this was associated with reduced ventrolateral and dorsomedial prefrontal cortical activity. By contrast, BD depressed individuals had a normal pattern of neural activity during the task. Moreover, greater reduction in VLPFC activity in UD depressed individuals during reversal shifting was associated with reduced amygdala activity to positive feedback. These findings were interpreted as a reduced capacity of prefrontal cortex to regulate the amygdala during negative feedback in UD, but not BD, depression (63).

A fourth study (64) used an executive control paradigm with emotional distracters (an emotional n-back task) to examine the functional integrity of neural circuitry supporting cognitive control and emotion regulation in eighteen BD depressed females, twenty-three UD depressed females, and sixteen healthy females. The key finding was significantly elevated dorsal anterior midcingulate cortical activity in UD depressed individuals relative to the other two groups during the demanding 2-back condition of the paradigm with neutral face distracters, that suggested abnormal recruitment of attentional control circuitry to maintain task performance (64).

Neural circuitry abnormalities that differentiate BD from UD in depressive episode: toward biomarkers of BD

The very small number of structural neuroimaging studies indicates three main findings. First, BD depressed individuals may display more significant abnormalities than UD depressed individuals in white matter connecting key regions in emotion processing and regulation neural circuitry (51). Axonal disorganization, axonal demyelination or apoptosis,

manifested as white matter tracts abnormalities, might be related to altered expression of oligodendrocyte and myelin genes (65). Furthermore, lower densities of oligodendroglial and glial cells are reported in the prefrontal cortex of BD versus healthy individuals (66–68). These findings suggest that BD may be characterized by more global, rather than localized, abnormalities in white matter connectivity in emotion regulation neural circuitry than UD depression, that may in turn underlie the greater mood lability observed in BD.

Second, BD depressed individuals have a greater number of DWMH than UD depressed individuals (52). White matter hyperintensities are one of the most replicated structural neuroimaging findings in BD (69), with six times greater frequency than in healthy individuals (69). These hyperintensities are also observed during normal aging (70), cardiovascular and metabolic disorders (70–72), migraine (73), developmental (74) and demyelinating (75) disorders. These findings may thus suggest that the higher levels of white matter hyperintensities in BD may reflect the higher levels of comorbid cardiovascular and metabolic disorders in the illness (53). In addition, greater comorbidity of alcohol and substance abuse dependence, greater number of suicide attempts, and presence of manic episodes could also be potential modifying/mediating factors for the development of white matter hyperintensities in BD (41).

Thirdly, BD, but not UD, depressed individuals have abnormally reduced habenula volume (55). Given that the habenula appears to have an inhibitory influence upon ventral tegmental area dopamine transmission (57), specifically in the absence of expected rewards (56), abnormal reduction in habenula gray matter volume may underlie the heightened reward sensitivity (76) and abnormally elevated activity in ventral striatal and prefrontal cortical regions in reward circuitry observed in BD (77, 78).

The four functional neuroimaging studies directly comparing BD and UD depression point to potentially different neural mechanisms underlying depression in BD and UD. BD depressed individuals showed abnormally elevated amygdala activity to mild sad and neutral facial expressions (61); and abnormally reduced bilateral amygdala-vmPFC effective connectivity to happy faces (62). The former may reflect an abnormally elevated attention to displays of internal distress; and the latter, reduced regulation of amygdala by ventromedial prefrontal cortex during positive emotion processing that may represent a predisposition to hypo/mania. Conversely, UD depressed individuals showed inverse left-sided top-down ventromedial prefrontal cortex-amygdala effective connectivity to happy faces (62); abnormally elevated dorsal anterior midcingulate cortical activity during the demanding 2-back condition with neutral face distracters (64); and abnormally reduced VLPFC and amygdala activity to negative feedback (63). The first findings may represent an “over-regulation” by ventromedial prefrontal cortex over the amygdala to these stimuli and a potential neural basis for the increased negative and reduced positive emotional attentional bias that is frequently observed in UD. The second finding may reflect a need for greater recruitment of attentional control circuitry to successfully direct attention away from ambiguous, neutral face distracters. The third finding further suggests abnormal recruitment of prefrontal cortical attentional control circuitry in response to emotional contexts in UD depression.

Despite the small number of neuroimaging studies directly comparing BD and UD depression, and their different methodologies, the potential benefits of such direct comparison for identification of biomarkers to differentiate the two types of depression is very clear. A main purpose of this review is thus a “call to action”, to encourage other researchers to conduct further neuroimaging research in this clinically highly important and yet under-researched area. There is clearly a need for more studies using larger samples sizes to directly compare BD and UD depressed individuals. Moreover, some of the extant

studies included both BD- I and BD-II depressed individuals, some included BD and UD depressed groups that were not well matched clinically, and some included individuals taking a diverse array of medications (51, 62, 63, 79), although see (55, 60). Future neuroimaging studies should aim also to address these limitations, and elucidate relationships between structural and functional neuroimaging findings that differentiate the two types of depression in order to move toward identifying biomarkers that reflect pathophysiologic processes supporting the development of BD.

Future approaches in neuroimaging research comparing BD and UD depression

Here, we highlight novel approaches that should be the focus of future neuroimaging studies of BD and UD depression. These include dimensional approaches; studies of at risk individuals; and novel neuroimaging approaches.

Dimensional approaches

An increasing literature conceptualizes BD and recurrent UD along a spectrum of affective disorders, with increasing “bipolarity” evident in the progression from UD to BD (16, 18, 21, 80, 81).

For example, recent re-analyses of two epidemiological studies have demonstrated that the dichotomy unipolar/bipolar is questionable and that hypomanic syndromes that do not meet DSM-IV criteria for BD-II are present in about 40% of individuals with recurrent UD (15, 20). The prospective longitudinal study “Early Developmental Stages of Psychopathology” (EDSP)(20) followed a large community sample of 2210 individuals for 10 years, including 586 individuals with a major affective disorder based on DSM-IV criteria (5.6% with BP-II, 11% with BP-I, and 83.3% with UD). Of the individuals with DSM-IV UD, 286(58.6%) were found to have pure UD; 202(41.4%) had additional subthreshold hypomania symptoms and could be reclassified as having subthreshold BD according to the study criteria. The “National Comorbidity Survey Replication”(NCS-R) study, was a nationally representative face-to-face household survey of the prevalence of different mental disorders based on DSM-IV criteria among 5,692 individuals (15). The authors found that nearly 40% of the study sample with a history of recurrent UD had a history of subthreshold hypomania. The Bridge Study (Bipolar Disorders: Improving Diagnosis, Guidance, and Education), is a cross-sectional multi-ethnic investigation of 5,635 individuals across three continents in depressive episode, according to DSM-IV criteria (82, 83). The authors found that 16.1% of individuals with MDE met criteria for either bipolar I or II disorder, and when the “bipolarity specifier criteria” was applied (inclusion of increased activity/energy, and reduction of duration cutoff for hypomanic symptoms), this rate increased to 47%. Therefore, one third of individuals with MDE also had subthreshold hypomania/mania.

The Spectrum approach is a dimensional criteria with a unitary and continuous approach to the assessment of both manic-hypomanic and depressive symptoms, coupled with the longitudinal, lifetime perspective that may better conform to clinical reality than categorical diagnoses (84)(<http://www.spectrum-project.org/>). Using the MOODS (Spectrum scale specific for mood symptoms), individuals with recurrent UD were shown to present with a significant number of hypomanic/manic symptoms, although fewer than those with BD- I (80). These clinical variables, more than the conventional DSM categories of affective disorders, may be more closely linked to biomarkers that reflect pathophysiologic processes related to BD.

These approaches parallel the dimensional approach advocated by the RDoC, of the National Institute of Mental Health (<http://www.nimh.nih.gov/research-funding/rdoc/nimh-research-domain-criteria-rdoc.shtml>). The RDoC initiative, proposes a reclassification of mental disorders for research purposes in a neuroscience-based framework that might contribute to a nosology in which disorders are grouped by underlying pathophysiological similarities rather than by phenomenological observations. The RDoC comprises five complementary systems: I) negative valance system; II) positive valance system; III) cognitive system; IV) system for social process; and V) arousal/regulatory systems. The value of the RDoC lies in its ability to characterize groups (e.g. UD, BD) with regard to their profiles on the five dimensions and to accommodate individuals that fall in between (to be) established dimensional patterns. Given findings from the above studies that directly compare BD and UD depressed individuals, it is likely that such a dimensional approach may be able to redefine “bipolarity” in terms of different underlying pathophysiological processes that are likely to include abnormalities in neural circuitry supporting emotion processing, reward and emotion regulation.

Studies of individuals at risk of future affective disorders

Studies of individuals genetically –or symptomatically– at risk of future affective disorders, including UD and BD, allow identification of biomarkers that may reflect underlying pathophysiologic processes conferring risk or resilience toward future development of these disorders. Prospective, longitudinal studies of these individuals are needed to determine whether abnormalities in neural circuitries identified by neuroimaging predict future development of affective disorders across the affective disorder spectrum, or protect against future development of these disorders.

While it is beyond the scope of this manuscript to review all neuroimaging studies that examined individuals at risk for BD, emerging findings from these studies indicate that genetically and symptomatically at-risk individuals show similar patterns of abnormal structure and function in emotion processing and regulation circuitry as BD adults. For example, one study in healthy offspring of BD parents (85) showed abnormally reduced FA in right inferior longitudinal fasciculus and left corpus callosum in these individuals versus healthy, age-matched youth, paralleling findings in BD depressed adults (51). A systematic review and meta-analysis of the few structural and functional neuroimaging studies of individuals at genetic risk for BD (86) revealed no significant differences between high risk individuals and controls), although high-risk individuals did show increased global grey matter volume compared with individuals with BD. Moreover, the high-risk group showed increased activity in a variety of different neural regions implicated in emotion processing and regulation compared with healthy individuals, independent from the fMRI task used (86). Examination of the development of neural abnormalities that occur before the behavioral changes associated with BD, or other mood disorders, is an important future direction that might aid the discovery of biomarkers reflecting pathophysiologic processes underlying development of symptom dimensions related to BD.

Novel neuroimaging approaches

In addition to the development of MRI technologies, several analytical advances in neuroimaging are under current development. The field is now shifting from conventional analyses of neural activity to more advanced analyses based on functional integration within specific neural circuitries, including analyses of functional (e.g. psychological-physiological interaction –PPI (87)) and effective (e.g. dynamic causal modeling (62, 88)) connectivity and resting state connectivity (88, 89). Future paradigm development should focus on those paradigms that show robust patterns of activation and good test/retest reliability across

different scanners (90, 91). Furthermore, the combination of different neuroimaging techniques, i.e., multimodal neuroimaging, is now possible. This may allow a more comprehensive understanding of neural circuitry abnormalities in affective disorders.

Machine learning, a branch of artificial intelligence, develops algorithms that allow computers to automatically learn and recognize complex patterns and make intelligent decisions based on large amount of data. Pattern recognition, one example of machine learning, is now used in combination with neuroimaging and psychiatric disorders (92–94). The combination of these techniques has potential to significantly impact clinical practice in the future because it allows classification of individuals, case by case, into groups, and might also provide measures to help predict future outcome at the individual level. For example, we recently used pattern recognition and fMRI to discriminate eighteen BD depressed, eighteen UD depressed and eighteen healthy individuals based upon wholebrain activity to emotional and neutral faces (95), and to discriminate healthy youth at high genetic risk for future BD by virtue of having a parent with BD from healthy, low-risk youth (96). In the latter study, exploratory analyses revealed that the magnitude of the predictive probability of the pattern recognition classifier could help predict which of the youth classified as high-risk subsequently developed a psychiatric disorder during follow-up.

Summary

While BD and UD depression often remain extremely difficult to distinguish in clinical practice, promising findings from studies using different neuroimaging modalities indicate that neuroimaging measures might identify biomarkers to help differentiate BD from UD depression. In parallel, dimensional approaches, including the RDoC initiative, have the potential to help redefine “bipolarity” in terms of different underlying pathophysiological dimensions. Such approaches may facilitate identification of biomarkers reflecting relationships among genetic, molecular neural circuitry-level, and behavioral-level abnormalities that underlie different dimensions of psychopathology across the affective disorder spectrum (Figure 1). Ultimately, these approaches, in combination with advances in neuroimaging and other methodologies, such as machine learning, have potential to provide biomarkers to identify individuals at future risk for BD versus UD, and biological targets for more personalized treatment and novel treatment developments for both BD and UD depression.

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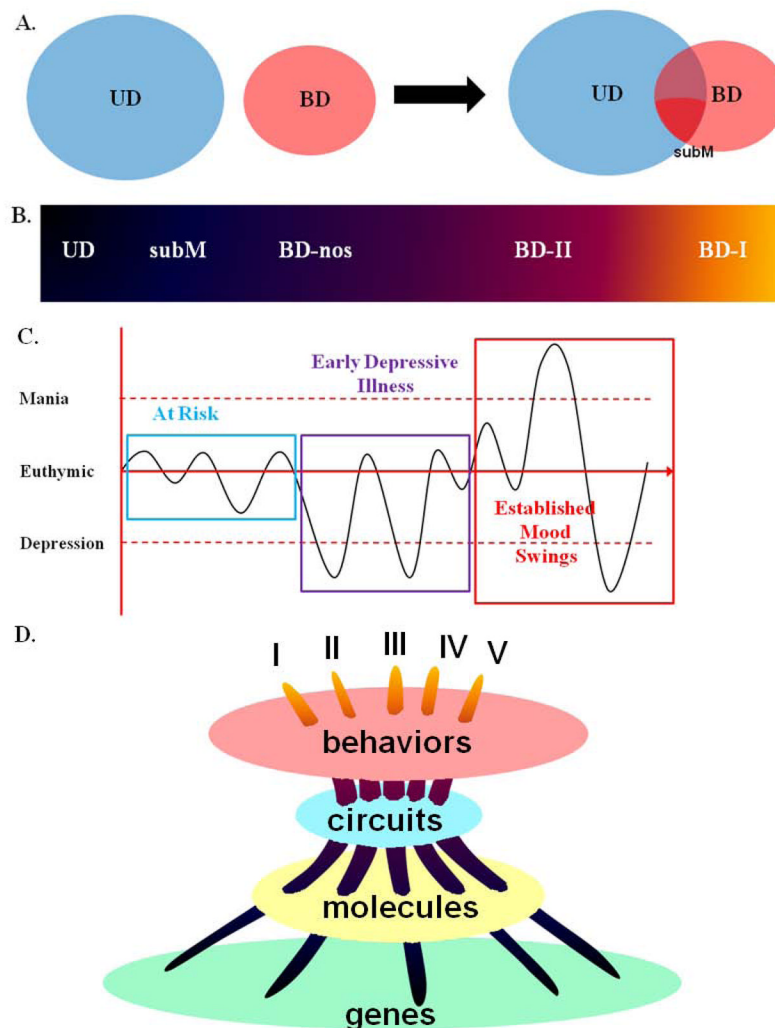


Figure 1. Current and future perspectives in the classification of affective disorders

Panel A: Left: The present categorical dichotomization of bipolar versus unipolar depression. Right: The clinical overlap between bipolar and unipolar depression, with subthreshold hypomanic symptoms (subM) evident in both disorders during a depressive episode.

Panel B: A dimensional perspective for mood disorder classification. Symptoms reflect a spectrum varying from lower to higher severity of hypo/manic symptoms.

Panel C: Periods during development for early detection of hypomanic/mixed symptoms and diagnosis of bipolar disorder during the course of the disorder.

Panel D: The potential of dimensional approaches, including the RDoC initiative to redefine “bipolarity” in terms of different underlying pathophysiological dimensions (labeled with Roman numerals in the figure) that cut across conventionally defined diagnostic categories of affective disorders, leading to the construction of disease profiles. Such approaches may facilitate identification of biomarkers reflecting relationships among genetic, molecular neural circuitry-level, and behavioral-level abnormalities that underlie different dimensions of psychopathology across the affective disorder spectrum.

Table 1

Neuroimaging Studies Directly Comparing BD depression and UD depression

STUDY	n	Group (M/F)	Age (yy)	Main findings
Structural				
Silverstone et al. 2003 (40)	13	BD-I depression (7/6)	40.2	Increased deep white matter hyperintensities in bipolar depression individual in comparison with unipolar depression and HI.
	11	UD depression (4/7)	34.4	
	19	HI (9/10)	35.9	
MacMaster et al. 2008 (48)	10	BD-I depression (4/6)	17.2	Increased pituitary gland volume in bipolar and unipolar depression individuals compared with HI.
	10	UD depression (4/6)	16.8	
	10	HI (4/6)	16.3	
Versace et al. 2010 (39)	15	BD-I depression (1/14)	36.3	Decreased FA of the left superior longitudinal fasciculus in bipolar depression individuals compared to unipolar depression and HI. Decreased FA in right uncinate fasciculus in bipolar depression individuals compared to HI. Decreased FA in left inferior longitudinal fasciculus in unipolar depression individuals compared to HI.
	16	UD depression (4/12)	32.3	
	24	HI (9/15)	29.5	
Savitz et al. 2011 (43)	22	unmed. BD I and II depression (7/15)	34.4	Decreased left and right habenula volume in unmedicated individuals with bipolar depression (but not medicated individuals) compared to unipolar depressed and HI.
	15	med. BD I and II depression (5/10)	45.1	
	28	UD depression (13/15)	43.9	
	32	UD remitted (8/24)	41.3	
	74	HI (29/45)	37.1	
Functional				
Taylor Tavares et al. 2008 (51)	12	BD depression (3/9)	33.4	Decreased activation in the ventrolateral and dorsomedial prefrontal cortex in unipolar depressed individuals to reverse response following misleading negative feedback compared to bipolar depression and HI.
	13	UD depression (3/10)	38.3	
	15	HI (4/11)	33.9	
Almeida et al. 2009 (50)	15	BD-I depression (1/14)	36.6	Left-sided, top-down orbitomedial prefrontal cortex - amygdala effective connectivity distinguished bipolar and depression individuals from HI; and right-sided, bottom-up, amygdala-orbitomedial prefrontal cortex effective connectivity distinguished bipolar depression individuals from unipolar depression individuals during positive stimuli.
	16	UD (3/13)	32.3	
	16	HI (4/12)	28.3	
Almeida et al. 2010 (49)	15	BD-I depression (1/14)	36.6	Elevated left amygdala activity to negative emotional facial expression in bipolar depression individuals compared to bipolar disorder remission individuals, unipolar depression individuals and HI.
	15	BD-I remission (5/10)	33.3	
	15	UD (2/13)	32.7	
	15	HI (3/12)	32.7	
Bertocci et al. 2011 (52)	18	BD-I depression (0/18)	31.9	Elevated dorsal anterior midcingulate cortex activity in unipolar depression individuals during the demanding 2-back condition with neutral face distracters relative to bipolar depression individuals and HI.
	23	UD depression (0/23)	29.7	
	16	HI (0/16)	32.8	

BD: bipolar disorder; UD: unipolar disorder; HI: healthy individuals; FA: fractional anisotropy