Review

Biological Psychiatry

Toward a Valid Animal Model of Bipolar Disorder: How the Research Domain Criteria Help Bridge the Clinical-Basic Science Divide

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ABSTRACT

Bipolar disorder is a diagnostically heterogeneous disorder, although mania emerges as a distinct phenotype characterized by elevated mood and increased activity or energy. While bipolar disorder's cyclicity is difficult to represent in animals, models of mania have begun to decode its fundamental underlying neurobiology. When psychostimulants such as amphetamine or cocaine are administered to rodents, a resulting upsurge of motor activity is thought to share face and predictive validity with mania in humans. Studying black Swiss mice, which inherently exhibit proclivity for reward seeking and risk taking, also has yielded some insight. Further, translating the biology of bipolar disorder in humans into animal models has led to greater understanding of roles for candidate biological systems such as the *GRIK2* and *CLOCK* genes, as well as the extracellular signal-related kinase pathway involved in the pathophysiology of the illness. The National Institute of Mental Health Research Domain Criteria initiative seeks to identify building blocks of complex illnesses like bipolar disorder in hopes of uncovering the neurobiology of each, as well as how each fits together to produce syndromes like bipolar disorder or why so many mental illnesses co-occur together. Research Domain Criteria-driven preclinical models of isolated behaviors and domains involved in mania and bipolar disorder will ultimately inform movement toward nosology supported by neurobiology.

Keywords: Animal models, Bipolar disorder, *CLOCK*, ERK, Mania, RDoC

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Bipolar disorders are clinical syndromes characterized by the presence of a constellation of symptoms that typically cluster into two divergent poles of mania and depression. During the early part of the 19th century, Emil Kraeplin is credited with demarcating for the international psychiatric community the bounds of bipolar disorder, as well as how it is clinically distinct from schizophrenia (1). However, significant diagnostic heterogeneity coupled with at present only an early understanding of its complex genetic, neurobiological, and neuroanatomical underpinnings have complicated the quest to hone in on valid animal models for bipolar disorder.

Mania, the hallmark syndrome of bipolar I disorder in DSM-5 and one of the clearest phenotypes in psychiatry, is reasonably homogenous in presentation, and a majority of animal models for bipolar disorder represent prototypes of mania. Generating and characterizing mania, on a behavioral and cellular level, in model animals provides important etiological clues for symptoms needed to make the diagnosis of bipolar I disorder. In clinical settings, bipolar disorder diagnoses are based on a spectrum of clustered symptoms, complicating the application of animal models (2,3). Animal models of both mania and depression provide insight into the underlying pathophysiology of bipolar disorder, which, in turn, informs clinical study design in humans.

In recent years, as outlined in its Research Domain Criteria (RDoC) initiative, the National Institute of Mental Health has advocated for studies that employ a dimensional framework of psychiatric classification focused on multilevel analyses including genes, molecules, cells, and behavior (4). In some ways, RDoC relieves the burden of designing a perfect blueprint for an animal with bipolar disorder, since it encourages focused study on the mediating biology possibly related to dimensions or domains of behavior and associated constructs (Table 1). RDoC-inspired animal models of bipolar disorder, instead of modeling a constellation of symptoms, may attempt to model a single clinical behavior, such as impulsivity or decreased need for sleep, commonly observed in bipolar I disorder and across the range of bipolar diagnoses and focus on uncovering the respective underlying biology. RDoC allows for a research agenda focused on modeling the neurobiology of behaviors rather than disease.

This brief commentary, which seeks to encourage the dialogue between clinical and basic scientists studying bipolar disorder, will focus primarily on mania. First, the integrity of the well-recognized and clinically studied manic phenotype will be discussed. Next, we will present a concise review and critique of strategies that have been used to represent mania and some key model animals that have received the most investigatory attention. Finally, we will argue for the importance of iterative and frequent exchanges between basic and clinical scientists whereby RDoC-driven preclinical models of isolated

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Table 1. Proposed Research Domain Criteria Domains and Constructs That Can Be Studied on Multiple Levels (e.g., Genes, Cells, Behavior)

Domain	Constructs
Negative Valence Systems	Acute threat (fear)
	Potential threat (anxiety)
	Sustained threat
	Loss
	Frustrative nonreward
Positive Valence Systems	Approach motivation
	Initial responsiveness to reward
	Sustained responsiveness to reward
	Reward learning
	Habit
Cognitive Systems	Attention
	Perception
	Working memory
	Declarative memory
	Language behavior
	Cognitive (effortful) control
Systems for Social Processes	Affiliation/attachment
	Social communication
	Perception/understanding of self
	Perception/understanding of others
Arousal/Modulatory Systems	Arousal
	Biological rhythms
	Sleep-wake

behaviors and domains, DSM-5 driven preclinical syndrome models, and clinical judgment will all inform a novel nosology for bipolar disorder fundamentally grounded in neurobiology.

HOW STRONG ARE THE BIPOLAR DISORDER AND MANIC PHENOTYPES?

Animal models of disease are ultimately only as strong as the clinical phenotypes upon which they are based. A DSM-5 diagnosis of bipolar I disorder requires at least one distinct period of elated, expansive, or irritable mood (e.g., mania), lasting at least a week, accompanied by increased energy or activity and other changes in mood and behavior (5). The majority of patients endorsing symptoms consistent with a manic episode during their lifetime will also report one or more major depressive episodes (6). While a DSM-5 bipolar II diagnosis requires only four concurrent days of hypomanic symptoms, patients must also endorse the occurrence of one or more lifetime major depressive episodes. Bipolar II is primarily a clinical diagnosis that includes characteristics of some of the key bipolar qualities, including cyclicity of mood and energy. The overall phenotype has not been represented in basic neurosciences yet in favor of studying the clearer phenotype of mania (Table 2).

DSM-5 psychiatric diagnoses including bipolar disorder are reached when an aggregate of symptoms is present. A recent article cleverly estimated, given a high number of possible symptom combinations, that there are 636,120 ways to reach a diagnosis of posttraumatic stress disorder (7). Because of this multifinality, bipolar I may be comprised of a different constellation of manic and depressive symptoms for each patient.

Episodes of acute mania are reasonably uniform across individuals. While there is still some individual variance in symptom presentation, mania generally involves the initiation of euphoric or elevated mood, significant alterations in cognition and perception, and diversification of activity and behavior. In a clinical realm, mania is easily recognized by a practitioner familiar with its trademark symptoms. However, valid animal models of mania must also consider that many episodes of mania are also characterized by the presence of concurrent depressive symptoms (i.e., mixed features).

ANIMAL MODELS OF MANIA IN BIPOLAR DISORDER: STRENGTHS, WEAKNESSES, AND NEUROBIOLOGICAL INSIGHTS

Many obstacles impede the ability to design animal models of complex mental illnesses such as bipolar disorder (8–10). An animal model that attempts to re-create any disease strives to maximize construct (i.e., etiologic), face, and predictive (i.e., pharmacologic) validities. Strategies to model bipolar disorder in representative animals have largely focused on one or more symptoms of mania (11). The cyclicity of bipolar disorder phenotypes in humans has proven difficult to replicate in animals, which means that considering independent animal models of mania alongside separate models of depression has provided a majority of insight into the biology of the overall disorder.

Table 2. DSM-5 Symptoms of Bipolar Disorder

Bipolar I Disorder	Bipolar II Disorder	Major Depressive Episode
At least one manic episode: A. Abnormally elevated, expansive, or irritable mood and increased activity or energy for at least 1 week B. ≥ 3 (4 if irritable) of the following: 1. grandiosity 2. decreased need for sleep 3. pressured speech 4. racing thoughts 5. distractibility 6. increase in goal-directed activity 7. risky behavior	At least one hypomanic episode, identical criteria to mania but lasting no longer than 4 days At least one major depressive episode	≥ 5 of the following: 1. depressed mood 2. diminished interest or pleasure 3. weight/appetite loss or gain 4. insomnia or hypersomnia 5. psychomotor agitation or retardation 6. fatigue or loss of energy 7. worthlessness or guilt 8. diminished ability to concentrate 9. recurrent thoughts of death or suicidal ideation