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Animal Models of Bipolar Mania: The Past, Present and Future

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Abstract

Bipolar disorder (BD) is the sixth leading cause of disability in the world according to the World Health Organization and affects nearly 6 million (~2.5% of the population) adults in the United State alone each year. BD is primarily characterized by mood cycling of depressive (e.g., helplessness, reduced energy and activity, and anhedonia) and manic (e.g., increased energy and hyperactivity, reduced need for sleep, impulsivity, reduced anxiety and depression), episodes. The following review describes several animal models of bipolar mania with a focus on more recent findings using genetically modified mice, including several with the potential of investigating the mechanisms underlying 'mood' cycling (or behavioral switching in rodents). We discuss whether each of these models satisfy criteria of validity (i.e., face, predictive, and construct), while highlighting their strengths and limitations. Animal models are helping to address critical questions related to pathophysiology of bipolar mania, in an effort to more clearly define necessary targets of first-line medications, lithium and valproic acid, and to discover novel mechanisms with the hope of developing more effective therapeutics. Future studies will leverage new technologies and strategies for integrating animal and human data to reveal important insights into the etiology, pathophysiology, and treatment of BD.

Introduction

Bipolar disorder (BD) is a complex disease defined by periods of both mania and depression with euthymic or normal mood states between episodes. Manic episodes can consist of hyperactivity, elevated mood or agitation, racing thoughts, reckless behavior, little need for sleep, and sometimes psychosis. Depressive episodes as defined by the DSM V can include persistent sadness, fatigue, eating disturbances, sleep disturbances, suicidal thoughts, guilt and social withdrawal. The cause of BD is unknown and may involve both genetic and environmental factors (Shinozaki and Potash, 2014). The mood stabilizing therapeutic effects of lithium (a salt) and valproate (an anticonvulsant) were discovered by accident and in the absence of any significant mechanistic understanding of BD (Can et al., 2014). While current treatments are generally effective for the reversal of manic episodes and preventing future episodes, these medications have limited, if any, efficacy on their own in the acute

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treatment of depressive episodes (McInerney and Kennedy, 2014). Moreover, standard antidepressant medications used either as monotherapies, or in conjunction with mood stabilizers or antipsychotics, are generally ineffective for treating depressive episodes, and may induce mood switching in a subset of patients with rapid cycling BD (De Wilde and Doogan, 1982, Himmelhoch et al., 1982, Gijsman et al., 2004, Amsterdam and Shults, 2005, Sachs et al., 2007, McElroy et al., 2010, Sidor and Macqueen, 2011, McInerney and Kennedy, 2014). Although there are a few studies suggesting therapeutic efficacy of antidepressant monotherapy for bipolar depression, current recommendations indicate antidepressants be used only in combination with mood stabilizers if those first line medications fail (McInerney and Kennedy, 2014). Despite their effectiveness in the treatment of mania, chronic treatment with current mood stabilizing drugs often result in serious side effects that make patient compliance difficult and burdensome. Our understanding of the etiological mechanisms of BD is poor. Therefore, the use of appropriate animal models should ultimately aid in the development of novel, potentially more efficacious treatments for this complex disorder.

The screening of compound libraries in animal models could also prove fruitful in the search for new medications. Most of the early mechanistic studies of BD in animals have focused on changes that occur following administration of lithium or other agents often on animals that are comparatively “normal”, which may limit the interpretability and applicability of these studies since lithium has very little effect on healthy individuals while having therapeutic effects on those suffering from mania (Calil et al., 1990). Therefore the changes in the brain that occur in wild-type rodents may not represent the same changes that occur in a rodent displaying mania-like behavior.

Evaluating animal models of BD: Issues of face, predictive, and construct validity

The use of rodent models that cut across multiple types of validity are vitally important to our understanding of psychiatric diseases and the search for better treatments. Face validity refers to the extent to which an animal model recapitulates important features of the human disease, such as neuroanatomical, biochemical, and/or behavioral phenotypes. There are few, if any, neurobiological pathologies that are known, with any certainty, to be biomarkers of the psychiatric disease. Even single behaviors may not completely map onto the clinical symptomology they are intended to model, especially when considering diagnoses are ‘inaccurate’ and ‘imprecise’ due to poor diagnostic criteria. Face validity is typically considered to be the requirement for reasonable ‘symptomatic’ homology or overlap with diagnostic criteria. This could pose a problem when diagnostic criteria are poorly defined or based solely on phenomenology (Chesler and Logan, 2012). Another issue arises when adhering to strict definitions of face validity—excessive anthropomorphization of rodent behavior. Most, if not all, of the animal models discussed here recapitulate at least one, but usually several, of the core behavioral phenotypes of bipolar mania, such as reduced depression, and increased impulsivity, or risk-taking behaviors. Face validity means also recapitulating anatomical, biochemical, or neuropathological features of the disease. Another form of this is sometimes referred to as pathological validity, whereby animal

models recapitulate observed postmortem pathology from brains or other tissues found in the human disease. Human postmortem studies, along with the advent of newer technologies to derive neurons from pluripotent stem cells collected from patients with disease, should provide a clearer understanding of the mechanisms involved in the pathophysiology of BD.

Construct validity is the degree to which a test measures what it claims to measure. It often refers to the relevance or translational nature of the methods by which a model is constructed. This might be achieved by exposing an animal to an environmental risk factor, knocking in a genetic mutation, or by altering the function of proteins, signaling pathways, or neurocircuitry that is postulated to be involved in the pathogenesis. However, we currently do not know with much certainty the disease-causing genes, proteins, or neurocircuitry for many mental illnesses, as most present with highly complex etiologies. It is true that many of the variants identified in large-scale GWAS studies in those with a psychiatric disease are of small effect. Transgenic animals expressing any of these common variants of small effect do provide some translational utility, although we would argue that these results are approached with some awareness of their limitations. Construct validity of any animal model of psychiatric disease should be interpreted with caution because our understanding of how genes correlate with disease phenotypes is continuously evolving. Throughout the review, we allude to type of validity and primarily highlight facets of each model with importance to bipolar mania (Table).

Predictive validity is usually defined as the extent to which a model responds to a treatment that is efficacious in humans. Animal models of mania are usually administered medications used for the treatment of BD, most commonly lithium or valproic acid, to investigate whether these compounds normalize or reverse these mania-like phenotypes. This too is complicated because of there are multiple factors involved in the interpretation of behavioral data. For example, an animal may show less hyperactivity in a particular assay because the medication was successful in reversing the “manic-like” neuronal activity, or because the animal is instead spending time compulsively grooming, or is sick or heavily sedated. Newer, highly validated cross-species translational approaches should improve the success for identifying novel, more effective therapeutics, where classical behavioral assays fail too often.

In this review we will discuss some of the pharmacological, environmental and genetic models that have been used over the years to study BD. We will discuss the rationale for these particular models as well as provide critiques related to their validity. The vast majority of these models attempt to recapitulate specific aspects related to mania, like hyperactivity or several different features of mania (Table 1). Although more recently, newer models are attempting to reproduce ‘mood’ switching, the hallmark feature of BD, such that we can better understand the precipitation of these episodes (Young and Dulcis, 2015). While no animal model will ever be able to fully, and precisely reproduce all the features of this complex disease, the use of multiple models could still be highly informative (Tables 2,3).

Pharmacological models of mania

Amphetamine-induced hyperactivity

The initial animal models of human mania relied heavily on the induction of hyperactivity in response to drugs that modulate dopaminergic activity (Table 2). People with BD have higher urinary dopamine levels with the emergence of manic symptoms (Joyce et al., 1995). Furthermore, many studies have found that psychostimulants (such as amphetamine) can produce symptoms that resemble human mania in normal healthy subjects (Meyendorff et al., 1985, Peet and Peters, 1995, Cousins et al., 2009) as well as exacerbate symptoms or induce a manic episode in bipolar patients. Therefore, the effects of psychostimulants on behavior became widely used as an animal model of mania (Young et al., 2011a). Amphetamine-induced hyperactivity in rodents was thought to be the ‘gold-standard’ rodent model of mania for many years (Berggren et al., 1978, Gould et al., 2001). This is despite evidence showing that amphetamine-induced alterations of behavior in humans without BD are often quite different to those seen in rodents (Silverstone et al., 1998). Amphetamine-induced hyperactivity can be reversed with certain mood stabilizing medications. Recent studies found that microinjection of valproic acid (VPA) in the ventricle, amygdala, striatum, and prefrontal cortex blocked the hyperactivity induced by methamphetamine (Arent et al., 2011). Amphetamine-induced hyperactivity can also be reversed by acute lithium in certain mouse strains but not others. For example, Gould et al., found this effect in C57BL/6 mice but not in C3H mice (Gould et al., 2001). Moreover, this effect of lithium can be confounded by lithium-induced reductions in activity in untreated mice, particularly in habituated animals during the inactive phase of their circadian cycle (Berggren et al., 1978), Chronic treatment with lithium does not appear to reverse amphetamine-induced hyperactivity even though chronic treatments are often necessary in humans to obtain a therapeutic response (Fessler et al., 1982, Cappeliez and Moore, 1990). In randomized controlled trials, patients can still exhibit mania rating scores high enough to meet criteria for enrolling in the study even after 3 weeks of mood stabilizer treatment (Sachs and Gardner-Schuster, 2007). Another major limitation of this model is that human mania is characterized by a broad set of symptoms beyond simple hyperactivity. Thus, this model only captures one particular facet of this complex phenotype. Mania is also a chronic disease which may lead to significant neuroplasticity while this amphetamine treatment is normally acute (Machado-Vieira et al., 2014). However, locomotor sensitization to repeated doses of amphetamine has also been suggested as a model of human mania (Cappeliez and Moore, 1990). This model could be viewed as a more relevant model to mania than acute treatment with these drugs since the sensitization paradigm induces a greater locomotor response over time via neuroplasticity of the dopaminergic circuitry. Acute administration of lamotrigine, lithium, valproate, retigabine and carbamazepine all reverse amphetamine-induced sensitization (Dencker and Husum, 2010), although valproate alone also reduces activity in vehicle-treated mice. A recent study looked at cognitive behavior and levels of BDNF in several brain regions in response to either seven or thirty five days of amphetamine with the goal of modeling cognitive impairments often seen in bipolar subjects with progression of this disorder. They found that both treatments led to impaired habituation memory and inhibitory avoidance with greater levels of habituation memory impairment in the chronic group (Fries et al., 2015). Moreover, they found increased brain derived neurotrophic factor

(BDNF) expression in the prefrontal cortex and amygdala and decreased BDNF protein in the hippocampus with these treatments (Fries et al., 2015). Thus, it is possible that very chronic treatment with amphetamine could be used to model the neuroprogression and cognitive impairment often seen in BD.

Amphetamine + CDP

Other animal models have used amphetamine in combination with other agents with the hopes of reproducing other symptoms of human mania beyond hyperactivity (Table 2). The benzodiazepine derivative chlordiazepoxide (CDP), which has anxiolytic and sedative effects alone, has been used in combination with amphetamine as a rodent model of mania (Poitou et al., 1975, Arban et al., 2005). However, the most common behavioral output measure used is still locomotor activity, since amphetamine and chlordiazepoxide (AMP + CDP) treatment increases activity in both rats and mice. Similar to amphetamine alone, AMP + CDP–induced hyperactivity is reversed by acute lithium, retigabine, lamotrigine and levetiracetam (Lamberty et al., 2001, Dencker et al., 2008, Redrobe and Nielsen, 2009). However, similar to amphetamine alone, the predictive validity of the AMP + CDP model is questionable, since both lamotrigine and levetiracetam have limited efficacy for treating mania (Goldberg and Burdick, 2002, Grunze et al., 2003, Kruger et al., 2008). One of the major concerns when using the AMP + CDP model of mania is the number of control groups required for each study (vehicle alone, amphetamine alone, CDP alone, AMP + CDP in combination, AMP + CDP plus each treatment, amphetamine plus each treatment and CDP plus each treatment) (Young et al., 2011a). Arban et al. (2005) conducted a complete control comparison study employing the AMP + CPD model in conjunction with several potential anti-manic agents (Arban et al., 2005). CPD alone often potentiated the locomotor activity-suppressant effects of known therapeutic treatments. Thus, it is unclear if the combined model provides any meaningful data on the action of anti-manic agents, or whether changes in activity simply represent a combination of additive drug effects. Furthermore, the complexity of controls required in the AMP + CPD model of mania makes it difficult to interpret the responses to novel putative anti-manic agents. For example, Kozikowski et al. (2007) examined the effects of a novel GSK-3β inhibitor in the AMP + CPD model of mania, and found that consistent with a high dose of valproate, the novel inhibitor attenuated but did not reverse AMP + CDP–induced hyperactivity (Kozikowski et al., 2007). However, the authors did not assess the effects of valproate treatment alone or in combination with either amphetamine or CPD, and the inhibitor effect was not compared to the vehicle treatment which appeared to reduce activity on its own. Therefore the complexity of factors make implementation and interpretation difficult in this model. Moreover, Kelly et al. (2009) found that the combination of amphetamine +CDP produced an inverted-U dose response in measures of hyperactivity in outbred CD1 and inbred C57BL/6N or 129S6 mice (Kelly et al., 2009). The important implications of this are in the interpretation of any effects seen with the addition of mood stabilizing drugs in that one cannot be certain as to whether the drug produces a “blockade” or a “potentiation” of the effects of amphetamine + CPD.

Oubain

The adenosine triphosphotase inhibitor, ouabain, administered ICV also induces hyperactivity in the open field and this treatment has been proposed as a model of mania (el-Mallakh et al., 1995) (Table 2). Moreover, this effect can last for seven days after a single ICV infusion (Riegel et al., 2009). OUA treatment is associated with severe neuronal damage and high levels of oxidative stress through the increased formation of lipid and protein oxidation products along with decreased BDNF levels in the brain (Riegel et al., 2009, Jornada et al., 2010). Some of these changes were modified by lithium and valproate (Jornada et al., 2011). For example, ouabain decreased levels of Bcl-2 and increased oxidative stress factors such as BAX and pp53 in rat brain (Valvassori et al., 2015). Treatment with both lithium and valproate improved most of these measures, however they were not protective against the increases in BAX in frontal cortex or hippocampus (Valvassori et al., 2015). In patients with BD, decreased BDNF levels have been described when compared with healthy controls (Machado-Vieira et al., 2007). The typical antipsychotic, haloperidol decreases ouabain-induced hyperactivity in rats, an effect which is confounded by haloperidol-induced reduction in activity alone (El-Mallakh et al., 2006). In contrast, the atypical antipsychotic olanzapine does not significantly reduce activity alone, nor does it attenuate ouabain-induced hyperactivity (El-Mallakh et al., 2006). Moreover, when one compares behaviour in a well lit open field and in a dark activity chamber (Decker et al., 2000); the results indicate that ouabain increases activity only in the open-field test. Thus, a novel and somewhat anxieogenic environment is needed to see the measurable effects of this compound. Furthermore, repeated exposure to an open-field chamber may induce a ‘floor effect’, where activity levels are so low that a drug effect alone could not lower them further. For example, Li et al. (1997) habituated rats for several days in the open field prior to quantifying ouabain-induced hyperactivity and acute lithium ‘reversal’ of effects. Lithium failed to decrease activity levels in this study since they were already minimal due to environmental familiarity (Li et al., 1997).

D2 receptor stimulation

Acute administration of the dopamine D2 receptor agonist, quinpirole can induce hyperactivity at certain doses and this treatment has also utilized as an animal model of mania. Chronic administration of the anti-manic drugs valproate and carbamazepine can reverse quinpirole-mediated locomotor activation (Shaldubina et al., 2002). The attenuation of quinpirole-induced hyperactivity was also found however with topiramate (Shaldubina et al., 2002), which is not a treatment for mania (Kushner et al., 2006, Vasudev et al., 2006) and may in fact induce a manic episode in certain patients (Jochum et al., 2002). It is relevant to note that topiramate has not been assessed in many other models of mania.

Environmental models of mania

Sleep deprivation and circadian rhythm disruption

Some labs have attempted to use environmental manipulations to induce manic-like symptoms in animals. Since it is well known that circadian rhythm disruption and sleep disturbances can often trigger manic episodes (Malkoff-Schwartz et al., 1998, McClung, 2007), researchers have used various sleep deprivation paradigms to model human mania

(Gessa et al., 1995) (Table 2). These paradigms often involve placing a rat or mouse on a small platform (3–7 cm) surrounded by water for an extended period of time, typically 72 hours (Gessa et al., 1995). If the animal falls asleep it will fall into the water, therefore the animal stays awake to prevent this from happening. When rodents are placed back into their home cage after the sleep deprivation period, they exhibit a cluster of manic-like behaviours that include insomnia, hyperactivity, aggressive behavior, hypersexuality (an increase in mounting behaviour) and increased stereotypy (sniffing and rearing) (Morden et al., 1967, Hicks and Moore, 1979, Hicks et al., 1979, Moore et al., 1979). This abnormal behavior is at its peak 30–40 min period immediately after the sleep deprivation treatment but there can be lasting effects (Einat, 2006). A recent study looked at individual differences in the response to a 3 day circadian rhythm disruption protocol in mice and found that those mice that had a delay in the recovery of normal sleep/wake behavior displayed an increase in quinpirole-induced hyperactivity 10 days after the paradigm ended, suggesting that these particular mice showed a lasting “manic-like” response following a short circadian rhythm disruption (Jung et al., 2014). Gessa et al. (1995) found that 10 days of lithium treatment significantly reduced hyperactivity and decreased the latency to fall asleep compared with vehicle in 72 hour sleep-deprived rats (Gessa et al., 1995). In addition, rats given four injections of haloperidol in the last hours of the sleep deprivation period also demonstrated a decreased latency to fall asleep relative to vehicle-treated animals, which was interpreted as a reduction in manic-like insomnia. Thus in contrast with pharmacological models of mania, acute sleep deprivation induces a range of abnormal behaviors beyond simple hyperactivity and is responsive to chronic treatment with mood stabilizing drugs, making it perhaps more relevant for the study of human BD. However, while studies of sleep deprivation in healthy human controls can produce a temporary manic-like state, they rarely develop full-blown mania as seen with subjects with BD, and this state in healthy controls usually only lasts until the subject is able to sleep again.

While the sleep-deprivation paradigm described above may be useful in understanding the role of sleep in the development of manic-like behavior, it is important to note that this paradigm includes several stressors aside from simple sleep deprivation, including isolation, immobilization and the experience of falling into water. So it is not clear which of these stressors leads to the abnormal behaviors. A study by Benedetti et al. administered intervals of 24 hour sleep deprivation to CD1 mice while also including a stress control group with a larger stable platform enabling sleep, but enforcing isolation and immobilization (Benedetti et al., 2008); only the sleep-deprived mice exhibited increased locomotion and aggressive behaviour relative to controls, indicating that lack of sleep is key to the development of a manic-like phenotype.

How does sleep deprivation lead to a manic-like phenotype? One study examined the effect of lithium and sleep deprivation on brain protein kinase C (PKC) activity, an enzyme signaling pathway implicated in locomotor hyperactivity, risk-taking and excessive hedonic drive associated with mania (Szabo et al., 2009). Wistar-Kyoto rats subjected to a relatively short period of sleep deprivation (4 h during the light cycle) exhibited increased PKC phosphorylation of AMPA receptors, neurogranin and myristoylated alanine-rich C kinase substrate (MARCKS) in frontal cortex relative to non-sleep deprived animals. In contrast, C57BL/6 mice treated with lithium in food for 4 weeks showed significantly reduced

phosphorylation of these PKC molecular targets compared with animals fed a normal diet. While behavioural symptoms such as hyperactivity or aggression were not assessed in this study, the data indicate that a sleep deprivation paradigm may have construct validity in representing the neurobiological alterations that may precipitate manic episodes.

Resident-intruder Paradigm

Human mania is often characterized by increased aggression, agitation and intrusive actions. These behaviors can be induced in rodents using variations of the resident–intruder test (Einat, 2006). This task typically starts with the introduction of a group-housed intruder rodent into the home cage of an isolated mouse or rat. The aggressive acts committed by the resident and the defensive acts and postures exhibited by the intruder are recorded (Miczek et al., 2001). Aggressive behaviours by the resident, including biting, threatening postures and tail rattling, can be increased by prolonged isolation or exposure to acute stressors such as foot shock (Legrand and Fielder, 1973, Miczek and O'Donnell, 1978). Typically the resident–intruder test has been employed as a model of depression by studying the social defeat characteristics displayed by the intruder. However, treatment with lithium can reduce resident aggression in both rats and mice (O'Donnell and Gould, 2007) suggesting that the aggressive nature of the resident may in some way model the aggressive behavior seen often in human mania (Table 1,2). Lithium administration has also consistently reduced aggression induced by mild electric foot shock in rats and mice, as well as attenuate combative behaviour augmented by stimulants such as D-amphetamine (Eichelman et al., 1973, Mukherjee and Pradhan, 1976, Prasad and Sheard, 1982, Kovacsics and Gould, 2010). However, lithium also decreases the response to shock in the jump-flinch test which could confound the interpretation of lithium's effects on shock-mediated aggression paradigms (Kovacsics and Gould, 2010). Lithium also reduces isolation-induced fighting outside the home cage, as well as resident–intruder fighting within the home cage (Brain and Al-Maliki, 1979, Oehler et al., 1985). One study examined the effects of both lithium and valproate on aggression using a resident–intruder paradigm in C57BL/6 mice (Einat, 2007). Resident mice treated with lithium for 4 weeks before the test exhibited a significant reduction in the number of attacks against intruder mice compared with controls but did not show any difference in non-aggressive interactions such as rearing or sniffing. Finally, it is also worth mentioning that chronic treatment with a variety of antidepressant drugs increases aggression in the resident–intruder paradigm (Mitchell, 2005), suggesting that this may constitute a model of antidepressant-induced mania in individuals with BD (Koszewska and Rybakowski, 2009).

While the resident–intruder test has been in use for several decades (Miczek et al., 2001), a different model of dominant–submissive behaviour has also been proposed to induce symptoms of both depression and mania (Malatynska and Knapp, 2005). This paradigm is based on the notion that subordinate animals, similar to depressed humans, show increased defensive behaviour and reduced locomotor activity; in contrast, dominant animals, similar to humans in a manic state, are characterized by self-confident, assertive and aggressive behavior (Gardner, 1982). In this paradigm, two rats are placed in opposite chambers connected by a narrow tunnel allowing only one animal at a time access to a food source. When tested over 2 weeks in 5 min daily sessions, approximately half the animal pairs

develop a dominant–submissive relationship, where one dominant animal monopolizes access to the food, defined as spending 40% more time at the feeder compared with the submissive rodent. When treated with antidepressant medications such as imipramine, desipramine and fluoxetine, submissive rats become more assertive, resulting in a significantly greater access to the food after 2 to 4 weeks of treatment. Conversely, dominant rats injected with lithium, carbamazepine or valproate become less aggressive and lose their dominant status (Malatynska and Knapp, 2005, Malatynska et al., 2007). In addition, the mood stabilizers exert an effect over a time course that is similar to that observed in bipolar patients in that lithium and carbamazepine treatment reduced rodent dominance only after 2–3 weeks of treatment. It is important to mention, however, that resident–intruder paradigms are also sensitive to the effects of anxiolytic and anxiogenic drugs, suggesting that behavioural changes in this model could be due to changes in anxiety, limiting the predictive validity of this model for BD (Vassout et al., 2000).

Genetic models of bipolar mania

Human genetic studies have identified many gene polymorphisms associated with psychiatric diseases, such as depression, anxiety, and BD, which implicate altered gene function in these disorders. Rodent models that leverage single gene mutation, knockout, or transgenic technologies are highly valuable for understanding the impact of a specific gene, or polymorphism, on behavior and the underlying mechanisms, although there are several limitations in their ability to fully resemble the pathogenesis in humans. For example, it is highly unlikely that BD is related to a single gene mutation. As stated earlier, psychiatric diseases emerge from complex etiologies of environmental and genetic origins (Bagot et al., 2014, Nestler, 2014, Pena et al., 2014). Nevertheless, there is a tremendous amount of scientific and translational utility in studying single gene mutation or knockout animal models for understanding basic mechanisms of brain function, behavior, and their relation to psychiatric diseases (Table 3). Several genetic animal models continue to be used for modeling specific endophenotypes that are common to many psychiatric diseases, or related to a particular illness. These models are also being used to identify the potential mechanisms underlying the therapeutic effects of existing treatments, or to screen the therapeutic potential of novel compounds.

BD is characterized by mood episodes accompanied by shifts in energy and activity. Over the past several years, there are several newly developed transgenic mice to model human mania. However, it has been incredibly difficult to develop models with spontaneous cycling between manic and depressive behavioral states (Young and Dulcis, 2015). We will discuss these new genetic models and recent attempts to investigate ‘mood’ switching. Some of these models are able to induce switching between manic and depressive related behaviors to different environmental stimuli or by probing the potential circadian variation of these behaviors, thus improving on their validity as a model of the human condition (Le-Niculescu et al., 2008, Sidor et al., 2015).

ClockΔ19 mutant mice

While the exact cause of BD is unknown, abnormalities in circadian rhythms may contribute to the pathogenesis of the disorder (Frank et al., 2000, Wirz-Justice, 2006, McClung, 2007),

and markers of circadian disruption may predict susceptibility to mood changes, as well as treatment response (Kripke et al., 1978, Milhiet et al., 2011, McCarthy et al., 2013). A polymorphism in the 3′ flanking region of the *Clock* gene was associated with a greater frequency of manic episodes, insomnia, early morning waking, and reduced need for sleep in bipolar patients (Benedetti et al., 2003, Serretti et al., 2003). Efforts are underway in our laboratory to determine the consequences of these polymorphisms on CLOCK expression and function. The most well-characterized genetic mouse model of mania is the *Clock* mutant mouse (*Clock*Δ19) (King et al., 1997b, Vitaterna et al., 2006) (Table 3). CLOCK, along with its binding partner BMAL1, form heterodimers that drive the positive loop of the molecular clock. The molecular clock is comprised of interconnecting transcriptional-translational positive and negative feedback loops oscillating over a 24 hour period (Gustafson and Partch, 2015). *Clock*Δ*19* mutant mice have a single base mutation that leads to a loss of exon 19 during an aberrant gene-splicing event, which effectively deletes the coding region for the transactivational domain that is required for CLOCK-mediated transcription (King et al., 1997a). Hence, circadian rhythms of gene transcription and behavior are significantly altered in *Clock* mutant mice (Antoch et al., 1997). It is worth noting that behavioral rhythms of *Clock* mutant mice almost fully breakdown under constant conditions, which is more severe than those measured in individuals with BD. However, *Clock* mutant mice share other circadian phenotypes with BD, including reduced circadian amplitude and delayed phase (Vitaterna et al., 1994, Challet et al., 2000, Vitaterna et al., 2006, Etain et al., 2014, Rock et al., 2014).

Recent efforts have begun to develop and employ translational approaches providing cross-species validation of behavioral phenotypes relevant to BD (Henry et al., 2010, van Enkhuizen et al., 2013b). Impaired sensorimotor gating and hyperactivity are core features of acutely manic patients, which can also be readily assessed in rodent models. *Clock* mutant mice also have sensorimotor deficits along with attenuated startle habituation during paired pulse inhibition (PPI) paradigms (van Enkhuizen et al., 2013b). More systematic studies are necessary to determine whether sensorimotor gating and startle responses vary based on sex and/or ‘mood’ state, as has been shown in BD patients (Barrett et al., 2005, Gogos et al., 2009). In addition to sensorimotor impairments, future studies should continue to expand on the performance of *Clock* mutant mice during ‘cognitive’ tasks, such as spatial working memory, attention, and decision-making, because cognitive impairments may be a hallmark of the disorder, at least in certain individuals. Indeed, neurocognitive deficits often accompany sensorimotor impairments in patients experiencing either manic or depressive episodes (Torres et al., 2011).

A change in activity is another core feature of BD, particularly during manic episodes, and can also be measured in humans within a laboratory setting. The behavioral pattern monitor (BPM) is essentially an open-field area designed for humans to explore, investigate and interact with different stimuli, such as familiar and novel objects, as a standardized paradigm to assess level, pattern, and organization of activity, in addition to goal-directed behavior (Young et al., 2007, Perry et al., 2009, Minassian et al., 2010, Young et al., 2010). The human BPM is an intriguing approach to investigating activity related phenotypes in BD and assessing whether rodent models display similar patterns (Geyer et al., 1986) van Enkhuizen

et al., 2013c) (Table 1). Acutely manic patients are hyperactive, with more object exploration and goal-directed behavior (linear, direct movements) (Perry et al., 2010, Minassian et al., 2011). *Clock* mutant mice, on the other hand, display subtle dissimilarities with acutely manic patients. While mutant mice are hyperactive and have the ability to habituate to repeated testing environments similar to manic patients (Easton et al., 2003, McClung et al., 2005), their pattern and organization of locomotor activity are different (referred to as their 'spatial d', which ranges from 1 to 2, where 1 represents a straight path and 2, highly circumscribed small scale movements; (Perry et al., 2009). Acutely manic patients tended to have more linear movements, represented by a lower spatial d, whereas spatial d was higher, more circumscribed repetitive movements, in *Clock* mutant mice (Perry et al., 2009, van Enkhuizen et al., 2013c). These discrepancies require further study, such as elucidating the underlying neurobiological mechanisms regulating these activity phenotypes, which may be related to altered dopamine transmission in striatum and VTA. Nevertheless, *Clock* mutant mice display both hyperactivity and sensorimotor deficits similar to acutely manic patients.

Clinical symptoms used for diagnoses include reduced depression and increased risk-taking behavior during manic episodes. Much of our work has focused on discovering the cellular and molecular mechanisms that regulate anxiety, risk taking, and depression related behaviors in *Clock* mutant mice. Turek and colleagues were the first to report increased exploratory and escape seeking behaviors in both male and female *Clock* mutant mice (Easton et al., 2003). These findings have been replicated and expanded by our group and others and include a wide range of manic-like phenotypes (Table 3) (Roybal et al., 2007, van Enkhuizen et al., 2013b). We have found that these mania-like behaviors are driven by enhanced dopamine release from VTA neurons (e.g., enhanced dopamine cell bursting and firing and increased extracellular dopamine) (Coque et al., 2011, McClung et al., 2005, Sidor et al., 2015). Indeed, selectively driving dopamine neurons of the VTA with optogenetics recapitulates the hyperdopaminergic state and the anxiety and depression related behaviors of *Clock* mutants (Sidor et al., 2015).

These behaviors can be completely normalized to wild-type levels by chronic lithium treatment (Roybal et al., 2007). Interestingly, we found that *cholecystokinin* (*Cck*), a gene encoding for a peptide that is co-released with dopamine to inhibit further dopamine release by activation of presynaptic receptors, is a gene that is rhythmically transcribed by CLOCK:BMAL1 heterodimers, and significantly reduced in the VTA of *Clock* mutants (Arey et al., 2014). Lithium increased *Cck* expression in the VTA of *Clock* mutants through epigenetic modifications and recruitment of other transcription factors to the gene promoter (Arey et al., 2014). Interestingly, *Cck* expression was significantly increased in human postmortem VTA tissue collected from medicated patients with BD (Arey et al., 2014). Thus, *Cck* may be a primary target of lithium treatment that is relevant for its therapeutic effects on mania.

The mechanisms underlying CLOCK's regulation of these behaviors is complicated, mostly due to our findings of a mixed behavioral state (greater novelty exploration, hyperactivity and increased depression-like behavior) following knockdown of *Clock* specifically within the VTA of wild-type mice (Mukherjee et al., 2010). Consistent with this, CLOCK

overexpression (OX) in the VTA of *Clock* mutants only rescued hyperactivity and anxiety-related behaviors (Roybal et al., 2007). Other molecular mechanisms in alternative brain areas seem to be involved based on these findings and should be explore in the future. In fact, CLOCK in the hippocampus may be involved in depression related behaviors (Jiang et al., 2013).

Alterations in circadian rhythms may be a common factor in the vulnerability to highly comorbid psychiatric diseases, substance use and abuse disorders and BD (Sjoholm et al., 2010). It is well known that individuals with BD are more prone to developing substance use problems and addiction. In addition to the mania-like phenotypes, *Clock* mutant mice display 'hyperhedonia'—an increase in reward sensitivity and motivation. At lower doses of cocaine, *Clock* mutant mice were more prone to developing conditioned place preference, a proxy of contextual reward conditioning (McClung et al., 2005). Additionally, these mice had increased locomotor sensitization to repeated cocaine injections and lowered reward thresholds during intracranial self-stimulation (ICSS) of the medial forebrain bundle, an intensely pleasurable and rewarding action (McClung et al., 2005, Carlezon and Chartoff, 2007). During operant self-administration paradigms, *Clock* mutant mice administered higher levels of cocaine across a range of doses and reached higher break-points than wild-type mice (i.e., enhanced seeking and motivation) (Ozburn et al., 2012). Diurnal patterns of cocaine self-administration found in wild-type mice were completely lost in *Clock* mutants (Ozburn et al., 2012), suggesting a 'loss of control' of normal circadian regulation of drug-taking behavior. Finally, *Clock* mutant mice consume more alcohol at higher concentrations during two-bottle free choice paradigms (Ozburn et al., 2013). Collectively, these data suggest a hyperdopaminergic state observed in the *Clock* mutants contributes to anxiety, depression, and addiction related phenotypes. Disrupted circadian rhythms contribute to the vulnerability and emergence of addiction and mood disorders (Logan et al., 2014). However, there are very few studies investigating the potential interplay between *Clock* gene variants, addiction, and mood disorders. One study reported specific variants of *Clock* may increase the vulnerability to depression in individuals with an alcohol use disorder (Sjoholm et al., 2010).

Communication across multiple brain areas is required for processing of information, decision-making, motor planning, and behavioral action. Disrupted connectivity or coherence between certain brain areas during discrete visual or auditory, or more demanding cognitive tasks has been repeatedly found in BD and may be related to mood state. Functional neuroimaging and electroencephalography (EEG) are techniques used to measure 'connectivity' and coherence. With EEG, coherence is defined as the coupling of or relationship between specific signals in a given frequency band, and thus represents the functional relationship or synchronization between cortical regions (Nunez et al., 1997, Sarnthein et al., 1998). EEG signals are filtered into delta (0.5–3.5 Hz), theta (4–7 Hz), alpha (9–13 Hz), beta (18–30 Hz), and gamma (28–48 Hz) oscillations. Disrupted coherence is thought to depict abnormal or poorly integrated brain function.

The generation of beta oscillations depend on the synchronization of gamma signals that originate from networks of inhibitory GABAergic interneurons (Gray and McCormick, 1996, Whittington et al., 2000). Long-distance gamma coherence was substantially reduced

in both euthymic and manic patients (Ozerdem et al., 2010, Ozerdem et al., 2011), which may underlie elevated beta activity associated with mania (Ozerdem et al., 2008). Reduced gamma oscillations could reflect dysfunctional GABA signaling in cortical regions. Whether these markers are relevant for treatment response remains an open area of exploration (Ozerdem et al., 2010), these findings indicate altered beta and gamma activity are fairly robust representations of impaired functional connectivity of frontal and temporal cortical brain regions in BD (O'Donnell et al., 2004, Kam et al., 2013, Ozerdema et al., 2013). Neuroimaging studies have been able to more precisely identify the brains regions and define localities of the impaired connectivity. Dysfunction of subcortical, striatal-thalamic, and prefrontal networks, along with regions that send inputs to these areas, such as the amygdala, is associated with BD (Strakowski et al., 2005, Ongur et al., 2010). These networks may change over the course of the disease process. For example, abnormal activation patterns in the PFC, striatum, and amygdala preceded awry activation in the cerebellar vermis, lateral ventricles, and prefrontal regions that were more associated with repeated mood episodes (Strakowski et al., 2005).

Synchronization and coherence among areas of the cortico-striatal neurocircuitry is also disrupted in *Clock* mutant mice. Simultaneous extracellular recordings from nucleus accumbens (NAc), prelimbic cortex, and the VTA of freely behaving *Clock* mutant mice revealed severely impaired phase coupling and synchrony between limbic regions during the exploration of a novel environment (Dzirasa et al., 2010). Phasic entrainment, or coherence, of NAc low gamma (30–55 Hz) and delta (1–4 Hz) oscillations negatively correlated with exploratory behavior in wild-type mice, (i.e., more phase coherence, less exploratory drive). In *Clock* mutants, there were profound deficits in low gamma oscillations and single neuron phase coupling in the NAc, along with enhanced exploratory drive, which were reversed by chronic lithium treatment (Dzirasa et al., 2010). Reductions in gamma oscillations were also associated with reduced anxiety related behavior (Dzirasa et al., 2011). Overall, general circuit synchronization and coherence among the NAc and amygdala, or the VTA, predicted fear or anxiety related behavior, respectively, in wild-type mice, but failed to do so in *Clock* mutants (Dzirasa et al., 2011). Thus, low gamma coherence in the NAc and impaired phase synchrony within the limbic system may be contribute to the mania-like behaviors of the mutants. Although the precise mechanisms that drive these oscillations, or those that lead to impaired synchrony are unknown, we hypothesize an imbalance, or shift towards, dopaminergic and glutamatergic signaling within and from the limbic circuitry is primarily responsible. If so, this model may be useful for investigating the cellular and molecular mechanisms contributing to circuit level deficits associated with BD that likely involve the dysfunctional dopamine and glutamate crosstalk at the postsynaptic density believed to be a major contributor to the pathophysiology of the disease (de Bartolomeis et al., 2014).

GSK-3β overexpressing (OX) mice

At therapeutic concentrations, lithium inhibits several enzymes via competition with magnesium, including inositol monophosphatase, phosphoglucomutase, and glycogen synthase kinase-3 (GSK-3) (Can et al., 2014, Gould et al., 2004, Gould and Manji, 2005, Klein and Melton, 1996, Li et al., 2007, Phiel and Klien, 2001, Stambolic et al., 1996). Lithium inhibits GSK-3 in the mouse brain (De Sarno et al., 2002, Munoz-Montano et al.,

1997, Noble et al., 2005, (O'Brien et al., 2004, O'Brien et al., 2011) and in peripheral blood cells of those with BD (Li et al., 2007, Polter et al., 2010). In several rodent models of mania, synthetic inhibitors of GSK-3β mimic the 'therapeutic' effects of lithium (Kozikowski et al., 2007, 2011). Furthermore, polymorphisms in GSK-3β are associated with certain symptoms of BD, as well as treatment response to lithium (Jope and Roh, 2006, Lin et al., 2013, Tang et al., 2013). The antipsychotic valproic acid also inhibits GSK-3β activity via mechanisms less characterized than lithium action (Chen et al., 1999, De Sarno et al., 2002, Jin et al., 2005, Sintoni et al., 2013).

GSK-3β has numerous cellular and molecular functions, including cell development, gene transcription, metabolic homeostasis, neurogenesis, and apoptosis (Doble and Woodgett, 2003). GSK-3β signaling pathways also form feedback loops with the molecular circadian clock to modulate circadian amplitude and period (Besing et al., 2014, Lavoie et al., 2013). The molecular clock regulates the activity of GSK-3β, and almost every core circadian protein, including BMAL1 and CLOCK, is directly phosphorylated by GSK-3β (Besing et al., 2014, Spengler et al., 2009). Interestingly, GSK-3β variants predicted the effects of lithium on molecular rhythms of skin fibroblasts cultured from bipolar patients (McCarthy et al., 2013). In general, lithium tended to resynchronize dampened rhythms of only those cells from bipolar patients (McCarthy et al., 2013). Thus, GSK-3β regulation of circadian rhythms may contribute to the mood-stabilizing properties of lithium (Kaladchibachi et al., 2007, Lamont et al., 2010, Li et al., 2012).

Perhaps the most investigated pathway by which GSK-3β might exert therapeutic action is via the Wnt signaling pathway that controls the expression and activity β-catenin, a nuclear transcription factor. GSK-3β inhibits the activation of this pathway by phosphorylating β-catenin for ubiquitin dependent degradation (Aberle et al., 1997, Orford et al., 1997). Protein expression of GSK-3β, pGSK-3β-ser-9, and β-catenin is significantly reduced in the dorsolateral prefrontal cortex and the temporal cortex of human post-mortem brains from bipolar patients (Pandey et al., 2015). A substantial effort needs to be put forth to investigate the transcriptional networks regulated by GSK-3β control of β-catenin-mediated gene transcription. Early efforts suggest there is tremendous overlap between genes previously identified as candidates involved in the pathophysiology of BD and those genes directly regulated by β-catenin-mediated transcription (Pedrosa et al., 2010), although this likely depends on brain region, treatment duration, and the course of the disorder. During chronic lithium treatment, GSK-3β is inactivated, preventing β-catenin degradation, and thus increasing protein expression (Yost et al., 1996, Behrens et al., 1998). A loss of GSK3β activity has consequences on synaptic plasticity and behavior via β-catenin signaling. Recent evidence suggests increased β-catenin activity destabilizes the formation of new dendritic spines and attenuates excitatory transmission (Ochs et al., 2015). β-catenin overexpression in the mouse brain leads to reduced depression related behaviors, and attenuated amphetamine induced hyperlocomotion and sensitization, quite similar to the effects of lithium treatment (Gould et al., 2007). GSK-3β haplosufficient mutant mice, lacking one copy of the GSK-3β gene, display an antidepressant-like behavioral phenotype, which also mimics the effects of lithium treatment mice (O'Brien et al., 2004). Together these results suggest the therapeutic action of lithium depends on inhibiting GSK-3β activity (O'Brien et al., 2011), possibly through the regulation of dopaminergic activity and signaling pathways downstream of

dopamine receptor activation (Beaulieu et al., 2011, Beaulieu, 2012, de Bartolomeis et al., 2014, Gomez-Sintes et al., 2014).

GSK-3β-OX mice may have some relevance for modeling certain behaviors related to BD (Table 3). These mice are hyperactive and have reduced food intake across the circadian cycle (Prickaerts et al., 2006). Although, it is worth noting that both hyper- and hypo-phagia are associated with BD (Kishi and Elmquist, 2005, Krishnan, 2005). GSK-3β-OX mice are also hyperactive with impaired habituation to a novel environment and reduced depression related behavior (Prickaerts et al., 2006). These mice also have an increased startle response, which is in contrast to reports of low startle response, in acutely manic (Perry et al., 2001), mixed episode (Carroll et al., 2007), and remitted bipolar patients (Giakoumaki et al., 2010).

Other discrepancies between GSK-3β-OX mice and BD patients are worth noting—the corticosterone response to acute stress is normal in these mice (Prickaerts et al., 2006), while a blunted hormonal response is observed in BD patients (Houtepen et al., 2015), representative of altered HPA axis and autonomic nervous system regulation in response stress. In line with this, knockin mice carrying a transgene that impairs serine phosphorylation of GSK-3β (P-GSK-3β-KI), which effectively prevents GSK-3β inactivation, are more susceptible to stress-induced depression related behaviors (Polter et al., 2010). The relationship between stress and BD is complex and likely depends on a number of factors, such as chronicity of the disorder, treatment regimen, mood state, and uncontrollable environmental factors. The role of GSK-3β in stress regulation of neurocircuitry related to behavior relevant to psychiatric disorders requires further investigation (e.g., brain region or cell type specificity, compensatory signaling or plasticity). Indeed, mouse models of increased GSK-3β activity appear to have different behavioral phenotypes. Unlike GSK-3β-OX mice, P-GSK-3β-KI mice were hyperactive and more sensitive to amphetamine-induced hyper-locomotion (i.e., mania-like), yet exhibited increased anxiety and depression related behaviors (i.e., depressive-like) (Polter et al., 2010). As previously mentioned, this discrepancy may be due to enhanced sensitivity of the P-GSK-3β-KI mice to acute stress experienced during FST, TST, and learned helplessness paradigms (Polter et al., 2010). Acute stress decreased P-GSK-3β in the brains of wild-type mice, which indicates stress-induced GSK-3β activity (Polter et al., 2010). These effects suggest other molecular pathways are involved, but do lead to the hypothesis that the level of GSK-3β activity may be correlated with mood state. In peripheral blood mononuclear cells (PBMCs) from BD patients, P-GSK-3β levels negatively correlated with mania symptom severity, but not depression (Polter et al., 2010). The inhibitory effects of lithium on GSK-3β activity depend on serine phosphorylation, and thus offer a putative mechanism for mood stabilization, especially when considering lithium’s effectiveness for treating bipolar mania.

Dopamine transporter knockdown (DAT-KD) mice

Dysfunction in DAT has been proposed as a putative mechanism for altered dopaminergic neurotransmission in BD. Based on genetic, molecular, and imaging evidence indicating reduced DAT expression in BD (Horschitz et al., 2005, Greenwood et al., 2006, Anand et al., 2011, Pinsonneault et al., 2011), Young, Geyer, and colleagues have demonstrated mice

with reduced DAT expression (~10% of wild-type DAT levels; Zhuang et al., 2001), exhibit a wide range of mania-like behaviors (Young et al., 2010, Young et al., 2011b, van Enkhuizen et al., 2013a, van Enkhuizen et al., 2014a, van Enkhuizen et al., 2014b) (Table 3). As mentioned previously, acutely manic bipolar patients display reduced spatial d (more linear movements) and increased goal directed behavior (object exploration) than healthy volunteers and schizophrenic patients in the hBPM (Perry et al., 2009). DAT-KD mice, however, display increased spatial d relative to other animal models of reduced dopamine uptake, including pharmacological inhibition of DAT by GBR12909 and acute amphetamine administration (Perry et al., 2009, Young et al., 2010). Mice treated with GBR-12909 were strikingly similar to bipolar patients in the BPM—hyperactive, increased exploration, with more predictable and repetitive locomotor patterns (Perry et al., 2009). When compared to their wild-type counterparts, DAT-KD mice displayed modest and sometimes inconsistently reduced spatial d, which is sometimes reflected by increased perseverative behavior (Ralph-Williams et al., 2003), Young et al., 2007, 2010, van Enkhuizen et al., 2013). While DAT-KD mice display these activity phenotypes, these mice fail to show sensorimotor deficits during PPI tests (Ralph-Williams et al., 2003), in contrast to other rodent models of mania, including the *Clock* mutant mice. Intriguingly, DAT knock-out mice (KO) which lack the gene encoding DAT, display significant sensorimotor deficits that could be reversed by clozapine and quetiapine treatment, two antipsychotics used for schizophrenia or BD (Powell et al., 2008). Chronic administration of valproic acid attenuated hyperactivity, while goal directed behavior remained unaffected and spatial d was further reduced (van Enkhuizen et al., 2013a). Acute treatment with the dopamine depleting agent, alpha-methyl-p-tyrosine (AMPT), attenuated hyperactivity, increased goal directed behavior, and failed to have any effect on spatial d (van Enkhuizen et al., 2014a). In patients with BD, the effects of AMPT on mood symptoms are mixed (Bunney et al., 1977, Anand et al., 1999). Thus, valproic acid selectively reverses some phenotypes related to locomotor activity potentially through dopamine independent mechanisms. The BPM has tremendous utility for investigating certain endophenotypes of BD and effects of common or novel treatments, and has the potential for integrating analyses across human patients and animal models of BD. The BPM represents a tractable translational approach for studying new and exciting endophenotypes important for BD.

Other features of bipolar mania include increased impulsivity and risk-taking behaviors, which may impair decision-making and resemble underlying cognitive deficits. One strategy for assessing impulsivity and its relation to decision-making in patients with BD has been the structured Iowa Gambling Task (IGT) (Bechara et al., 1994, Clark et al., 2001, Kim et al., 2006) (Table 1). In the IGT, participants have to select the best of four options varying both the size and probability of the reward and loss (Bechara et al., 1997, 2005). The IGT has proved reliable for investigating the relationships between impulsivity and risk-taking, decision-making, response inhibition, and drug use and dependence in BD (Christodoulou et al., 2006, Adida et al., 2008, Yechiam et al., 2008, Nejtek et al., 2013).

Researchers have developed a version of the IGT to study decision-making in rodents (Homberg et al., 2008, Rivalan et al., 2009, de Visser et al., 2011, Young et al., 2011b). An animal is presented with four distinct options with different probabilities and magnitudes of

expected gains and losses—two are advantageous and the other two are distinctly disadvantageous. Impulsivity is defined as the frequency of premature responses (before options are presented) and risk-taking behavior is measured as the percentage of advantageous choices (advantageous-safe versus disadvantageous-risky choices). The impulsive choice or risk-taking behavior has the most translational validity to the human task (Evenden, 1999, van Enkhuizen et al., 2013a).

The rodent IGT has been used to investigate the role of serotonergic and dopaminergic mechanisms in impulsivity, risk-taking, and decision-making. Various DAT inhibitors have differential effects on IGT task performance in mice. Amphetamine treatment potentiated the choice of the advantageous-safe options, whereas more selective DAT inhibitors, modafinil or GBR12909, increased impulsivity in 'normal' C57BL/6 mice (van Enkhuizen et al., 2012, 2014). Similar to the effects of selective dopamine inhibitors, DAT KD mice are more impulsive and more motivated during the IGT, which impairs decision-making during risk-reward tasks (van Enkhuizen et al., 2014). Similar to DAT-KD mice, bipolar patients have impaired decision-making during the IGT, often exhibiting impulsive choices (van Enkhuizen et al., 2014). The IGT is another example besides the BPM of a cross-species, translational, and entirely tractable approach to investigating relevant disease constructs of BD. These approaches are necessary for understanding the neurobiological mechanisms driving disease-related functional impairments. Initial studies strongly suggest that hyperdopaminergic states in the brain, potentially due to reduced DAT efficiency, impairs decision-making processes by promoting the 'system's that drive impulsivity and motivation, or reward-seeking behavior. A neuroimaging study has shown reduced activation of ventral and dorsal PFC and heightened activation of the lateral temporal regions during the gambling task (Frangou et al., 2008). The ventral and dorsal PFC are involved in working memory and incentive value of stimuli, and communication between these two areas modulates reward—ventral PFC processes salience and incentive value, followed by input to the dorsal PFC, which influences the behavioral action. In light of these findings, ventral-dorsal PFC communication during decision-making tasks may be disrupted, requiring compensatory activation from other brain regions. Dysfunctional dopamine transmission in these patients could be responsible for these deficits (St Onge et al., 2012).

SHANK3-OX mice

Several human studies have suggested the SHANK3 protein is involved in the etiology of BD. Altered expression or function of this scaffolding protein, and others of the same family, are linked to several human synaptopathies, including schizophrenia and BD (Guilmatre et al., 2014). Case studies have provided further support for a link between SHANK3 dysfunction and BD (Vucurovic et al., 2012). The SHANK family of proteins is crucial for synapse formation, maintenance, and modulation of excitatory and inhibitory balance (Sudhof and Malenka, 2008). These proteins are primarily localized to excitatory synapses, which form large protein complexes at the postsynaptic density to connect with the actin cytoskeleton of dendritic spines (Han et al., 2013, Guilmatre et al., 2014). Mice that overexpress SHANK3 were hyperactive in both homecage and novel environments, and hypersensitive to the locomotor stimulating effects of amphetamine (Han et al., 2013).

SHANK3-OX mice also had elevated acoustic startle response, sensorimotor deficits, reduced depression related behaviors in the TST, and altered circadian rhythms of locomotor activity (Han et al., 2013), much like some of other animal models of mania (Table 3).

A few of these behaviors of the SHANK3-OX mice were reversed by valproic acid treatment, including hyperactivity, amphetamine-induced locomotor activity, sensorimotor deficits, and abnormal EEG in the frontal cortex and hippocampus (Han et al., 2013). Surprisingly, lithium treatment had no effect on any of these phenotypes (Han et al., 2013), which could be consistent with a subset of those with BD who fail to respond to lithium treatment. Further investigation into the neurophysiological correlates of the behavior indicated these mice have an imbalance towards enhanced excitatory signaling within the hippocampus. SHANK3-OX mice had increased VGLUT1 and decreased VGAT postsynaptic markers, along with reduced GABA-A initiated miniature inhibitory postsynaptic frequencies, and enhanced amplitudes of spontaneous excitatory postsynaptic currents (EPSCs), without changes in AMPA/NMDA ratios (Han et al., 2013). This shift from synaptic excitatory-inhibitory balance towards excitation was directly due to enhanced interactions between SHANK3 and ARP2/3 complexes, which promoted the formation of excitatory dendritic spines along with a reduction in the number of inhibitory synapses (Han et al., 2013). Impaired GABAergic signaling may be a robust neurobiological endophenotype of schizophrenia and BD (Benes, 2007). A shift toward excitatory signaling in the hippocampus or striatum may further alter dopaminergic and glutamatergic signaling at the postsynaptic density, or may even be a consequence of a dysfunctional dopamine system (de Bartolomeis et al., 2014). Other mouse models with altered excitatory signaling in the brain display similar behavioral phenotypes as the SHANK3-OX mice, such as the glutamate receptor subtype 6 knockout mouse (Shaltiel et al., 2008). Importantly, a recent study reported certain SHANK3 variants as potential biomarkers for predicting treatment response with ketamine in patients with bipolar depression (Ortiz et al., 2014).

ANK3 disruptions

The ANK3 gene encodes isoforms of the scaffold protein, Ankyrin G, which is involved in the formation and maintenance of the axon initial segment of neurons. Ankyrin G links subsets of sodium and potassium channels to the cytoskeleton and is necessary for action potential propagation (Zhou et al., 1998, Bennett and Lambert, 1999). A meta-analysis of several large genome wide association studies of BD identified ANK3 as among the most significantly associated genes, though the results were not totally consistent across samples, and it may be a shared risk factor between schizophrenia and BD (Ripke et al., 2011, Lee et al., 2012, Lee et al., 2013). *ANK3* levels are also downregulated in postmortem brain of schizophrenics (Roussos et al., 2012). Leussis et al.(2013) used RNA interference to knock-down the expression of *Ank3* specifically in the dentate gyrus of the hippocampus. They found that this manipulation produced a reduction in anxiety-related behavior in the elevated plus maze and light/dark test (Leussis et al., 2013). It also produced increased locomotor activity specifically during the light phase, suggesting a disruption in the circadian rhythm amplitude of these mice (Leussis et al., 2013). These behavioral changes were reversed with lithium treatment. The authors also tested a heterozygote mouse in which *Ank3* exon1b is disrupted, resulting in a loss of ANk3 transcript variants that are exclusively expressed in the

brain (Leussis et al., 2013). These mice had a similar behavioral profile to those with the DG specific knock-down. In addition, these mice also had an increase in sucrose preference compared to wild type littermates. Importantly, in contrast to some of the other models discussed, both the knock-down animals and the heterozygotes show no behavioral abnormalities at baseline when measured in open field, forced swim test, acoustic startle, PPI, contextual and cued fear conditioning or overall motor activity in the EPM or dark-light box tasks (Leussis et al., 2013) (Table 3). The authors then measured behavior in the heterozygote animals following 6 weeks of social isolation stress and found increased latencies to enter the open arm of the EPM and light side of the dark-light box compared to wild type animals, suggestive of increased anxiety. However, given this interpretation, wild type animals tended to have less anxiety following social isolation in this study, which is not typical. Nevertheless, social isolation stress does appear to produce a reversal of phenotypes in the heterozygote mice, suggesting a 'mood' switch. Social isolation also decreased their sucrose preference to that of wild type animals and increased immobility of the *Ank3* heterozygotes in the FST (Leussis et al., 2013). Thus, these animals seem to be very responsive to stress and indeed the mutants had greater levels of corticosterone following acute stress (Leussis et al., 2013). Taken together, ANK3 appears to be an important mediator of mood-related behavior and this model has great construct validity since the choice of gene for manipulation came directly from a human GWAS meta analysis. The fact that knock-down of *Ank3* specifically in the DG leads to several manic-like behaviors is intriguing given the fact that most other models of mania have focused primarily on the manipulation of dopaminergic activity. It will be interesting in future studies to determine how this DG specific manipulation changes overall hippocampal function and if it leads to any changes in dopaminergic or glutamatergic signaling in the ventral striatum. A recent study found that ankyrin-G appears to regulate β-catenin anchoring in the progenitor cell membrane through an interaction with E-cadherin (Durak et al., 2015). This controls the level of β-catenin available for Wnt signaling and progenitor cell proliferation during development (Durak et al., 2015). Given the effects of lithium on Wnt signaling described earlier in this review, it is interesting to speculate that the behavioral effects caused by *Ank3* knock-down in the DG may be mediated through changes in Wnt signaling and may potentially involve changes in adult neurogenesis.

Redox signaling mutants

Dysfunctional redox signaling and elevated oxidative stress have been reported in brains of patients with schizophrenia or BD. One of the primary intracellular regulators of redox and antioxidant signaling is glutathione (GSH). GSH protects against oxidative damage caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS). Maintenance of cellular redox state is important for modulating receptor activation, signal transduction, and transcription factor binding to DNA. In human postmortem PFC, GSH levels were reduced in subjects with BD compared to controls (Gawryluk et al., 2011a, Gawryluk et al., 2011b). GSH deficits were associated with GABA dysfunction in parvalbumin (PV) neurons within the ventral hippocampus and the anterior cingulate cortex of bipolar subjects (Chen et al., 2010). Evidence from both GSH-deficient mice and rats suggests these PV neurons are particularly sensitive to oxidative stress, while other GABA interneurons are unaffected (Cabungcal et al., 2006, Steullet et al., 2010). Clinical trials have reported that adjunct

treatment with the GSH precursor antioxidant N-acetylcysteine improves the remission of depressive symptoms and general functioning in bipolar patients (Dean et al., 2011, Berk et al., 2012). Thus impaired redox signaling and increased oxidative stress could contribute to dysfunction of PV neurons that is associated with schizophrenia and BD and may be secondary to poor neuronal metabolism and mitochondrial dysfunction.

Glutamate-cysteine ligase modifier unit (GCLM) KO mice have ~70–80% reductions in GSH levels in the brain relative to wild-type mice (Yang et al., 2002, Cole et al., 2011, Kulak et al., 2012). GCLM-KO mice display a range of mania-like behaviors, including enhanced sensitivity to the locomotor stimulating effects of amphetamine, altered social behavior, and impaired sensorimotor gating (Kulak et al., 2012) (Table 3). In response to mild stress, GCLM-KO mice become more exploratory, risky, and less ‘anxious’ and ‘depressed’ (Kulak et al., 2012). Transient GSH depletion in the adult rodent brain impaired performance during cognitive tasks, including object memory, place discrimination, and spatial working memory (Jacobsen et al., 2005, Mamiya et al., 2008). Thus chronic or transient deficits of GSH lead to different behavioral phenotypes, where transient depletion of GSH may have more selective impairments on cognitive performance. Low GSH may increase oxidative burden in the brain and impair mitochondrial function, both of which are posited to be involved in the pathophysiology of bipolar disorder and schizophrenia (Dean et al., 2009).

Changes in excitatory signaling and dopamine transmission may underlie the mania-like behaviors of GCLM-KO mice. The exaggerated locomotor response to amphetamine suggests hyperdopaminergia in these mice (Kulak et al., 2013). Fluctuations in neuronal redox state have functional consequences on excitatory and inhibitory signaling via NMDA and GABAA receptors, and L-type voltage gated calcium channels. For example, NMDA receptor mediated excitatory postsynaptic potentials were weaker in hippocampal slices from GSH depleted rats, while basal AMPA receptor mediated transmission was unaltered (Steullet et al., 2006). Transient reductions in GSH elevated dopamine metabolites in the mouse PFC, NAc, and hippocampus and altered dopamine modulation of neuronal calcium signaling (Jacobsen et al., 2005). In neurons, redox state and GSH also epigenetically regulate a host of genes directly involved in dopamine and glutamate signaling pathways (Trivedi and Deth, 2014). Dopamine fluctuations alter intracellular levels of GSH-based cellular redox status, subsequently affecting DNA methylation (Trivedi and Deth, 2014). Thus, redox and dopamine signaling pathways are intimately connected to regulate gene transcription and neuronal stimulation. Together, these studies support the hypothesis that impaired redox signaling, increased oxidative stress, and metabolic dysfunction are involved in the pathophysiology of BD. Currently, it is unknown whether these deficits precede or are a consequence, or function, of the chronicity and progression of the disease and secondary to abnormalities within other, more primary systems. GSH deficits selectively within PV neurons of bipolar subjects warrants further study of cell-type specific mechanisms regulating redox status in rodent models of mania. Targeted treatments to restore redox balance may prove to have therapeutic utility.

Myshkin mutant mice

Originally identified through ENU mutagenesis and developed as a preclinical model of epilepsy, the *Myshkin* mutant mouse has also been proposed as a model of bipolar mania (Snead et al., 2006) (Table 3). The *Myshkin* allele contains a mutation in the Na^+, K^+-ATPase α3-isoform that inactivates its enzymatic properties and consequently promotes neuronal excitability and seizure-susceptibility (Grisar et al., 1992, Clapcote et al., 2009). The *ATP1A3* gene encodes for Na^+, K^+-ATPase α3 sodium pump and has been linked to BD (Goldstein et al., 2009) and human post-mortem studies have reported significantly reduced expression of the Na^+, K^+-ATPase α2-isoform in the temporal cortex (Rose et al., 1998) and the α2-isoform in the prefrontal cortex (Tochigi et al., 2008). Each of these α-isoforms (α1-3) has been associated with BD (Mynett-Johnson et al., 1998, Goldstein et al., 2009).

More recently, the *Myshkin* allele has been backcrossed to the seizure-resistant C57BL/6NCr strain, effectively producing mutants without seizures. *Myshkin* mutant mice (*Myk/+*) are hyperactive and display exaggerated locomotor response to repeated amphetamine, increased exploration of novel objects, reduced anxiety related behavior, impaired sensorimotor gating, and disrupted sleep patterns with altered circadian behavioral rhythms (Kirshenbaum et al., 2012). Chronic treatment with lithium or valproic acid normalized only the anxiety and hyperactivity phenotypes (Kirshenbaum et al., 2012). Interestingly, adjunct therapies for BD and other mood disorders, including exercise and melatonin, are effective for reversing mania-like behaviors in *Myk/+* mice (Ng et al., 2007, Kucyi et al., 2010, Kirshenbaum et al., 2012, Sylvia et al., 2012, Kirshenbaum et al., 2014). More than a month of running wheel access or chronic treatment with melatonin supplementation improved sleep quality and reduced locomotor activity and normalized anxiety related behaviors in these mice (Kirshenbaum et al., 2014), suggesting these mice as a relevant model for studying the potential mechanisms underlying the therapeutic effects of these treatments. These treatments have not been systematically investigated in other genetic models of mania.

The mechanisms underlying these behaviors are due to impaired α3 sodium pump function. Transgenic restoration of the functional Na^+, K^+-ATPase α3-isoform completely normalized the anxiety related behaviors in the EPM, open-field, and dark-light box tests (Kirshenbaum et al., 2012). Activation of Na^+, K^+-ATPase α3 sodium pumps initiates intracellular calcium signaling and the phospho-activation of extracellular signal regulated kinase (P-ERK) and Akt (Dietz et al., 2007, Kim et al., 2008). Not surprisingly, *Myk/+* mice have increased P-ERK and acute treatment with an ERK inhibitor (SL327) normalized anxiety behavior (Kirshenbaum et al., 2012). The role of ERK signaling is of particular interest for designing novel treatments because many mood stabilizers activate both ERK1 and ERK2 pathways, and many of the upstream regulators of ERK, such as BDNF, DISC1, GluR6, RASGRP1, and EGFR, are believed to be involved in the pathophysiology of BD (Dick et al., 2003, Chubb et al., 2008, Engel et al., 2009, Shinozaki and Potash, 2014). Moreover, ERK1 KO mice display a similar behavioral repertoire as *Myk/+* mice (Engel et al., 2009). Other mice with impaired Na^+, K^+-ATPase signaling are susceptible to depression behavior following chronic stress (Kirshenbaum et al., 2011). It may be worthwhile to investigate whether *Myk/+* mice are also vulnerable to environmental perturbations, such as chronic stress or

acute sleep deprivation, to induce depression phenotypes, which could lead to more mechanistic studies underlying the susceptibility to triggers that induce mood cycling.

Mouse models amenable to systems neuroscience and functional genomics approaches

The Black Swiss mice

The major disadvantages of using single gene knockout, knockdown, or overexpressing, transgenic mouse models to study bipolar mania or depression are sometimes poor construct validity and poor translational interpretations of the findings. Most, if not all, of the genetic association studies, which have identified polymorphisms associated with BD, have small effect sizes, explaining very little of the genetic variance. Highly penetrant, large effect alleles associated with psychiatric disorders are rare. Psychiatric disorders are genetically heterogeneous, complex, and emerge from multiple trajectories, influenced by many, often nuanced, environmental and biological factors.

Inbred mouse strains have been used over decades of behavior genetics research to discover genetic loci associated with complex behavioral and biological phenotypes, albeit with very little success in elucidating the functional consequences of those polymorphisms. Inbred strains have also been investigated for their differential response to lithium following amphetamine induced hyperlocomotion (Gould et al., 2007). Using a mouse model with more genetic heterogeneity, may have distinct advantages over single gene mutant mice for modeling BD, including improved construct validity (i.e., polygenic mechanisms of complex behaviors).

Several groups have identified outbred mouse populations that model multiple domains of bipolar mania (Table 3). The Black Swiss mouse population was developed from crossing Swiss outbred and C57BL6/JN mice. When compared to the founder strains, Black Swiss mice are hyperactive and display elevated sucrose preference, reduced anxiety and depression behavior, enhanced sensitivity to amphetamine, and increased aggression (Flaisher-Grinberg and Einat, 2010, Ene et al., 2015). Therefore these mice may provide certain advantages for investigating the complex etiology of the disorder by modeling multiple behavioral domains and presumably more heterogeneous genetics (Flaisher-Grinberg et al., 2010).

Treatment with either lithium or valproic acid normalized certain mania-like behaviors of Black Swiss mice. Both lithium and valproic acid reduced sucrose preference, increased immobility time of the FST, and reduced amphetamine-induced hyperlocomotion, with no measurable effect on hyperactivity or anxiety behavior (Flaisher-Grinberg and Einat, 2010, Kalinichev and Dawson, 2011). Notably, GSK-3β inhibitors selectively attenuated amphetamine-induced hyperactivity in Black Swiss mice (Kalinichev and Dawson, 2011), consistent with the proposed GSK-3β-mediated mechanism of action for mood stabilizers. The atypical antipsychotic asenapine, which is indicated for schizophrenia and bipolar mania or mixed mood states (Marston et al., 2009, Gonzalez et al., 2011, Azorin et al., 2013), was more effective in normalizing multiple mania-like phenotypes of Black Swiss mice (Ene et al., 2015). In common with other antipsychotics, asenapine has a high affinity

for dopamine receptor subtype 2 (D2R), which most likely mediates the anti-manic mechanism (Shahid et al., 2009). Differential responses to lithium and between antipsychotics of Black Swiss mice can be explained by inherent genetic factors (Gould et al., 2007).

To date, there has been only a single study investigating the construct (or biological) validity of Black Swiss mice. As mentioned previously, β-catenin is proposed as a downstream target of GSK-3β inhibition by lithium and Black Swiss mice have reduced β-catenin protein expression in the hippocampus, but not in the PFC, relative to C57BL6/J (Hannah-Poquette et al., 2011). However, BDNF is expressed normally in the hippocampus and frontal cortex of Black Swiss mice (Hannah-Poquette et al., 2011). In human postmortem tissue, BDNF transcripts (I, IIc, and IV) were reduced in hippocampus, but not the PFC or striatum, in subjects with BD (Reinhart et al., 2015). Circulating blood levels of BDNF in bipolar subjects correlated with mood state (Hashimoto, 2014) and treatment response (Dwivedi and Zhang, 2014, Tunca et al., 2014, Polyakova et al., 2015). Collectively, support the use of Black Swiss mice for modeling bipolar mania with high face and predictive validity, and possible construct validity.

The Madison mice

Another mouse model of mania derived from outbred stocks is the Madision (MSN) strain (Table 3). MSN mice display reduced anxiety and depression, increased sexual behavior, hyperactivity, and circadian abnormalities (Scotti et al., 2011, Saul et al., 2012, Saul et al., 2013). Lithium and olanzapine, an atypical antipsychotic, only reduced hyperactivity, with no changes observed for anxiety behavior in these mice (Scotti et al., 2011). In addition to face and predictive validity, MSN mice may also have high construct validity. MSN mice share genetic correlates with BD (Saul et al., 2012). A number of transcripts show abnormal expression levels in hippocampus of MSN mice, many of which are previously associated with BD (Saul et al., 2012). For example, genes encoding proteins involved in chromatin packaging and remodeling are altered in MSN mice, such as *Smarca4*, which has been implicated in neurodevelopmental disorders, including autism schizophrenia, and BD (Li et al., 2013). MSN mice also share synteny with several loci identified in human BD (Saul et al., 2012). Very little is known as to whether these loci are causative or structural variants with any functional consequences—MSN mice provide a model for investigating these mechanisms. Further studies are necessary to expand on the validity of the model, as well as to understand the polygenic contributions to mania-like behaviors (Saul et al., 2012). MSN mice have potential for being a tractable and highly valid model of bipolar mania to leverage the power of genomics and systems neuroscience approaches to begin to understand some of the mechanisms underlying the biological complexity of phenotypes related to mania.

Mood cycling mouse models: A focus on the role of circadian mechanisms of behavioral state switching

Over the past several decades, there have been attempts to model mood cycling in rodents. Many have used pharmacological or environmental triggers to induce behavioral state switching (see (Young and Dulcis, 2015)). More recently, researchers have employed

circadian and/or sleep perturbations to affect behavior in rodent models with the intention to achieve higher construct, or etiological validity. Sleep and circadian disruptions are hallmarks of those suffering with BD and used as diagnostic criteria (Wirz-Justice, 2006, Kripke et al., 2009, McCarthy and Welsh, 2012, McClung, 2013, Gonzalez et al., 2014). Social rhythm therapy (SRT), which aims to stabilize circadian and sleep domains via daily scheduling, is efficacious for treating BD (Frank et al., 2008, Goldstein et al., 2014). The social rhythm disruption (SRD) theory of affective disorders hypothesizes rhythm disruption, whether social or biological, induces mood changes in vulnerable individuals (Ehlers et al., 1988, Hlastala, 2003, Boland et al., 2012). Stress can be a precipitating factor for rhythm disruption, sleep disturbances, and mood changes (Ellicott et al., 1990, Post, 1992). Rodent models have really just begun to investigate the mechanisms underlying the effects of circadian disruption and sleep disturbances on behavioral switching related to BD.

It has been evident for some time that seasonality in related to changes in mood in those with BD and other mood disorders (Geoffroy et al., 2013, Wang and Chen, 2013, Moore et al., 2014). Seasonal changes in mood may be driven by changes in circadian photoperiod. The most consistent environmental trigger of depressive episodes in BD is the shortening of day length (Wang and Chen, 2013). In diurnal rodents, shortened photoperiods induced depression related behaviors (Einat et al., 2006), which were reversed with bright light therapy administered at specific circadian phases (Ashkenazy et al., 2009), similar to the antidepressant effects of bright light therapy in human BD (Postolache and Oren, 2005, Wu et al., 2009).

Several mechanisms likely regulate the effects of photoperiod on mood related behavior. In the adult rat brain, long and short day photoperiods induced neurotransmitter plasticity and bidirectionally modulated anxiety and depression behavior (Dulcis et al., 2013). Under long days (19 h of light and 5 h of dark) over 7 days, hypothalamic neurons switched from dopamine to somatostatin phenotype, while the opposite was found under short days (19 h of dark and 5 h of light). Long days induced D2R expression on postsynaptic corticotropin release factor (CRF) hypothalamic neurons and increased CRF levels in the CSF and periphery. Long days increased anxiety and depression behavior. Lesions to presynaptic dopaminergic hypothalamic neurons or pharmacological blockade of dopamine D1 or D2 receptors recapitulated the behavioral effects of long days and could be partially rescued via photoperiodic induction of newly switched dopaminergic neurons (Dulcis et al., 2013). Short day exposure reduced anxiety and depression behaviors. Thus, the photoperiodic dependent switch between dopamine and somatostatin neuronal phenotypes, along with CRF levels, can modulate mood related behavior, revealing a potential mechanism by which seasonal variation could rapidly induce neurocircuit level changes that lead to shifts in mood.

Genetic models of circadian disruption have also shown promise for modeling mood switching in rodents. As previously mentioned, *Clock* mutant mice have disrupted molecular and behavioral rhythms (Vitaterna et al., 2006) and display a mania-like behavioral repertoire (McClung et al., 2005, Roybal et al., 2007). We have recently reported that anxiety and depression behaviors of *Clock* mutant mice naturally varied across the circadian day under entrained 12:12 light-dark conditions (Sidor et al., 2015). During the day, anxiety

and depression behavior was reduced, while during the night, these behaviors normalized to wild-type levels (Sidor et al., 2015). Mania-like behaviors were found only when dopamine cell firing was highest during the day and these behaviors were normalized by dopamine depletion with AMPT treatment. Optogenetic stimulation of VTA dopamine neurons of wild-type mice during the day almost fully mimicked the mania-like behaviors of *Clock* mutant mice (Sidor et al., 2015). Thus diurnal variation of neurocircuit function underlies 'normal' variation of mood and altered circadian regulation of dopaminergic transmission could promote mania. We consider this 'rapid cycling' to be mostly related to an individual cycling from a manic to euthymic states. Sensorimotor gating and wheel-running activity, which is inherently rewarding, remain elevated during the night phase in *Clock* mutant mice (van Enkhuizen et al., 2014), suggesting diurnal variation may be specific to mood related behaviors and disparate mechanisms regulate these behaviors. Future studies will determine whether chronic stress can induce anxiety and depression behavior in *Clock* mutant mice. Preliminary also data suggests that *Clock* mutants may be more vulnerable to stress-induced mood related behaviors (unpublished results) similar to those described in the Ank3 mutant mice (Leussis et al., 2013).

Another circadian genetic model of BD is the D-binding protein (*Dbp*) KO mouse and actually has the opposite phenotypes to *Clock* mutant mice (Table 3). *Dbp* is a basic leucine zipper transcription factor involved in the regulation of circadian locomotor behavior and a component of the molecular clock (Lopez-Molina et al., 1997, Ripperger et al., 2000). A genetic locus has been mapped near the chromosomal region of *Dbp* for BD (Morissette et al., 1999). Using convergent functional genomics approaches to integrate gene expression data with human genetic linkage and association studies, highlighted *Dbp* among the highest ranked candidate genes related to BD (Le-Niculescu et al., 2008).. *Dbp*-KO mice had abnormal circadian behavior, disrupted homeostatic sleep regulation, reduced locomotor activity, a blunted locomotor response, and stereotopy following acute amphetamine (Le-Niculescu et al., 2008). Intriguingly, following chronic stress (i.e,. social isolation with intermittent acute stress exposure), *Dbp*-KO mice became hyperactive, whereas wild-type mice were hypoactive. Acute sleep deprivation induced a similar phenotype in these mice and was completely blocked by valproic acid treatment prior to sleep deprivation (Le-Niculescu et al., 2008). Additionally, *Dbp*-KO mice switched to a hyperhedonic phenotype during long periods of continuous access to alcohol containing drinking fluids (Le-Niculescu et al., 2008). It is unclear whether stress or acute sleep deprivation also induces anxiety and depression behaviors in *Dbp*-KO mice, or whether these mice are more vulnerable to circadian disrupting effects of changes in photoperiod. The *Dbp*-KO mouse model of depression and stress-induced mania seems promising for studying the cellular and molecular mechanisms regulating behavioral switching in mice.

Future directions

The major challenge for the field of translational neuroscience will continue to be the development, investigation, and interpretability of animal models of psychiatric diseases. In the absence of known etiology of BD, models based on clinical observations should be positioned to provide greater impact on our understanding of the disease process. Collaborative efforts are necessary to integrate data across many pharmacological,

environmental, and genetic models of BD in order to elucidate shared and distinct disease related mechanisms. Further integration of these changes in animal models with data from patient samples should identify common mechanisms of a heterogeneous disease and potentially narrow the targets for therapeutic development. For example, transcriptome profiling in animals and human post-mortem tissues of well-defined disease cohorts will identify shared molecular patterns (Krishnan and Nestler, 2011).

With new technology come new opportunities, and neuroscience is benefiting tremendously from new tools and approaches. Pharmacological models that recapitulated a few of the core behavioral phenotypes of BD were the research standard. Despite their limitations and confounds, genetically engineered mutant, knockin, or knockout mice pushed the research into investigating the causal relationship between risk loci associated with the disease and their interaction with environmental factors. Now with readily available and more affordable genome editing tools, such as TALEN or CRISPR/Cas9 technologies, investigators can recreate the precise genetic polymorphisms associated with BD. For example, ‘humanized’ mice carrying either Val or Met alleles in the catechol-o-methyltransferase (COMT) gene, an enzyme that degrades cathecholamines, dopamine, epinephrine, and norepinephrine, support the human genetic findings suggesting the human COMT Val158Met polymorphism modulates behavioral and cognitive functioning (Risbrough et al., 2014). ‘Humanized’ rodent models can systematically investigate the effects of risk loci on the developmental and behavioral factors of BD (Malkesman et al., 2009). These models still present with a major challenge facing single gene knockout mice, whereby the selection of genetic background can be critical for observing any relevant phenotype and should be considered when creating these models of human disease.

Newly available genetically and phenotypically heterogenous and diverse mouse populations, such as the Collaborative Cross (Threadgill and Churchill, 2012) and Diversity Outbred (Svenson et al., 2012), are valuable resources for discovering and interrogating new loci related to mania and depression (Logan et al., 2013). High-density mapping and high-throughput genotyping tools are readily accessible for investigating the genetics of common or disparate behavioral phenotypes. Integrative functional genomics can then be used to eludicate biological and genetics mechanisms that cut across animal models and human disease. An example of this type of strategy has identified new mechanisms common to bipolar and addiction disorders that could be recapitulated in a mouse model (Le-Niculescu et al., 2008). Collaborative Cross and Diversity Outbred mice may also help in our understanding of how genetics contributes to differential treatment responses, such as in the case of haloperidol response (Crowley et al., 2014). Thus, the major advantage of using these mice to investigate disease relevant phenotypes and treatment response is to study the continuous and more complete spectrum of the behavior by maximizing the genetic and phenotype variance, eventually moving the field from the classical approach of the simple presence or absence of an intended phenotype. The Black Swiss mice model of mania has more genetic diversity than standard inbred strains and other genetic mouse models, making them a positive step in this direction.

In addition to developing better animal models, there should be equal efforts into creating more tractable translational behavioral assays. Efforts in this arena will provide cross-

species validation and interpretation of animal findings. The BPM, PPI, and drug self-administration models are examples where behavioral phenotypes observed in patients can be readily tested and interpreted in animals. The field also needs cross-species validated assays of cognition, particularly those that assess risk-taking and impulsivity—constructs that interfere with problem solving and decision-making abilities. As discussed previously, BD patients are more impulsive and have impaired decision-making during risky situations, and cognitive deficits correlate with their functional outcome (Green, 2006, Burdick et al., 2011).

New technologies, tools, and cross-species models may push the field beyond past shortcomings. As technology improves and researchers adopt approaches that cut across multiple domains, translational research of neuroscience and psychiatry will make huge strides forward. Integrating data from self-report, neuroimaging, optogenetics, epigenetics, genetics, and postmortem, along with other approaches, will be critical for uncovering the etiology of BD and the development of novel therapeutics.

Conclusions

Rodent models are limited in their ability to capture the entirety of human BD. The combination of pharmacological, environmental, and genetic approaches will continue to bring the field closer to understanding the environmental, biological, and genetic etiological factors of the human disease. Preclinical models are also useful for screening novel compounds or discovering the therapeutic mechanisms of current treatments. It is important to continue to elucidate the cellular and molecular pathways regulating motivation, reward, and mood, and how alterations to these lead to behavioral and biological phenotypes related to BD. With the advent of new, more heterogeneous mouse populations, we can use forward genetics to begin to unravel the complex genetic mechanisms and environmental factors of mania related behaviors. Models of behavioral switching should aid in our understanding of biological mechanisms that contribute to mood cycling, which is the hallmark of BD.

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Highlights

In this review we highlight the work that has been done on multiple animal models of bipolar mania.

1. Pharmacological approaches to induce hyperactivity as a model of human mania have been used for many years.
2. Environmental manipulations are used to induce manic-like states which mimic multiple facets of this complex disorder.
3. Most recent studies have focused on genetic models.
4. Certain outbred strains of mice may be useful in modeling the polygenic nature of this disease.
5. Ultimately, models that cycle through various mood states are needed.

Table 1

Modeling human bipolar mania in rodents

Behavioral endophenotype	Rodent paradigm
Reduced anxiety, increased novel exploration	Elevated plus maze; dark-light box; open field arena; social interaction test, novelty suppressed feeding
Reduced depression	Forced swim test, tail suspension test, learned helplessness test
Impaired sensory processing	Paired-pulse inhibition (PPI)—sensorimotor gating*
Risk-taking behavior	Iowa Gambling Task (IGT)*
Impulsivity	IGT*
Impaired decision-making	IGT*
Psychostimulant-induced hyperactivity	Cocaine or amphetamine injection, repeated injections for locomotor sensitization
Hedonia	Sucrose preference; cocaine or amphetamine self-administration*; intracranial self-stimulation (ICSS) of medial forebrain bundle; two bottle free-choice alcohol drinking; cocaine conditioned place preference (CPP)
Hyperactivity	Open field arena; homecage monitors; wheel-running; behavioral pattern monitor (BPM)*
Increased sexual activity	Mounts, intermission, and ejaculation events
Increased goal-directed	BPM*
Repetitive movements	BPM*
Aggressive behavior	Resident-intruder test
Reduced or disrupted sleep	EEG; circadian activity; sleep-wake monitoring*
Disrupted circadian rhythms	Circadian wheel-running activity; temporal patterns of behavior

*Demonstrated direct translational relevance to human bipolar disorder

Table 2

Pharmacological and environmental mouse models of bipolar mania

	Validity		
Manipulation	**Face**	**Predictive**	**Construct**
Amphetamine-induced hyperactivity	Hyperactivity, cognitive deficits with chronic treatment	Activity reversed by acute lithium and haloperidol	Hyperdopaminergia
Amphetamine + CDP	Hyperactivity	Activity reversed with acute lithium	Hyperdopaminergia, anxiolytic effects of CDP
Ouabain	Hyperactivity, spatial learning deficits	Activity reversed by haloperidol, lithium and valproate. Some neurodegenerative markers were reversed by lithium and valproate	Increased levels of oxidative stress, changes in BDNF levels
D2 receptor stimulation	Hyperactivity	Activity reversed by valproate and carbamazepine	Increased dopaminergic signaling
Sleep deprivation	Hyperactivity, insomnia, aggressive behavior, hypersexuality, increased stereotypy, cognitive deficits, circadian rhythm disruption	Sleep latency and hyperactivity reversed by lithium and haloperidol. PKC changes reversed by lithium	Acute circadian rhythm and sleep changes can precipitate mania in humans. PKC signaling is altered.
Resident-intruder paradigm	Increased aggression	Aggression reduced by lithium and valproate	Stress is associated with changes in mood state

Table 3

Genetic mouse models of bipolar mania

	Validity		
Manipulation	**Face**	**Predictive**	**Construct**
ClockΔ19 mutant	Reduced anxiety, depression; increased impulsivity, reward-seeking; hyperactivity; impaired decision-making, sensorimotor gating; disrupted circadian rhythms (phase and amplitude) and sleep; episodic mania (mania and euthymia)	Lithium and valproic acid normalized anxiety and depression behavior. Lithium normalized dopaminergic activity and defects in cross frequency phase coupling in the NAc.	CLOCK polymorphisms; disrupted phase coherence, synchronization, and communication of cortico-striatal circuitry; hyperdopaminergia and altered glutamatergic neurotransmission
GSK-3β OX	Hyperactivity; reduced depression	Lithium reduced activity	GSK-3β polymorphisms; reduced expression human bipolar DLPFC and temporal cortex; disrupted downstream targets of GSK-3β (e.g., β-catenin); hyperdopaminergia
DAT-KD	Hyperactivity (reduced spatial *d*); increased goal-directed behavior; repetitive locomotor patterns; impaired decision-making	Valproic acid reduced hyperactivity	DAT polymorphisms; impaired DAT function; hyperdopaminergia
SHANK3-OX	Hyperactivity; hypersensitivity to reward stimuli (e.g., amphetamine); elevated acoustic startle response; impaired sensorimotor gating; reduced depression; altered circadian rhythm behavior	No effect of lithium; valproic acid reduced hyperactivity, amphetamine-induced locomotion, normalized sensorimotor deficits; reversed abnormal EEG patterns in frontal cortex and hippocampus	SHANK3 polymorphisms; variants predict treatment response to ketamine in patients with bipolar depression; imbalance between excitatory and inhibitory neurotransmission; altered dopaminergic and glutamatergic signaling
ANK3 disruptions	Hyperactivity; reduced anxiety; altered circadian activity rhythms; increased reward-seeking; stress-induced anxiety, anhedonia	Lithium reduced hyperactivity, normalized anxiety	Potential regulation of β-catenin and Wnt signaling pathways
GCLM-KO	Hypersensitivity to amphetamine locomotor effects; altered social behavior; impaired sensorimotor gating	Untested	Reduced GSH levels in human postmortem PFC and other brain regions from bipolar patients; GSH alterations associated with GABA dysfunction, oxidative stress markers, and altered dopaminergic neurotransmission
Myshkin mutant	Hyperactivity; hypersensitivity to amphetamine locomotor effects; impaired sensorimotor gating; disrupted sleep homeostasis; altered circadian rhythm behavior	Lithium or valproic acid normalized anxiety and hyperactivity; exercise and melatonin improved sleep quality, reduced hyperactivity and normalized anxiety	ATP1A3 polymorphisms, NA+K +ATPase a3 sodium pump dysfunction, multiple isoforms associated with bipolar disorder; altered ERK signaling and downstream effectors, such as BDNF, DISC1, GluR6, RASGRP1, and EGFR
Black Swiss	Hyperactivity; hypersensitivity to amphetamine locomotor effects; reduced anxiety and depression; elevated sucrose preference	Lithium and valproic acid reduced sucrose preference, amphetamine-induced locomotion, normalized depression behavior; asenapine (antipsychotic) normalized depression, reduced hyperactivity and amphetamine induced activity	Genetic heterogeneity; reduced β-catenin expression in various brain regions
Madison	Hyperactivity; reduced anxiety and depression; increased sexual behavior; disrupted circadian rhythm behaviors	Lithium and olanzapine selectively reduced hyperactivity	Genetic heterogeneity; abnormal expression patterns of numerous genes associated with bipolar disorder (e.g., *Smarca4*)

	Validity		
Manipulation	**Face**	**Predictive**	**Construct**
DBP-KO	Abnormal circadian rhythm behaviors; disrupted sleep homeostasis; reduced activity; mania-like behaviors induced by chronic stress or acute sleep deprivation include hyperactivity, increased drug-taking	Valproic acid blocked stress-induced hyperactivity	Gene locus mapped near coding region for *Dbp*; ranked highly among candidate genes for bipolar disorder