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Modeling mania in preclinical settings: a comprehensive review

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Abstract

The current pathophysiological understanding of mechanisms leading to onset and progression of bipolar manic episodes remains limited. At the same time, available animal models for mania have limited face, construct, and predictive validities. Additionally, these models fail to encompass recent pathophysiological frameworks of bipolar disorder (BD), e.g. neuroprogression. Therefore, there is a need to search for novel preclinical models for mania that could comprehensively address these limitations. Herein we review the history, validity, and caveats of currently available animal models for mania. We also review new genetic models for mania, namely knockout mice for genes involved in neurotransmission, synapse formation, and intracellular signaling pathways. Furthermore, we review recent trends in preclinical models for mania that may aid in the comprehension of mechanisms underlying the neuroprogressive and recurring nature of BD. In conclusion, the validity of animal models for mania remains limited. Nevertheless, novel (e.g. genetic) animal models as well as adaptation of existing paradigms hold promise.

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Conflicts of interest

None.

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Keywords

Mood disorders; Mania; Neuroprogression; Preclinical models; Animal models; Psychiatry; treatment-resistance

1. Introduction

Manic episodes are psychopathological hallmarks of bipolar disorder (BD) (Koukopoulos and Ghaemi, 2009), and are defined as distinct periods characterized by abnormal and persistent elevated, expansive or irritable mood, lasting at least one week (or any duration if hospitalization is required) (American Psychiatric Association. et al., 2013).

Notwithstanding the pathophysiology of BD remains elusive, several lines of evidence indicate that neuroinflammatory pathways, oxidative and nitrosative stress (O&NS), neurotrophic factors, as well as apoptosis-related mechanisms are involved (Berk et al., 2011; Maletic and Raison, 2014). Furthermore, evidence indicates that recurring manic episodes may lead to neuroprogression in BD, which is clinically reflected as a greater likelihood for subsequent episodes, treatment-resistance, as well as cognitive and functional impairments (Fries et al., 2012; Kapczinski et al., 2014).

A plethora of studies has aimed to unravel the neurobiology of mania and ultimately identify novel therapeutic targets for BD. However, the pathophysiology of mania remains incompletely elucidated. Animal models of mania may aid in the elucidation of mechanisms underlying this complex behavioral state, since they enable the investigation of specific brain structures, as well as genetic and pharmacological manipulations that would otherwise be impossible to be carried out in human subjects.

Nevertheless, preclinical models for psychiatric disorders face significant methodological limitations, including but not limited to incomplete face, construct, and predictive validity (vide infra) (Nestler and Hyman, 2010; Razafsha et al., 2013). In addition, the subjective nature of many symptoms and the lack of biologically-validated diagnostic criteria further challenge the development of preclinical models for neuropsychiatric illnesses (Nestler and Hyman, 2010). Similarly, mania is a complex phenotype which encompasses both objective and subjective behavioral changes in nature (Machado-Vieira et al., 2004b). While behavioral responses, such as fear, aggressiveness, irritability, euphoria, and dysphoria may be regarded as subjective components of mania, other manifestations such as locomotor activity and aberrations in circadian rhythms may be considered objective manic-like behaviors. Likewise, other physiological responses may also be measured in preclinical models of mania providing insights on molecular and cellular pathophysiological processes involved in the genesis, persistence, and treatment of BD in humans (Teixeira and Quevedo, 2013; Valvassori et al., 2013; Young et al., 2011a). Recently, the field has witnessed significant advances with the development of novel preclinical models of mania (Dzirasa et al., 2011; Einat, 2014a; Sidor et al., 2015). Therefore, a critical appraisal of the validity of animal models for mania is timely.

In light of this, the aims of this narrative review are: (i) to comprehensively review characteristics and validity criteria of current animal models for mania; (ii) to discuss the

limitations of available animal models for mania; and (iii) to ultimately identify bottlenecks, alternatives, and future perspectives for this very expanding field.

2. Validity criteria

Different criteria have been proposed for the evaluation of animal models for neuropsychiatric disorders (Table 1). Basically, these criteria aim to establish the translational relevance of preclinical findings taking the modelled human condition into consideration (i.e. external validity). Willner (1984) initially developed a set of validity criteria (Willner, 1984), which were further developed by other groups (Nestler and Hyman, 2010). Briefly, an animal model of a given mental disorder should mimic the manifestations of the equivalent clinical phenomenon (face validity), resemble pathophysiological aspects of the illness (construct validity), and respond to existing clinically successful treatments (predictive validity) (Hamani and Nobrega, 2010, 2012; Nestler and Hyman, 2010; Valvassori et al., 2013; Willner, 1984). Of note, while this terminology was first adopted by Willner and colleagues and later by many others, the definitions of these validity criteria in the field of animal models in general and animal models for neuropsychiatric disorders in particular are much more limited. This is particularly the case for the ‘construct validity’, where we are in fact searching for its etiological validity at best (which is really only a component of construct validity). Similarly, we cannot really achieve what is broadly defined as predictive validity, and what we are really looking for is at best ‘treatment validity’.

Thus far, animal models of mania have fulfilled significantly less validity criteria than models developed for the study of depression-like behaviors in rodents (Valvassori et al., 2013). In addition to external validity criteria, internal validity should also be taken into account. This has to do with the experimental design, including the reproducibility of the model, robustness, blindness, and randomization (Belzung and Lemoine, 2011). In this review, we will focus on the external validity of different animal models of mania.

Interestingly, a recent study has proposed a reformulation of the classic validity criteria of animal models of mental disorders (Belzung and Lemoine, 2011). These new criteria include five major criteria, including homological validity (which considers animal species and strains used for modelling the condition), pathogenic validity (i.e., the similarity of the process that leads to the condition), mechanistic validity (similarity of the mechanisms working in the model to the mechanisms working in the human condition, including biological markers), face validity (encompassing both ethological and a biomarker validities), and predictive validity (similarity between triggering factors and treatment response between the model and the human disease) (Belzung and Lemoine, 2011).

3. Modelling mania in animals: pharmacological, environmental and genetic approaches

In terms of the stimuli used for the induction of manic-like behavior in animals, models may be divided into three different types: pharmacological, environmental, and genetic models of mania, which will be separately discussed in the next sections (see Table 2).

3.1 Pharmacological models of mania

Psychostimulant-induced hyperactivity—An increase in dopaminergic neurotransmission may promote manic-like behaviors in rodents, which may reflect to some extent the clinical phenomenon. Furthermore, pathophysiological processes and therapeutic responses to classic antimanic agents (e.g., lithium, valproic acid, and antipsychotics) consistent with the BD phenotype have also been repeatedly reported (Kara and Einat, 2013; Valvassori et al., 2013). These animal models of mania have relied on the effects of stimulant administration on the locomotion behavior of rodents as assessed in the open-field test (Berggren et al., 1978; Davies et al., 1974; Gould et al., 2001). In rodents, the administration of stimulants, such as d-amphetamine, produces an increase in dopamine (DA) efflux, inhibition of DA reuptake, or DA degradation by the enzyme monoamine oxidase (MAO) (Robinson et al., 1985; Schaeffer et al., 1976), ultimately inducing an increase in locomotor activity and psychomotor agitation (Kara and Einat, 2013; Paszti-Gere and Jakus, 2013; Shaldubina et al., 2002). Moreover, cognitive functioning typically reported to be impaired in BD patients has also been found to be significantly decreased in psychostimulant-induced models for mania (Fries et al., 2015; Rygula et al., 2015; Trevizol et al., 2013). Accordingly, several preclinical models combining reversal and prevention paradigms with mood stabilizers and potential new targets for manic-like behaviors induced by d-amphetamine, lisdexamfetamine dimesylate (LDX), GBR12909, and fenproporex have been published (Frey et al., 2006b; Macedo et al., 2013; Macedo et al., 2012; Queiroz et al., 2015; Rezin et al., 2014). These pharmacological agents share a common dopamine-enhancing activity, which may have a significant role in the pathophysiology of human mania (Berk et al., 2007).

Regarding the construct validity of these models, sustained DA overactivity has been shown to produce a decrease in the levels of brain derived neurotrophic factor (BDNF) in the rat brain (Cechinel-Recco et al., 2012; Frey et al., 2006a; Macedo et al., 2012), resembling reported findings for BDNF in manic patients (Cunha et al., 2006; Fernandes et al., 2011). While basic psychostimulant-induced mania model employs acute administration, their chronic exposure effects may have limited specificity because of their overlapping features with psychostimulant-induced sensitization models. Interestingly, the chronicity of dopaminergic overflow in the striatum (ST) and the reduction of BDNF expression seem to be linked to epigenetic changes, e.g. altered DNA methylation at specific hippocampal regions (Rao et al., 2012a). Accordingly, alterations in DNA methylation have been suggested to play key roles in the pathophysiology of BD (Chen et al., 2014). Likewise, a diminished histone acetylation related to an overexpression of histone deacetylase (HDAC) has also been reported to be associated with increased DNA methylation and amphetamine-induced manic-like symptoms (Graff and Tsai, 2013). Of note, HDAC inhibitors such as valproate (VAP) and sodium butyrate (SB) have been shown to block stimulant-induced hyperactivity, thereby reversing manic-like behaviors in rodents (Arent et al., 2011; Moretti et al., 2011; Stertz et al., 2014). Additionally, HDAC inhibitors may also offer some protective effects over mitochondrial damage and OS promoted by psychostimulant administration (Frey et al., 2006b; Steckert et al., 2013). Tamoxifen, a protein kinase-C (PKC) inhibitor, was also shown to protect against d-amphetamine-induced hyperactivity,

mitochondrial complex damage and increased OS by increasing levels of the anti-apoptotic proteins BDNF and Bcl-2 (Cechinel-Recco et al., 2012).

Behavioral sensitization to psychostimulants has also been regarded as a classic validated animal model of mania (Cappelliez and Moore, 1990; Post, 2007). Initial studies by Post and colleagues showed that cocaine-induced behavioral sensitization and kindling responses can resemble manic-like behaviors and an increased vulnerability to recurrence following successive episodes (Post and Weiss, 1989), which also presented some degree of predictive validity (Baptista et al., 1993; Post et al., 1992). Accordingly, the administration of several anticonvulsants with mood-stabilizing properties, such as VAP, lamotrigine, and carbamazepine reverses amphetamine sensitization-induced hyperactivity in rodents, which indicates an adequate predictive validity for this model (Dencker and Husum, 2010). Of note, a combined preclinical model using both stimulants and benzodiazepines has also been tested previously (Arban et al., 2005), but it is still unclear whether this model provides accurate data on the action of antimanic agents (Kozikowski et al., 2007; Redrobe and Nielsen, 2009; Young et al., 2011a).

In summary, due to their accumulating evidence of face, construct and predictive validities, psychostimulant-induced models of mania have been repetitively used as a tool for the investigation of novel therapeutic targets with potential mood-stabilizing properties.

Quinpirole-induced hyperactivity—Another approach for mimicking mania in animals is the administration of quinpirole, a dopamine D2/D3 receptor agonist, which promotes biphasic hyper-locomotion that resembles the oscillating nature of BD (Shaldubina et al., 2002). In this model, mood stabilizing anticonvulsants have been shown to attenuate quinpirole-induced hyperactivity in rats (Shaldubina et al., 2002), proving some predictive validity to the model. Given that anticonvulsant drugs only reversed the hyperactive phase, authors have suggested that this model may not be more useful than the dextroamphetamine-induced model (Shaldubina et al., 2002). This model has also been extended to an antidepressant-induced dopaminergic supersensitivity approach to mimic antidepressant-related manic switch (D'Aquila et al., 2006), in which both lithium and valproate failed to prevent imipramine-induced behavioral sensitization (D'Aquila et al., 2000; D'Aquila et al., 2006).

Ouabain-induced hyperlocomotion—A significant reduction in sodium potassium-activated adenosine triphosphatase (Na^+, K^+ -ATPase) activity has also been shown to be associated with changes in mood states in preclinical models (Christo and El-Mallakh, 1993; El-Mallakh et al., 2003; el-Mallakh et al., 1995; el-Mallakh and Wyatt, 1995; Goldstein et al., 2012; Li et al., 1997; Ruktanonchai et al., 1998). This model was proposed based on previous evidence of Na^+, K^+ -ATPase alterations in patients with BD (el-Mallakh and Wyatt, 1995), which has been further confirmed by more recent studies (Banerjee et al., 2012; Huff et al., 2010). Of note, the inhibition of Na^+, K^+ -ATPase activity may be mediated by an increased production of endogenous ouabain-like compounds that potentiate enzymatic disturbances lying beneath the HPA axis dysregulation commonly encountered in BD (Christo and El-Mallakh, 1993). The first pharmacological challenge reported preliminary data suggesting that ouabain (OUA), a Na^+, K^+ -ATPase-inhibiting compound,

may induce a plausible, alternative preclinical model of mania (el-Mallakh et al., 1995). Along the same line, the efficacy of lithium in attenuating behavioral changes after a single dose of intracerebroventricular (i.c.v.) OUA was also reported (El-Mallakh et al., 2003; Li et al., 1997). Hence, due the recurrent and progressive nature of mania, a multiple-dose pharmacological challenge with OUA in an open-field test was performed in order to measure behavioral and enzymatic activities (Ruktanonchai et al., 1998). Furthermore, several antipsychotic medications with anti-manic properties have been tested implementing this OUA-induced preclinical model of mania (El-Mallakh et al., 2006).

Among several pathophysiological mechanisms assessed in this model, brain glucose uptake metabolism and the differential isoform expression of Na^+, K^+ -ATPase have been documented (Hamid et al., 2009; Houglund et al., 2008). While rodents receiving OUA showed reduced brain glucose utilization as assessed through 18-fluorodeoxyglucose (18-FDG) positron emission tomography (PET) (Houglund et al., 2008), an increased expression of both the glial-specific $\alpha 2$ and the neuron-specific $\alpha 3$ isoforms has been described in the basal ganglia and frontal cortex, respectively (Hamid et al., 2009). These preliminary findings led researchers to develop genetic preclinical models carrying an inactivated mutation in the neuron-specific α -3 subunit (ATP1A3), reported elsewhere (Heinzen et al., 2014; Kirshenbaum et al., 2014; Kirshenbaum et al., 2011a; Kirshenbaum et al., 2012; Kirshenbaum et al., 2013; Kirshenbaum et al., 2011b).

Na^+, K^+ -ATPase inhibition induced by ouabain (OUA) has also been shown to increase levels of OS and significantly decrease central BDNF levels associated with manic-like behaviors in rodents (Brocardo et al., 2010; Bruning et al., 2012; Jornada et al., 2010; Jornada et al., 2011; Riegel et al., 2009; Riegel et al., 2010). Moreover, manic-like behaviors induced by OUA can generate abnormal synaptic plasticity and DA release in the medial PFC of rodents (Sui et al., 2013). Accordingly, these findings related to a significant inhibition of Na^+, K^+ -ATPase activity, which has also been documented in human subjects with BD and may at least in part be ameliorated by lithium (Banerjee et al., 2012; Machado-Vieira et al., 2007). Of note, folic acid and diphenyl diselenide have been shown to reduce manic-like behaviors in rodents along with an attenuation of OUA-induced OS (Brocardo et al., 2010; Bruning et al., 2012). Similarly, chronic administration of memantine, a selective antagonist of the N-methyl-D-aspartate (NMDA) receptor approved for the treatment of moderate to severe Alzheimer's disease, has recently been shown to normalize OUA-induced hyperlocomotion (Gao et al., 2011), which resembles recent findings on the efficacy of this drug for the treatment of BD (Serra et al., 2015).

Ketamine-induced hyperlocomotion—Based on studies suggesting a glutamatergic hypofunction in BD (Dickerson et al., 2012; Rao et al., 2012b) and a case report of mania induction following ketamine therapy (Ricke et al., 2011), a study has proposed an animal model of mania induced by the rapid acting selective NMDA antagonist ketamine (Ghedim et al., 2012). During this paradigm, both lithium and VAP were able to partially prevent and reverse ketamine-induced hyperlocomotion with a significant reduction in OS measures in discrete brain areas involved in the pathophysiology of BD (Ghedim et al., 2012). This model was later employed to suggest the potential use of curcumin as a preventive intervention for BD (Gazal et al., 2014). Even though further studies are required, initial

evidence suggests some predictive, face, and construct validity for this model. However, a clear limitation of this model refers to its lack of specificity for mania, as ketamine-induced hyperactivity is also regarded as a putative animal model for schizophrenia (Zugno et al., 2015a; Zugno et al., 2015b). On this same vein, not only has ketamine been shown to present antidepressant effects (Scheuing et al., 2015), but lithium has also shown synergic effects with ketamine (Chiu et al., 2014). All of these findings significantly hinder the excitement towards the use of ketamine as an animal of mania.

Cholera toxin-induced hyperlocomotion—Cholera toxin (CTX) catalyzes ADP-ribosylation and thereby activates G proteins, which may be implicated in both the pathophysiology and treatment of BD (Perez et al., 1999). Similarly, the injection of CTX into the nucleus accumbens (NAc) of rodents promotes sustained hyperactivity (Kofman et al., 1998). Therefore, one may argue that this CTX paradigm could provide another behavioral model of mania involving sustained hyperactivity (Kofman et al., 1998). In fact, the CTX paradigm has been proposed as a possible approach to model mania and anti-manic pharmacological responses (e.g. to carbamazepine) (Kofman et al., 1998; Machado-Vieira et al., 2004a). Nevertheless, the face, construct and predictive validity parameters of this model remain incompletely elucidated, and further investigations are warranted.

3.2. Environmental models of mania

Environmental models of mania in rodents include the rodent sleep deprivation, the resident-intruder test, and the dominant-submissive behavior paradigms (Einat, 2007a; Gessa et al., 1995; Malatynska and Knapp, 2005; Mansell and Pedley, 2008; Miczek et al., 2001).

Sleep deprivation—Preclinical models of mania involving aberrations in circadian rhythms associated with sleep deprivation have been developed (McClung, 2011; McClung et al., 2005). Although abnormal circadian rhythmicity is a frequent manifestation of mania, very little is known about its role and impact over the pathophysiology of mood disorders (Geddes and Miklowitz, 2013). Nevertheless, stress-induced circadian rhythm disturbances such as sleep deprivation may lead to manic episodes in humans (Frank et al., 2005; Malkoff-Schwartz et al., 1998). Therefore, sleep deprivation paradigms may also induce numerous manic-like behaviors in rodents, which may be related to a dysregulation in dopaminergic, glutamatergic and opioid neurotransmission systems that modulate PKC pathways associated with abnormal circadian rhythmicity (Armani et al., 2012; Benedetti et al., 2008; Gessa et al., 1995; Szabo et al., 2009). The sleep deprivation model has significant relevance regarding face validity as it may mimic one of the hallmark symptoms of mania (Kaplan and Harvey, 2013). After a 72-hour sleep deprivation period, rodents display numerous manic-like behaviors for about half an hour (Fratta et al., 1987; Hicks et al., 1979; Morden et al., 1968). Moreover, the sleep deprivation model has an adequate predictive validity as evidenced by the reversal of manic-like behaviors by lithium (Gessa et al., 1995). Recently, others have proposed a more sophisticated model controlling for additional stress factors, such as isolation, immobilization and the experience of falling to the water (Benedetti et al., 2008). During this paradigm the control group had a larger stable platform surrounded by water, enabling to some extent normal sleeping patterns, and only those animals that were sleep deprived continued to exhibit manic-like behaviors. In addition, an

increase in the PKC pathway signaling in the mPFC hints some components of construct validity to the model, whereas an adequate predictive validity is suggested by the fact that administration of food with lithium reduced manic-like behaviors in rodents compared to those receiving a mood stabilizer-free diet (Szabo et al., 2009).

Resident-intruder test—Notwithstanding less acknowledged as a model for mania, the resident-intruder test consists of confronting an intruder rodent with an isolated mouse (or rat) within a cage and quantifying both the aggressive acts from the resident and the defensive acts and postures displayed by the intruder (Miczek et al., 2001). Even though this is a test and not an animal model *per se*, the manipulations in the test are sufficient to induce an increase in aggression, agitation and intrusive actions, which can be quantified and have been related to mania-associated behavior. If necessary, manic-like behaviors may be augmented by prolonged isolation and/or foot shocks applied to resident rodents (Legrand and Fielder, 1973; Miczek and O'Donnell, 1978). While antimanic treatments with lithium and valproate have shown to reduce resident aggression towards intruders (Einat, 2007b; O'Donnell and Gould, 2007), antidepressant treatment has been related to an increase in aggression in this paradigm (Mitchell, 2005), suggesting predictive validity for this model. Of note, the aggression in this test has been shown to be ameliorated by anxiolytics and antipsychotics too (Vassout et al., 2000; Yang et al., 2015), suggesting a limited predictive validity and specificity to mania. On this sense, more investigations are necessary to better appreciate the validity of this paradigm as an animal model for mania.

Dominant-submissive behavior paradigm—A similar environmental model for mania related to dominant-submissive behavior paradigm has been proposed (Malatynska and Knapp, 2005). During this paradigm, two rodents are placed within separate cages connected by a tunnel through which only one animal can cross at a time (Gardner, 1982). After 14-days of time-controlled interactions between rodents, it is estimated that 50% of paired animals will develop a dominant-submissive behavior regarding the time spent over food consumption (Gardner, 1982). However, the administration of antimanic medications such as lithium, valproate, and carbamazepine reversed the previously established dominance status over food consumption (Malatynska and Knapp, 2005; Malatynska et al., 2007).

Of note, a feature that is particularly interesting about this model is that it includes a stage of selecting animals, i.e., not the entire cohort of animals is included in the final testing but only those that show specific behaviors. This is an important characteristic of the model since it relates to individual variability in response to environmental stimuli.

3.3. Genetic models for mania

Genetic rodent models for mania may provide greater construct validity compared to other preclinical models, leading to the identification of potential behavioral endophenotypes (Gould and Einat, 2007; Malkesman et al., 2009). Hence, some mice strains and genetically modified rodents may be more prone to manic-like behaviors, more susceptible to pharmacologically-induced changes in behavior, or have a pronounced expression of genetic mutations linked to mania (Young et al., 2011b). Altogether, genetic manipulation in rodent

models involving genes coding for the dopamine transporter (DAT) (Giros et al., 1996; Ralph-Williams et al., 2003; Zhuang et al., 2001), circadian locomotor output cycle kaput (CLOCK) (McClung et al., 2005; Roybal et al., 2007), glutamate receptor 6 (GluR6) (Shaltiel et al., 2008), GSK-3 β (Prickaerts et al., 2006), circadian gene D-box binding protein (DBP) (Le-Niculescu et al., 2008), pituitary adenylate cyclase-activating polypeptide (PACAP) (Hattori et al., 2012), extracellular signal-regulated kinase 1 (ERK1) (Engel et al., 2009), postsynaptic density protein (PSD) SHANK3 (Han et al., 2013), inositol-monophosphatase (IMPA)1 (Damri et al., 2015), and B-cell lymphoma 2 (Bcl-2) (Lien et al., 2008) may provide novel animal models for the study of mania and its treatment.

Dopamine transporter (DAT)—A dopamine transporter (DAT) knockout mice was initially generated to directly assess the role of this transporter in the function of the dopamine system (Giros et al., 1996). Accordingly, DAT knockout mice exhibit hyperactivity in an open-field and significantly reduced hyperlocomotor and stereotypic behavior response following the administration of psychostimulants (Giros et al., 1996). Its use as an animal model for mania has been proposed based on a hyperactive behavior phenotype, which resembles human mania, and on the fact that treatment with valproate reverses this behavior (Ralph-Williams et al., 2003; van Enkhuizen et al., 2013). These mice have also been shown to present increased risk-taking behaviors and an exploratory profile consistent with patients with BD mania (Young et al., 2011b). Moreover, treatment with clozapine or quetiapine, which are both effective treatments of schizophrenia and mania, attenuated behavioral alterations in DAT knockout mice (Powell et al., 2008). Due to the non-specificity of the hyperactive behavior, these mice have also been investigated as animal models for attention deficit hyperactivity disorder (ADHD) and schizophrenia, two disorders in which alterations in DA transmission play a significant patho-etiological role (Ford, 2014; Giros et al., 1996; Wong et al., 2012; Zhuang et al., 2001). Therefore, the validity of DAT knockout mice as a putative animal model for mania remains limited.

Circadian locomotor output cycle kaput (CLOCK)—Replicated evidence indicates that polymorphisms of the circadian gene CLOCK may contribute to the pathophysiology of BD (Benedetti et al., 2015; Kittel-Schneider et al., 2015; Mansour et al., 2005; Milhiet et al., 2014). *CLOCK* knockout mice have initially shown to display an increase in cocaine-related reward and excitability of dopaminergic neurons (McClung et al., 2005). Subsequently, these mice were shown to present an overall behavioral profile similar to human mania, including hyperactivity, increased specific exploration, decreased sleep, reduced sensorimotor gating, lowered depression-like behavior, lower anxiety, a greater sensitivity to photoperiod alterations, and an increase in the reward value of sucrose (Roybal et al., 2007; van Enkhuizen et al., 2013). The model has also found to present abnormalities in dopaminergic firing rates and associated morphology, which may contribute to alterations in anxiety-related behaviors in bipolar mania (Coque et al., 2011). On top of that, chronic administration of lithium reversed many of these alterations (Coque et al., 2011; Roybal et al., 2007), and this model alone has been used to propose the use of a new drug for the treatment of mania (Arey and McClung, 2012). In summary, *CLOCK* knockout mice seem to present adequate face validity along with some evidence of predictive validity, as well.

Circadian gene D-box binding protein (DBP)—Another circadian clock gene (DBP) was also identified as a potential candidate gene for BD, and DBP knockout mice have been tested as an animal model of mania (Le-Niculescu et al., 2008). These mice exhibited a switch from hypo- to hyperlocomotion after exposure to chronic stress, which was considered analogous to the switch from depression to mania frequently observed in BD, and the same pattern of activation was observed after sleep deprivation. Interestingly, this activation was prevented by treatment with valproate (Le-Niculescu et al., 2008), providing initial evidence of predictive validity to this model. Of note, since this first publication in 2008 no further studies have been published using these mice in the context of mania and BD.

Glutamate receptor 6 (GluR6)—This model was based on studies showing that the glutamate receptor 6 (GluR6) gene is located at a genetic linkage region associated with BD (Schulze et al., 2004), while cortical expression this receptor was shown to be lower in bipolar patients (Beneyto et al., 2007). Knockout mice for the GluR6 gene were shown to be more active, less anxious, more aggressive, hyper-responsive to amphetamine challenge, and more risk-taking in behavioral tests than wild-type animals (Shaltiel et al., 2008). Interestingly, chronic lithium was able to reduce most of these behavioral alterations (Shaltiel et al., 2008). In summary, this model seems to present face validity. Although promising, future studies are necessary to appreciate construct and predictive validity parameters for this model.

Glycogen synthase kinase-3 β (GSK-3 β)—Glycogen synthase kinase-3 β (GSK-3 β) is a well-known intracellular target for lithium and other mood stabilizers (Einat and Manji, 2006; Serretti et al., 2009), and this enzyme is thought to play a key role in the pathophysiology of BD (Hoertel et al., 2013). Based on this, transgenic mice overexpressing GSK-3 β have been tested as an animal model for mania, and they were shown to present altered plasticity processes, increased locomotor activity, reduced immobility in the forced swim test, a heightened acoustic startle response, and a decreased habituation to an open field test (Prickaerts et al., 2006). This behavioral phenotypes resemble manic-like manifestations. No differences in adrenocorticotrophic hormone (ACTH) or corticosterone levels were observed in these mice, and further analyses suggested the occurrence of compensatory mechanisms for the overexpression of GSK-3 β . It is important to point out that this model lacks specificity for mania, since the constitutive activation of the dopaminergic system observed in these animals is also a key feature in other disorders, such as ADHD and schizophrenia. In addition, it is worth mentioning that a later study did not replicate previous findings with this model (Bersudsky et al., 2008), suggesting that the initially reported effects of GSK-3b knockout on behavior are not robust.

Pituitary adenylate cyclase-activating polypeptide (PACAP)—A genetic linkage study has found that the pituitary adenylate cyclase-activating polypeptide (PACAP) gene is located close to a BD risk locus (McInnes et al., 2001). Furthermore, the PACAP protein has important neuromodulatory roles (Hashimoto et al., 2006), which may contribute to the pathophysiology of BD. Accordingly, PACAP knockout mice were shown to exhibit increased locomotor activity in a novel environment, abnormal anxiety-like behavior, a

slight decrease in depression-like behavior, an increase in social interaction, and mild performance deficits in working memory (Hattori et al., 2012). These transgenic mice have thus been suggested as a novel animal model for mania. The cognitive impairments in memory tests displayed by these mice were replicated (Takuma et al., 2014). It should be emphasized that PACAP has also been implicated in the pathophysiology of other mental disorders (e.g. schizophrenia) (Katayama et al., 2009), and there is a lack of data on the predictive validity of this model for mania.

Extracellular signal-regulated kinase 1 (ERK1)—The extracellular signal-regulated kinase 1 (ERK1) pathway has been shown to be activated by lithium and valproate, and this event may mediate neurite outgrowth, neuronal survival and hippocampal neurogenesis (Engel et al., 2009). Therefore, mice with a targeted disruption of the ERK1 gene have been tested as a potential animal model for mania. Hence, these mice displayed behavioral activation pattern that resembles manic-like manifestations induced by psychostimulants, including hyperactivity, enhanced goal-directed activity and increased reward-motivated behavior (Engel et al., 2009). These initial results suggest an adequate face validity for this model. However, treatment with valproate and olanzapine, but not with lithium, reduced these behavioral features (Engel et al., 2009), suggesting a limited predictive validity.

Postsynaptic density protein SHANK3—SHANK3 is a scaffolding protein important for organizing complexes at the postsynaptic density, and mutations at this gene have been reported in psychiatric disorders (Han et al., 2013). Mice with an overexpression of SHANK3 in mice leading to an excitatory-inhibitory imbalance exhibited several manic-like behaviors, including hyperlocomotion, a higher sensitivity to amphetamine, a reduced immobility time in the tail-suspension test, an elevated acoustic startle response with a reduced prepulse inhibition, abnormal circadian rhythms, and hyperphagia-like behavior (Han et al., 2013). Moreover, these behavioral features were alleviated by valproate, but not by lithium (Han et al., 2013).

Neuron-specific α -3 subunit (ATP1A3)—As mentioned before, genetic dysfunction of ATP1A3 has also been linked to mania- and depressive-related behaviors in preclinical models (Heinzen et al., 2014; Kirshenbaum et al., 2014; Kirshenbaum et al., 2011a; Kirshenbaum et al., 2012; Kirshenbaum et al., 2013; Kirshenbaum et al., 2011b). While homozygous rodents carrying this inactivated mutation have a significant reduction in Na^+ , K^+ -ATPase activity in the brain, which has been directly related to manic-like behaviors, heterozygous mice did not display significant behavioral differences compared to wild-type counterparts at baseline (Heinzen et al., 2014; Kirshenbaum et al., 2014). However, these same heterozygous mice may also exhibit a significant increase in Na^+ , K^+ -ATPase α 3 inhibition after a chronic stress paradigm associated with depressive-related behavior (Kirshenbaum et al., 2014). In other words, it seems that the degree of physiological dysfunction of Na^+ , K^+ -ATPase α 3 activity coupled with the magnitude of stressors may determine the expression of both manic and depressive-like behaviors in rodents. Interestingly, lithium and valproate were able to reduce the mania-like behaviors of these mice (Kirshenbaum et al., 2011a), and the model has also been used to propose the use of agrin, a proteoglycan implicated in the regulation of synapses, for the treatment of mania

(Kirshenbaum et al., 2012). However, these data deserve replication prior to the establishment of validity parameters for this putative animal model for mania.

B-cell lymphoma 2 (Bcl-2)—Bcl-2 is an antiapoptotic protein whose expression can be induced by treatments with mood stabilizers, some antidepressants and also atypical antipsychotic drugs. On this sense, a Bcl-2 heterozygous mouse has been developed and was shown to present increased anxious-like behavior (Einat et al., 2005), as well as reward seeking and amphetamine sensitization, which models different facets of mania (Lien et al., 2008). In addition, the amphetamine sensitization was attenuated by chronic treatment with lithium (Lien et al., 2008), adding a limited predictive validity to the model. Accordingly, knockout mice to the Bcl-2-associated athanogene (BAG1), which is also a Bcl-2-related protein, were also shown to exhibit an enhanced cocaine-induced behavioral sensitization (Maeng et al., 2008).

Mouse strains—Studies also report characteristic mania-like behavioral manifestations in *Black Swiss* (BS) mice (Flaisher-Grinberg and Einat, 2010; Hannah-Poquette et al., 2011). These mice are shown to exhibit peculiar risk-taking, aggressive and reward-seeking behaviors, a heightened response to psychostimulants (Flaisher-Grinberg and Einat, 2010), and specific biochemical alterations in distinct brain regions (Hannah-Poquette et al., 2011). Furthermore, lithium and valproate attenuated the manic-like behavior presented by these mice (Flaisher-Grinberg and Einat, 2010). Such strain-specific behavioral and biochemical differences have been used in studies evaluating existing and novel pharmacological anti-manic treatments, including asenapine (Ene et al., 2015), the protein kinase C inhibitor chelerythrine (Einat et al., 2014b), and GSK-3 inhibitors (Kalinichev et al., 2011). Interestingly, another mouse strain referred to as Madison (MSN) also displays a classical manic-like phenotype, while both lithium and olanzapine seem to reduce manic-like manifestations (Saul et al., 2012). Furthermore, MSN mice present dysregulation in several transcripts whose orthologs are associated with BD (Saul et al., 2012). Thus, MSN mice holds promise as an animal model of mania, with evidence to date suggesting adequate face, construct and predictive validity.

In summary, although animal models with genetic modifications may help to improve our understanding about underlying mechanisms orchestrating the origin and/or progression of BD, several limitations should be considered. It is also worth mentioning that some genetic models have also been developed to the study of manic-related mechanisms, but are not specifically taken as animal models of mania. These include knockout mice for the inositol monophosphatase (IMPase) enzyme, for instance, which behave like lithium-treated animals in a series of behavioral and neurochemical analyses (Agam et al., 2009; Damri et al., 2015; Toker et al., 2014). In general, the evidence base for these models remains limited, and therefore their validity parameters cannot be fully established. Nevertheless, genetic animal models for mania or BD hold promise, and may aid in the pathophysiological comprehension and in the search of novel therapeutic targets for bipolar mania.

4. Limitations of classic animal models of mania

Several major caveats have been discussed in the literature about inherent limitations in modeling mania in laboratory animals (Nestler and Hyman, 2010; Young et al., 2011a). Furthermore, most of the animal models for mania have not provided significant insights into the pathophysiology of this illness (Dzirasa and Covington, 2012). In fact, most of the behaviors assessed are nonspecific to mania, and they frequently overlap with pathophysiological processes encountered in other major mental disorders, such as schizophrenia, attention deficit hyperactivity disorder (ADHD), substance use disorders, and tardive dyskinesia (Young et al., 2011a). Moreover, with some exceptions as in the case of the psychostimulant sensitization model, strain and/or specific gene mutation models, in general, the simulation of manic-like behaviors in animals are limited to a short span. This contradicts with manic episodes characterized as intermittent but long-lasting behavioral disturbances (Valvassori et al., 2013; Young et al., 2011a).

Regarding predictive validity, while classic anti-manic agents have an acute and rapid onset of action in rodents, treatment response in humans can take several weeks to ensue. Moreover, it is still unclear if current animal models of mania are sensitive to all possible pharmacological probes of intervention, mostly due to that fact that most models were developed based on the mechanisms of action of known treatments (pharmacological isomorphism). In other words, if the mechanisms of action of a potential novel drug significantly differ from the currently available medications, it might not have positive effects in most animal models but that doesn't mean it won't be effective in treating actual patients.

Another important issue is that many specific animal models for mania measure 'hyperactivity' as the primary outcome of manic-like behavior (Young et al., 2011a). However, hyperlocomotion is non-specific for subjects with BD, and it has been rarely measured in controlled clinical trials for mania in humans (Einat, 2006, 2007b; Geyer, 2008; Young et al., 2007). Of note, a relatively novel approach to analyze alterations in exploratory behavior (known as the human behavioral pattern monitor) has been proposed as an improvement to the field and was shown to be a good translational model for mania and mania-like behaviors (Henry et al., 2010). In addition, dealing with environmental inconsistency of the rodents' tests and habituation to the test chamber may be a difficult task at hand as well as a critical issue when interpreting manic-like behaviors in the animals (Young et al., 2011a). Thus, both factors may limit the translational applicability of current animal models for mania (Li and Wolf, 1997; Vassout et al., 2000).

5. Prospective trends in animal models of mania

As the understanding about complex pathophysiological processes and mechanisms of BD continues to evolve, a flood of novel animal models for mania are expected to emerge in the near future. The investigation of neuroprogression and treatment-resistance in mania is of particular relevance.

Modeling the neuroprogressive nature of mania in preclinical settings—It is known that the neuroprogressive nature of mania involves several clinical correlates, such as an increase in frequency of manic episodes, shortening of inter-episodic intervals, a progressive decreased in treatment response rates to mood stabilizers, a cumulatively higher prevalence of comorbidities, as well as changes peripheral and systemic inflammatory activation, O&NS, and structural changes in specific brain regions, along with a decline in neurocognitive performance and functionality (Berk, 2009; Budni et al., 2013; Kapczinski et al., 2009).

Modelling neuroprogression related recurring mania in laboratory animals may provide unique insights into the pathophysiology of BD. Hence, exposing rodents to multiple, chronic, experimentally-induced manic-like behaviors may provide biobehavioral patterns, which could relate to staging systems and neuroprogression paradigms of BD in humans (Kapczinski et al., 2011; Kapczinski et al., 2014). Notwithstanding the assessment of cognitive impairment and changes in manic-like behaviors in rodents may be currently accomplished with adequate face validity, levels of immune activation, neurotrophic activity and histopathology could enable the development of a novel neuroprogressive preclinical model of mania with appropriate face validity. Of note, the subchronic or chronic administration of dextroamphetamine to rats lead to a worse impairment in habituation memory in the group more chronically treated with D-amphetamine, which correlated with alterations in brain-derived neurotrophic factor levels in the hippocampus, prefrontal cortex, and amygdala (Fries et al., 2015). On the other hand, reported differences in terms of prospective emergence of manic-like behaviors between rodents exposed to mood stabilizers compared to treatment-naïve counterparts, may enable the further validation of the neuroprogression paradigm. This scientific effort may provide a novel preclinical tool to dissect mechanisms driving neuroprogression in BD.

Preclinical modeling of treatment-resistant mania—Resistant/refractory mood disorders pose an additional challenge for scientists trying to design consistent preclinical models to approach new methods for biological intervention. To our knowledge, there is a dearth of preclinical models of resistant/refractory mania reported in the literature. To date, it seems likely that neurodevelopmental stress, brain lesions in strategic areas and/or permanent electric stimulation in specific areas may produce chronic changes resembling resistant/refractory mania in rodents (Machado-Vieira et al., 2004a; Swerdlow et al., 2001). Major drawbacks of these approaches refer to the fact that animal models which are refractory to mood stabilizers could have limited predictive and construct validity for mania. Furthermore, the underlying pathology of mania remains incompletely elucidated.

An early change induced by stress during neurodevelopment in the limbic system of the rodent brain may produce a neurochemical reorganization of excitatory and inhibitory neurotransmission (Bachevalier, 1996; Verwer et al., 1996). In fact, several behavioral changes associated with chronic manic-like behaviors have been described in such models of neurodevelopmental stress, such as hyperlocomotion, increased exploratory behaviors, and a significant decrease in seizure threshold (Bannerman et al., 2001; Wolterink et al., 2001). Moreover, these chronic manic-like behaviors may also be perpetuated by

amphetamine-induced release of DA in the ventral striatum (Bannerman et al., 1999; Kehoe et al., 1998; Kimble, 1963; Wilkinson et al., 1993).

Transient ischemia also seems to produce long-lasting manic-like behaviors in rodents associated with permanent changes in calcium channels-regulated release of DA (Kuroiwa et al., 1991; Wang and Corbett, 1990). The use of isradipine, an L-type calcium channel blocker, has been shown to attenuate this extracellular release of DA, leading to long-lasting significant changes in the behavior of rodents in ischemic mania models (Nakane et al., 1995). A similar pathophysiological process has been suggested in the past in vascular human models of refractory mania (Levy and Janicak, 2000).

Moreover, as mentioned in a previous section, a model of imipramine-induced sensitization to the dopamine receptor agonist quinpirole has been suggested as a model for antidepressant-induced manic switch; this model displays resistance to specific mood stabilizers (D'Aquila et al., 2000). Accordingly, the mood stabilizers lithium and valproate failed to prevent this dopaminergic sensitization (D'Aquila et al., 2000; D'Aquila et al., 2006), while carbamazepine did so (D'Aquila et al., 2001). These reports might contribute to explain the different responsiveness to mood stabilizers observed in manic patients, and are consistent with clinical observations that carbamazepine may be more effective to treat antidepressant-related mania (D'Aquila et al., 2001).

6. Conclusions and perspectives

Animal models remain a mainstay to investigate neurobiological mechanisms underlying complex mood disorders such as mania (Machado-Vieira et al., 2004b; Teixeira and Quevedo, 2013; Valvassori et al., 2013; Young et al., 2011a). Likewise, animal models for mania are considered a valuable tool for the screening of new agents with mood stabilizing properties (Armani et al., 2014). Even though stimulant-induced animal models of mania has allowed progress in this field, there are several limitations associated with such approaches. For instance, mania is a multifaceted behavioral disturbance, and d-amphetamine-induced hyperlocomotion is just one of its features. Furthermore, hyperlocomotion is not a specific manic-like manifestation. This notion is supported by several lines of evidence indicating that d-amphetamine-induced hyperlocomotion has also been employed as a proxy of behavioral aspects related to substance use disorders, schizophrenia and tardive dyskinesia (Young et al., 2011a).

Currently, no animal model for mania has been fully established to aid in the investigation of mechanisms underlying the neuroprogressive nature of BD, which is often accompanied with medication refractoriness. In addition, there is a need for new approaches to mimic more severe, chronic manic-like behaviors. Particularly, the kindling model for BD, which was first described in the early 80s (Post, 2007; Post et al., 1982), states that the progression of the illness is driven by a gradual reduction in the threshold (e.g. magnitude of stressors) required for the emergence of subsequent affective episodes (Kalynchuk, 2000; Post and Weiss, 1996). Although authors argue for an association with generalized motor seizures in BD, it seems that partial kindling in the amygdala and ventral areas of the hippocampus is independently responsible for the maintenance of behavioral changes observed in mania

(Adamec, 1990). Thus, the validity of this kindling model of refractory mania and neuroprogression remains inconclusive at the current state of knowledge in the field (Post and Weiss, 1998). Nevertheless, the kindling model continues to be considered a valuable model to understand neural dysfunction and pharmacological response to mood stabilizing agents in BD (Post et al., 2001).

A challenge that remains in modelling mania in BD is to mimic its cycling pattern, which is the hallmark of BD. There are several proposed models of depression and mania, which per se are already flawed and very limited, but a model for the cycling pattern of mania that is the hallmark of BD remains elusive. There are additional real-life challenges that manic BD patients experience apart from the neuroprogressive and treatment refractory nature of this illness (Kupfer, 2005). For instance, substance use disorders such as alcoholism (Frye and Salloum, 2006) and cocaine abuse (Post and Kalivas, 2013), metabolic disturbances (Galvez et al., 2015), obesity (Fagiolini et al., 2003), cardiovascular disorders (Weeke et al., 1987), and diabetes (Cassidy et al., 1999; Sharma et al., 2014) are common comorbid conditions in manic BD patients. Even though a handful of models related to common denominators of BD and its clinical comorbidities has been reported, including models for impulsivity or models for increased reward seeking (van Enkhuizen et al., 2014), which represent tentative endophenotypes related to both mania and drug abuse, to the best of our knowledge no direct attempts to date have investigated the role of these comorbidities in animal models of bipolar mania.

The aforementioned limitation may contribute to the failure of existing models for mania to properly translate animal findings to humans (Mak et al., 2014). The development and further investigation of existing novel (e.g. genetic) models is a necessary step. In the current state of knowledge in the field, researchers must consider combining different models to investigate novel therapeutic targets for bipolar mania, taking into consideration the methodological strengths and drawbacks of models reviewed herein.

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Abbreviations

18-FDG	18-fluorodeoxyglucose
ACTH	Adrenocorticotrophic hormone
ADHD	Attention deficit hyperactivity disorder
ATP1A3	Neuron-specific alpha-3 subunit
BCL-2	B-cell lymphoma 2

BD	Bipolar disorder
BDNF	Brain derived neurotropic factor
BS mice	Black Swiss mice
MSN mice	Madison mice
CLOCK	Circadian locomotor output cycle kaput
CTX	Cholera toxin
DA	Dopamine
DAT	Dopamine transporter
DBP	Circadian gene D-box binding protein
ERK1	Extracellular signal-regulated kinase 1
GluR6	Glutamate receptor 6
GSK-3β	Glycogen synthase kinase-3beta
HDAC	Histone deacetylase
i.c.v	Intra-cerebro-ventricular
LDX	Lisdexamfetamine dimesylate
MAO	Monoamino Oxidase
mPFC	Medial prefrontal cortex
NAc	nucleus accumbens
NMDA	N-methyl D-aspartate
OS	Oxidative stress
O&NS	oxidative and nitrosative stress
OUA	Ouabain
PACAP	Pituitary adenylate cyclase-activating polypeptide
PET	Positron emission tomography
PKC	Protein kinase-C
PSD	Post-synaptic density
SB	Sodium butyrate
SHANK3	SH3 and multiple ankyrin repeat domains 3
ST	Striatum
VAP	Valproate

References

- Adamec RE. Amygdala kindling and anxiety in the rat. *Neuroreport*. 1990; 1:255–258. [PubMed: 2129887]
- American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force., Psychiatry Online (Online service). Diagnostic and statistical manual of mental disorders : DSM-5. 5. American Psychiatric Association; Washington, D.C: 2013. p. xlvip. 947
- Agam G, Bersudsky Y, Berry GT, Moechars D, Lavi-Avnon Y, Belmaker RH. Knockout mice in understanding the mechanism of action of lithium. *Biochem Soc Trans*. 2009; 37:1121–1125. [PubMed: 19754464]
- Arban R, Maraia G, Brackenborough K, Winyard L, Wilson A, Gerrard P, Large C. Evaluation of the effects of lamotrigine, valproate and carbamazepine in a rodent model of mania. *Behavioural brain research*. 2005; 158:123–132. [PubMed: 15680200]
- Arent CO, Valvassori SS, Fries GR, Stertz L, Ferreira CL, Lopes-Borges J, Mariot E, Varela RB, Ornell F, Kapczinski F, Andersen ML, Quevedo J. Neuroanatomical profile of antimanic effects of histone deacetylases inhibitors. *Molecular neurobiology*. 2011; 43:207–214. [PubMed: 21424678]
- Arey R, McClung CA. An inhibitor of casein kinase 1 epsilon/delta partially normalizes the manic-like behaviors of the ClockDelta19 mouse. *Behavioural pharmacology*. 2012; 23:392–396. [PubMed: 22743604]
- Armani F, Andersen ML, Andreatini R, Frussa-Filho R, Tufik S, Galduroz JC. Successful combined therapy with tamoxifen and lithium in a paradoxical sleep deprivation-induced mania model. *CNS neuroscience & therapeutics*. 2012; 18:119–125. [PubMed: 22070228]
- Armani F, Andersen ML, Galduroz JC. Tamoxifen use for the management of mania: a review of current preclinical evidence. *Psychopharmacology*. 2014; 231:639–649. [PubMed: 24441937]
- Bachevalier J. Brief report: medial temporal lobe and autism: a putative animal model in primates. *Journal of autism and developmental disorders*. 1996; 26:217–220. [PubMed: 8744488]
- Banerjee U, Dasgupta A, Rout JK, Singh OP. Effects of lithium therapy on Na⁺-K⁺-ATPase activity and lipid peroxidation in bipolar disorder. *Progress in neuro-psychopharmacology & biological psychiatry*. 2012; 37:56–61. [PubMed: 22230647]
- Bannerman DM, Lemaire M, Beggs S, Rawlins JN, Iversen SD. Cytotoxic lesions of the hippocampus increase social investigation but do not impair social-recognition memory. *Experimental brain research*. 2001; 138:100–109. [PubMed: 11374076]
- Bannerman DM, Yee BK, Good MA, Heupel MJ, Iversen SD, Rawlins JN. Double dissociation of function within the hippocampus: a comparison of dorsal, ventral, and complete hippocampal cytotoxic lesions. *Behavioral neuroscience*. 1999; 113:1170–1188. [PubMed: 10636297]
- Baptista T, Weiss SR, Post RM. Carbamazepine attenuates cocaine-induced increases in dopamine in the nucleus accumbens: an in vivo dialysis study. *Eur J Pharmacol*. 1993; 236:39–42. [PubMed: 8319744]
- Belzung C, Lemoine M. Criteria of validity for animal models of psychiatric disorders: focus on anxiety disorders and depression. *Biology of mood & anxiety disorders*. 2011; 1:9. [PubMed: 22738250]
- Benedetti F, Fresi F, Maccioni P, Smeraldi E. Behavioural sensitization to repeated sleep deprivation in a mice model of mania. *Behavioural brain research*. 2008; 187:221–227. [PubMed: 17950929]
- Benedetti F, Riccaboni R, Dallaspezia S, Locatelli C, Smeraldi E, Colombo C. Effects of CLOCK gene variants and early stress on hopelessness and suicide in bipolar depression. *Chronobiology international*. 2015:1–6.
- Beneyto M, Kristiansen LV, Oni-Orisan A, McCullumsmith RE, Meador-Woodruff JH. Abnormal glutamate receptor expression in the medial temporal lobe in schizophrenia and mood disorders. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2007; 32:1888–1902. [PubMed: 17299517]
- Berggren U, Tallstedt L, Ahlenius S, Engel J. The effect of lithium on amphetamine-induced locomotor stimulation. *Psychopharmacology*. 1978; 59:41–45. [PubMed: 100811]

- Berk M. Neuroprogression: pathways to progressive brain changes in bipolar disorder. The international journal of neuropsychopharmacology/official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP). 2009; 12:441–445. [PubMed: 18922203]
- Berk M, Dodd S, Kauer-Sant'anna M, Malhi GS, Bourin M, Kapczinski F, Norman T. Dopamine dysregulation syndrome: implications for a dopamine hypothesis of bipolar disorder. *Acta psychiatrica Scandinavica. Supplementum*. 2007;41–49. [PubMed: 17688462]
- Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, Yucel M, Gama CS, Dodd S, Dean B, Magalhaes PV, Amminger P, McGorry P, Malhi GS. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neuroscience and biobehavioral reviews*. 2011; 35:804–817. [PubMed: 20934453]
- Bersudsky Y, Shaldubina A, Kozlovsky N, Woodgett JR, Agam G, Belmaker RH. Glycogen synthase kinase-3beta heterozygote knockout mice as a model of findings in postmortem schizophrenia brain or as a model of behaviors mimicking lithium action: negative results. *Behav Pharmacol*. 2008; 19:217–24. [PubMed: 18469539]
- Brocardo PS, Budni J, Pavesi E, Franco JL, Uliano-Silva M, Trevisan R, Terenzi MG, Dafre AL, Rodrigues AL. Folic acid administration prevents ouabain-induced hyperlocomotion and alterations in oxidative stress markers in the rat brain. *Bipolar disorders*. 2010; 12:414–424. [PubMed: 20636639]
- Bruning CA, Prigol M, Luchese C, Pinton S, Nogueira CW. Diphenyl diselenide ameliorates behavioral and oxidative parameters in an animal model of mania induced by ouabain. *Progress in neuro-psychopharmacology & biological psychiatry*. 2012; 38:168–174. [PubMed: 22459096]
- Budni J, Valvassori SS, Quevedo J. Biological mechanisms underlying neuroprogression in bipolar disorder. *Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999)*. 2013; 35:1–2.
- Cappelliez P, Moore E. Effects of lithium on an amphetamine animal model of bipolar disorder. *Progress in neuro-psychopharmacology & biological psychiatry*. 1990; 14:347–358. [PubMed: 2163063]
- Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. *The American journal of psychiatry*. 1999; 156:1417–1420. [PubMed: 10484954]
- Cechinel-Recco K, Valvassori SS, Varela RB, Resende WR, Arent CO, Vitto MF, Luz G, de Souza CT, Quevedo J. Lithium and tamoxifen modulate cellular plasticity cascades in animal model of mania. *Journal of psychopharmacology (Oxford, England)*. 2012; 26:1594–1604.
- Chen C, Zhang C, Cheng L, Reilly JL, Bishop JR, Sweeney JA, Chen HY, Gershon ES, Liu C. Correlation between DNA methylation and gene expression in the brains of patients with bipolar disorder and schizophrenia. *Bipolar disorders*. 2014; 16:790–799. [PubMed: 25243493]
- Chiu CT, Scheuing L, Liu G, Liao HM, Linares GR, Lin D, Chuang DM. The mood stabilizer lithium potentiates the antidepressant-like effects and ameliorates oxidative stress induced by acute ketamine in a mouse model of stress. *Int J Neuropsychopharmacol*. 2014; 18
- Christo PJ, El-Mallakh RS. Possible role of endogenous ouabain-like compounds in the pathophysiology of bipolar illness. *Medical Hypotheses*. 1993; 41:378–383. [PubMed: 8289709]
- Coque L, Mukherjee S, Cao JL, Spencer S, Marvin M, Falcon E, Sidor MM, Birnbaum SG, Graham A, Neve RL, Gordon E, Ozburn AR, Goldberg MS, Han MH, Cooper DC, McClung CA. Specific role of VTA dopamine neuronal firing rates and morphology in the reversal of anxiety-related, but not depression-related behavior in the ClockDelta19 mouse model of mania. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2011; 36:1478–1488. [PubMed: 21430648]
- Cunha AB, Frey BN, Andreazza AC, Goi JD, Rosa AR, Goncalves CA, Santin A, Kapczinski F. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. *Neuroscience letters*. 2006; 398:215–219. [PubMed: 16480819]
- D'Aquila PS, Collu M, Devoto P, Serra G. Chronic lithium chloride fails to prevent imipramine-induced sensitization to the dopamine D(2)-like receptor agonist quinpirole. *European journal of pharmacology*. 2000; 395:157–160. [PubMed: 10794822]

- D'Aquila PS, Panin F, Serra G. Chronic valproate fails to prevent imipramine-induced behavioural sensitization to the dopamine D2-like receptor agonist quinpirole. *European journal of pharmacology*. 2006; 535:208–211. [PubMed: 16533507]
- D'Aquila PS, Peana AT, Tanda O, Serra G. Carbamazepine prevents imipramine-induced behavioural sensitization to the dopamine D(2)-like receptor agonist quinpirole. *European journal of pharmacology*. 2001; 416:107–111. [PubMed: 11282119]
- Damri O, Sade Y, Toker L, Bersudsky Y, Belmaker RH, Agam G, Azab AN. Molecular effects of lithium are partially mimicked by inositol-monophosphatase (IMPA)1 knockout mice in a brain region-dependent manner. *Eur Neuropsychopharmacol*. 2015; 25:425–434. [PubMed: 25748680]
- Davies C, Sanger DJ, Steinberg H, Tomkiewicz M, U'Prichard DC. Lithium and alpha-methyl-p-tyrosine prevent “manic” activity in rodents. *Psychopharmacologia*. 1974; 36:263–274. [PubMed: 4152541]
- Dencker D, Husum H. Antimanic efficacy of retigabine in a proposed mouse model of bipolar disorder. *Behavioural brain research*. 2010; 207:78–83. [PubMed: 19815032]
- Dickerson F, Stallings C, Vaughan C, Origoni A, Khushalani S, Yolken R. Antibodies to the glutamate receptor in mania. *Bipolar disorders*. 2012; 14:547–553. [PubMed: 22672262]
- Dzirasa K, Covington HE 3rd. Increasing the validity of experimental models for depression. *Annals of the New York Academy of Sciences*. 2012; 1265:36–45. [PubMed: 22823549]
- Dzirasa K, McGarity DL, Bhattacharya A, Kumar S, Takahashi JS, Dunson D, McClung CA, Nicoletis MA. Impaired limbic gamma oscillatory synchrony during anxiety-related behavior in a genetic mouse model of bipolar mania. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2011; 31:6449–6456. [PubMed: 21525286]
- Einat H. Modelling facets of mania--new directions related to the notion of endophenotypes. *Journal of psychopharmacology (Oxford, England)*. 2006; 20:714–722.
- Einat H. Different behaviors and different strains: potential new ways to model bipolar disorder. *Neuroscience and biobehavioral reviews*. 2007a; 31:850–857. [PubMed: 17307253]
- Einat H. Establishment of a battery of simple models for facets of bipolar disorder: a practical approach to achieve increased validity, better screening and possible insights into endophenotypes of disease. *Behavior genetics*. 2007b; 37:244–255. [PubMed: 16865528]
- Einat H. Strategies for the development of animal models for bipolar disorder: new opportunities and new challenges. *Current topics in behavioral neurosciences*. 2011; 5:69–87. [PubMed: 25236550]
- Einat H. New ways of modeling bipolar disorder. *Harvard review of psychiatry*. 2014a; 22:348–352. [PubMed: 25377608]
- Einat H. Partial effects of the protein kinase C inhibitor chelerythrine in a battery of tests for manic-like behavior in black Swiss mice. *Pharmacol Rep*. 2014b; 66:722–725. [PubMed: 24948079]
- Einat H, Manji HK. Cellular plasticity cascades: genes-to-behavior pathways in animal models of bipolar disorder. *Biological psychiatry*. 2006; 59:1160–1171. [PubMed: 16457783]
- Einat H, Yuan P, Manji HK. Increased anxiety-like behaviors and mitochondrial dysfunction in mice with targeted mutation of the Bcl-2 gene: further support for the involvement of mitochondrial function in anxiety disorders. *Behav Brain Res*. 2005; 165:172–180. [PubMed: 16095731]
- El-Mallakh RS, Decker S, Morris M, Li XP, Huff MO, El-Masri MA, Levy RS. Efficacy of olanzapine and haloperidol in an animal model of mania. *Progress in neuro-psychopharmacology & biological psychiatry*. 2006; 30:1261–1264. [PubMed: 16815616]
- El-Mallakh RS, El-Masri MA, Huff MO, Li XP, Decker S, Levy RS. Intracerebroventricular administration of ouabain as a model of mania in rats. *Bipolar disorders*. 2003; 5:362–365. [PubMed: 14525557]
- el-Mallakh RS, Harrison LT, Li R, Changaris DG, Levy RS. An animal model for mania: preliminary results. *Progress in neuro-psychopharmacology & biological psychiatry*. 1995; 19:955–962. [PubMed: 8539431]
- el-Mallakh RS, Wyatt RJ. The Na,K-ATPase hypothesis for bipolar illness. *Biological psychiatry*. 1995; 37:235–244. [PubMed: 7711160]
- Ene HM, Kara NZ, Einat H. The effects of the atypical antipsychotic asenapine in a strain-specific battery of tests for mania-like behaviors. *Behav Pharmacol*. 2015; 26:331–337. [PubMed: 25590966]

- Engel SR, Creson TK, Hao Y, Shen Y, Maeng S, Nekrasova T, Landreth GE, Manji HK, Chen G. The extracellular signal-regulated kinase pathway contributes to the control of behavioral excitement. *Molecular psychiatry*. 2009; 14:448–461. [PubMed: 18227838]
- Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E. Obesity as a correlate of outcome in patients with bipolar I disorder. *The American journal of psychiatry*. 2003; 160:112–117. [PubMed: 12505809]
- Fernandes BS, Gama CS, Cereser KM, Yatham LN, Fries GR, Colpo G, de Lucena D, Kunz M, Gomes FA, Kapczinski F. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. *Journal of psychiatric research*. 2011; 45:995–1004. [PubMed: 21550050]
- Flaisher-Grinberg S, Einat H. Strain-specific battery of tests for domains of mania: effects of valproate, lithium and imipramine. *Front Psychiatry*. 2010; 1:10. [PubMed: 21423422]
- Ford CP. The role of D2-autoreceptors in regulating dopamine neuron activity and transmission. *Neuroscience*. 2014; 282c:13–22. [PubMed: 24463000]
- Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, Grochocinski V, Houck P, Scott J, Thompson W, Monk T. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Archives of general psychiatry*. 2005; 62:996–1004. [PubMed: 16143731]
- Fratta W, Collu M, Martellotta MC, Pichiri M, Muntoni F, Gessa GL. Stress-induced insomnia: opioid-dopamine interactions. *European journal of pharmacology*. 1987; 142:437–440. [PubMed: 2892686]
- Frey BN, Andreazza AC, Cereser KM, Martins MR, Valvassori SS, Reus GZ, Quevedo J, Kapczinski F. Effects of mood stabilizers on hippocampus BDNF levels in an animal model of mania. *Life sciences*. 2006a; 79:281–286. [PubMed: 16460767]
- Frey BN, Valvassori SS, Reus GZ, Martins MR, Petronilho FC, Bardini K, Dal-Pizzol F, Kapczinski F, Quevedo J. Effects of lithium and valproate on amphetamine-induced oxidative stress generation in an animal model of mania. *Journal of psychiatry & neuroscience : JPN*. 2006b; 31:326–332. [PubMed: 16951735]
- Fries GR, Pfaffenseller B, Stertz L, Paz AV, Dargel AA, Kunz M, Kapczinski F. Staging and neuroprogression in bipolar disorder. *Current psychiatry reports*. 2012; 14:667–675. [PubMed: 23090632]
- Fries GR, Valvassori SS, Bock H, Stertz L, Magalhaes PV, Mariot E, Varela RB, Kauer-Sant'Anna M, Quevedo J, Kapczinski F, Saraiva-Pereira ML. Memory and brain-derived neurotrophic factor after subchronic or chronic amphetamine treatment in an animal model of mania. *Journal of psychiatric research*. 2015
- Frye MA, Salloum IM. Bipolar disorder and comorbid alcoholism: prevalence rate and treatment considerations. *Bipolar disorders*. 2006; 8:677–685. [PubMed: 17156154]
- Galvez JF, Sanches M, Bauer IE, Sharma AN, Hamilton J, Mwangi B, Quevedo J, Zunta-Soares G, Soares JC. Premorbid obesity and metabolic disturbances as promising clinical targets for the prevention and early screening of bipolar disorder. *Med Hypotheses*. 2015; 84:285–293. [PubMed: 25678233]
- Gao Y, Payne RS, Schurr A, Hougland T, Lord J, Herman L, Lei Z, Banerjee P, El-Mallakh RS. Memantine reduces mania-like symptoms in animal models. *Psychiatry research*. 2011; 188:366–371. [PubMed: 21269711]
- Gardner R Jr. Mechanisms in manic-depressive disorder: an evolutionary model. *Archives of general psychiatry*. 1982; 39:1436–1441. [PubMed: 7149905]
- Gazal M, Valente MR, Acosta BA, Kaufmann FN, Braganhol E, Lencina CL, Stefanello FM, Ghisleni G, Kaster MP. Neuroprotective and antioxidant effects of curcumin in a ketamine-induced model of mania in rats. *European journal of pharmacology*. 2014; 724:132–139. [PubMed: 24384407]
- Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. *Lancet (London, England)*. 2013; 381:1672–1682.
- Gessa GL, Pani L, Serra G, Fratta W. Animal models of mania. *Advances in biochemical psychopharmacology*. 1995; 49:43–66. [PubMed: 7653334]

- Geyer MA. Developing translational animal models for symptoms of schizophrenia or bipolar mania. *Neurotoxicity research*. 2008; 14:71–78. [PubMed: 18790726]
- Ghedim FV, de Fraga DB, Deroza PF, Oliveira MB, Valvassori SS, Steckert AV, Budni J, Dal-Pizzol F, Quevedo J, Zugno AI. Evaluation of behavioral and neurochemical changes induced by ketamine in rats: implications as an animal model of mania. *Journal of psychiatric research*. 2012; 46:1569–1575. [PubMed: 22998743]
- Giros B, Jaber M, Jones SR, Wightman RM, Caron MG. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature*. 1996; 379:606–612. [PubMed: 8628395]
- Goldstein I, Lax E, Gispan-Herman I, Ovadia H, Rosen H, Yadid G, Lichtstein D. Neutralization of endogenous digitalis-like compounds alters catecholamines metabolism in the brain and elicits anti-depressive behavior. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2012; 22:72–79. [PubMed: 21700431]
- Gould TD, Einat H. Animal models of bipolar disorder and mood stabilizer efficacy: a critical need for improvement. *Neuroscience and biobehavioral reviews*. 2007; 31:825–831. [PubMed: 17628675]
- Gould TJ, Keith RA, Bhat RV. Differential sensitivity to lithium's reversal of amphetamine-induced open-field activity in two inbred strains of mice. *Behavioural brain research*. 2001; 118:95–105. [PubMed: 11163638]
- Graff J, Tsai LH. The potential of HDAC inhibitors as cognitive enhancers. *Annual review of pharmacology and toxicology*. 2013; 53:311–330.
- Hamani C, Nobrega JN. Deep brain stimulation in clinical trials and animal models of depression. *The European journal of neuroscience*. 2010; 32:1109–1117. [PubMed: 21039950]
- Hamani C, Nobrega JN. Preclinical studies modeling deep brain stimulation for depression. *Biological psychiatry*. 2012; 72:916–923. [PubMed: 22748616]
- Hamid H, Gao Y, Lei Z, Hougland MT, El-Mallakh RS. Effect of ouabain on sodium pump alpha-isoform expression in an animal model of mania. *Progress in neuro-psychopharmacology & biological psychiatry*. 2009; 33:1103–1106. [PubMed: 19524007]
- Han K, Holder JL Jr, Schaaf CP, Lu H, Chen H, Kang H, Tang J, Wu Z, Hao S, Cheung SW, Yu P, Sun H, Breman AM, Patel A, Lu HC, Zoghbi HY. SHANK3 overexpression causes manic-like behaviour with unique pharmacogenetic properties. *Nature*. 2013; 503:72–77. [PubMed: 24153177]
- Hannah-Poquette C, Anderson GW, Flaisher-Grinberg S, Wang J, Meinerding TM, Einat H. Modeling mania: Further validation for Black Swiss mice as model animals. *Behavioural brain research*. 2011; 223:222–226. [PubMed: 21570428]
- Hashimoto H, Shintani N, Baba A. New insights into the central PACAPergic system from the phenotypes in PACAP- and PACAP receptor-knockout mice. *Annals of the New York Academy of Sciences*. 2006; 1070:75–89. [PubMed: 16888150]
- Hattori S, Takao K, Tanda K, Toyama K, Shintani N, Baba A, Hashimoto H, Miyakawa T. Comprehensive behavioral analysis of pituitary adenylate cyclase-activating polypeptide (PACAP) knockout mice. *Front Behav Neurosci*. 2012; 6:58. [PubMed: 23060763]
- Heinzen EL, Arzimanoglou A, Brashear A, Clapcote SJ, Gurrieri F, Goldstein DB, Johannesson SH, Mikati MA, Neville B, Nicole S, Ozelius LJ, Poulsen H, Schyns T, Sweadner KJ, van den Maagdenberg A, Vilsen B. Distinct neurological disorders with ATP1A3 mutations. *The Lancet Neurology*. 2014; 13:503–514. [PubMed: 24739246]
- Henry BL, Minassian A, Young JW, Paulus MP, Geyer MA, Perry W. Cross-species assessments of motor and exploratory behavior related to bipolar disorder. *Neurosci Biobehav Rev*. 2010; 34:1296–1306. [PubMed: 20398694]
- Hicks RA, Moore JD, Hayes C, Phillips N, Hawkins J. REM sleep deprivation increases aggressiveness in male rats. *Physiology & behavior*. 1979; 22:1097–1100. [PubMed: 227007]
- Hoertel N, de Maricourt P, Gorwood P. Novel routes to bipolar disorder drug discovery. *Expert opinion on drug discovery*. 2013; 8:907–918. [PubMed: 23706065]
- Hougland MT, Gao Y, Herman L, Ng CK, Lei Z, El-Mallakh RS. Positron emission tomography with fluorodeoxyglucose-F18 in an animal model of mania. *Psychiatry research*. 2008; 164:166–171. [PubMed: 18930636]

- Huff MO, Li XP, Ginns E, El-Mallakh RS. Effect of ethacrynic acid on the sodium- and potassium-activated adenosine triphosphatase activity and expression in Old Order Amish bipolar individuals. *Journal of affective disorders*. 2010; 123:303–307. [PubMed: 19880188]
- Jornada LK, Moretti M, Valvassori SS, Ferreira CL, Padilha PT, Arent CO, Fries GR, Kapczinski F, Quevedo J. Effects of mood stabilizers on hippocampus and amygdala BDNF levels in an animal model of mania induced by ouabain. *Journal of psychiatric research*. 2010; 44:506–510. [PubMed: 19954800]
- Jornada LK, Valvassori SS, Steckert AV, Moretti M, Mina F, Ferreira CL, Arent CO, Dal-Pizzol F, Quevedo J. Lithium and valproate modulate antioxidant enzymes and prevent ouabain-induced oxidative damage in an animal model of mania. *Journal of psychiatric research*. 2011; 45:162–168. [PubMed: 20627318]
- Kalinichev M, Dawson LA. Evidence for antimanic efficacy of glycogen synthase kinase-3 (GSK3) inhibitors in a strain-specific model of acute mania. *Int J Neuropsychopharmacol*. 2011; 14:1051–67. [PubMed: 21208504]
- Kalynchuk LE. Long-term amygdala kindling in rats as a model for the study of interictal emotionality in temporal lobe epilepsy. *Neuroscience and biobehavioral reviews*. 2000; 24:691–704. [PubMed: 10974352]
- Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PV, Kauer-Sant'Anna M, Klamt F, Moreira JC, de Bittencourt Pasquali MA, Fries GR, Quevedo J, Gama CS, Post R. Peripheral biomarkers and illness activity in bipolar disorder. *Journal of psychiatric research*. 2011; 45:156–161. [PubMed: 20541770]
- Kapczinski F, Dias VV, Kauer-Sant'Anna M, Frey BN, Grassi-Oliveira R, Colom F, Berk M. Clinical implications of a staging model for bipolar disorders. *Expert review of neurotherapeutics*. 2009; 9:957–966. [PubMed: 19589046]
- Kapczinski F, Magalhaes PV, Balanza-Martinez V, Dias VV, Frangou S, Gama CS, Gonzalez-Pinto A, Grande I, Ha K, Kauer-Sant'Anna M, Kunz M, Kupka R, Leboyer M, Lopez-Jaramillo C, Post RM, Rybakowski JK, Scott J, Strejilevitch S, Tohen M, Vazquez G, Yatham L, Vieta E, Berk M. Staging systems in bipolar disorder: an International Society for Bipolar Disorders Task Force Report. *Acta psychiatrica Scandinavica*. 2014; 130:354–363. [PubMed: 24961757]
- Kaplan KA, Harvey AG. Behavioral treatment of insomnia in bipolar disorder. *The American journal of psychiatry*. 2013; 170:716–720. [PubMed: 23820830]
- Kara NZ, Einat H. Rodent models for mania: practical approaches. *Cell and tissue research*. 2013; 354:191–201. [PubMed: 23504091]
- Katayama T, Hattori T, Yamada K, Matsuzaki S, Tohyama M. Role of the PACAP-PAC1-DISC1 and PACAP-PAC1-stathmin1 systems in schizophrenia and bipolar disorder: novel treatment mechanisms? *Pharmacogenomics*. 2009; 10:1967–1978. [PubMed: 19958095]
- Kehoe P, Shoemaker WJ, Triano L, Callahan M, Rappolt G. Adult rats stressed as neonates show exaggerated behavioral responses to both pharmacological and environmental challenges. *Behavioral neuroscience*. 1998; 112:116–125. [PubMed: 9517820]
- Kimble DP. The effects of bilateral hippocampal lesions in rats. *Journal of comparative and physiological psychology*. 1963; 56:273–283. [PubMed: 14032719]
- Kirshenbaum GS, Burgess CR, Dery N, Fahnestock M, Peever JH, Roder JC. Attenuation of mania-like behavior in Na(+),K(+)-ATPase alpha3 mutant mice by prospective therapies for bipolar disorder: melatonin and exercise. *Neuroscience*. 2014; 260:195–204. [PubMed: 24342563]
- Kirshenbaum GS, Clapcote SJ, Duffy S, Burgess CR, Petersen J, Jarowek KJ, Yucel YH, Cortez MA, Snead OC 3rd, Vilsen B, Peever JH, Ralph MR, Roder JC. Mania-like behavior induced by genetic dysfunction of the neuron-specific Na⁺,K⁺-ATPase alpha3 sodium pump. *Proceedings of the National Academy of Sciences of the United States of America*. 2011a; 108:18144–18149. [PubMed: 22025725]
- Kirshenbaum GS, Clapcote SJ, Petersen J, Vilsen B, Ralph MR, Roder JC. Genetic suppression of agrin reduces mania-like behavior in Na⁺, K⁺-ATPase alpha3 mutant mice. *Genes, brain, and behavior*. 2012; 11:436–443.
- Kirshenbaum GS, Dawson N, Mullins JG, Johnston TH, Drinkhill MJ, Edwards IJ, Fox SH, Pratt JA, Brothie JM, Roder JC, Clapcote SJ. Alternating hemiplegia of childhood-related neural and

behavioural phenotypes in Na⁺,K⁺-ATPase alpha3 missense mutant mice. PloS one. 2013; 8:e60141. [PubMed: 23527305]

Kirshenbaum GS, Saltzman K, Rose B, Petersen J, Vilsen B, Roder JC. Decreased neuronal Na⁺, K⁺-ATPase activity in Atp1a3 heterozygous mice increases susceptibility to depression-like endophenotypes by chronic variable stress. Genes, brain, and behavior. 2011b; 10:542–550.

Kittel-Schneider S, Schreck S, Ziegler C, Weissflog L, Hilscher M, Schwarz R, Schnetzler L, Neuner M, Reif A. Lithium-induced Clock Gene Expression in Lymphoblastoid Cells of Bipolar Affective Patients. Pharmacopsychiatry. 2015; 48:145–149. [PubMed: 26011568]

Kofman O, Li PP, Warsh JJ. Lithium, but not carbamazepine, potentiates hyperactivity induced by intra-accumbens cholera toxin. Pharmacology, biochemistry, and behavior. 1998; 59:191–200.

Koukopoulos A, Ghaemi SN. The primacy of mania: a reconsideration of mood disorders. European psychiatry : the journal of the Association of European Psychiatrists. 2009; 24:125–134. [PubMed: 18789854]

Kozikowski AP, Gaisina IN, Yuan H, Petukhov PA, Blond SY, Fedolak A, Caldarone B, McGonigle P. Structure-based design leads to the identification of lithium mimetics that block mania-like effects in rodents. possible new GSK-3beta therapies for bipolar disorders. Journal of the American Chemical Society. 2007; 129:8328–8332. [PubMed: 17552518]

Kupfer DJ. The increasing medical burden in bipolar disorder. Jama. 2005; 293:2528–2530. [PubMed: 15914754]

Kuroiwa T, Bonnekoh P, Hossmann KA. Locomotor hyperactivity and hippocampal CA1 injury after transient forebrain ischemia of gerbils. Neuroscience letters. 1991; 122:141–144. [PubMed: 2027511]

Le-Niculescu H, McFarland MJ, Ogden CA, Balaraman Y, Patel S, Tan J, Rodd ZA, Paulus M, Geyer MA, Edenberg HJ, Glatt SJ, Faraone SV, Nurnberger JI, Kuczenski R, Tsuang MT, Niculescu AB. Phenomic, convergent functional genomic, and biomarker studies in a stress-reactive genetic animal model of bipolar disorder and co-morbid alcoholism. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2008; 147b:134–166.

Legrand R, Fielder R. Role of dominance-submission relationships in shock-induced fighting of mice. Journal of comparative and physiological psychology. 1973; 82:501–506. [PubMed: 4735923]

Levy NA, Janicak PG. Calcium channel antagonists for the treatment of bipolar disorder. Bipolar disorders. 2000; 2:108–119. [PubMed: 11252650]

Li R, el-Mallakh RS, Harrison L, Chagaris DG, Levy RS. Lithium prevents ouabain-induced behavioral changes. Toward an animal model for manic depression. Molecular and chemical neuropathology/sponsored by the International Society for Neurochemistry and the World Federation of Neurology and research groups on neurochemistry and cerebrospinal fluid. 1997; 31:65–72.

Li Y, Wolf ME. Ibotenic acid lesions of prefrontal cortex do not prevent expression of behavioral sensitization to amphetamine. Behavioural brain research. 1997; 84:285–289. [PubMed: 9079793]

Lien R, Flaisher-Grinberg S, Cleary C, Hejny M, Einat H. Behavioral effects of Bcl-2 deficiency: implications for affective disorders. Pharmacol Rep. 2008; 60:490–498. [PubMed: 18799817]

Macedo DS, de Lucena DF, Queiroz AI, Cordeiro RC, Araujo MM, Sousa FC, Vasconcelos SM, Hyphantis TN, Quevedo J, McIntyre RS, Carvalho AF. Effects of lithium on oxidative stress and behavioral alterations induced by lisdexamfetamine dimesylate: relevance as an animal model of mania. Progress in neuro-psychopharmacology & biological psychiatry. 2013; 43:230–237. [PubMed: 23333378]

Macedo DS, Medeiros CD, Cordeiro RC, Sousa FC, Santos JV, Morais TA, Hyphantis TN, McIntyre RS, Quevedo J, Carvalho AF. Effects of alpha-lipoic acid in an animal model of mania induced by D-amphetamine. Bipolar disorders. 2012; 14:707–718. [PubMed: 22897629]

Machado-Vieira R, Andreazza AC, Viale CI, Zanatto V, Cereser V Jr, da Silva Vargas R, Kapczinski F, Portela LV, Souza DO, Salvador M, Gentil V. Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. Neuroscience letters. 2007; 421:33–36. [PubMed: 17548157]

- Machado-Vieira R, Kapczinski F, Soares JC. Perspectives for the development of animal models of bipolar disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2004a; 28:209–224. [PubMed: 14751416]
- Machado-Vieira R, Kapczinski F, Soares JC. Perspectives for the development of animal models of bipolar disorder. *Progress in neuro-psychopharmacology & biological psychiatry*. 2004b; 28:209–224. [PubMed: 14751416]
- Maeng S, Hunsberger JG, Pearson B, Yuan P, Wang Y, Wei Y, McCammon J, Schloesser RJ, Zhou R, Du J, Chen G, McEwen B, Reed JC, Manji HK. BAG1 plays a critical role in regulating recovery from both manic like and depression like behavioral impairments. *Proc Natl Acad Sci USA*. 2008; 105:8766–8771. [PubMed: 18562287]
- Mak IW, Evaniew N, Ghert M. Lost in translation: animal models and clinical trials in cancer treatment. *American journal of translational research*. 2014; 6:114–118. [PubMed: 24489990]
- Malatynska E, Knapp RJ. Dominant-submissive behavior as models of mania and depression. *Neuroscience and biobehavioral reviews*. 2005; 29:715–737. [PubMed: 15876455]
- Malatynska E, Pinhasov A, Crooke JJ, Smith-Swintosky VL, Brenneman DE. Reduction of dominant or submissive behaviors as models for antimanic or antidepressant drug testing: technical considerations. *Journal of neuroscience methods*. 2007; 165:175–182. [PubMed: 17645948]
- Maletic V, Raison C. Integrated neurobiology of bipolar disorder. *Frontiers in Psychiatry*. 2014; 5:98. [PubMed: 25202283]
- Malkesman O, Austin DR, Chen G, Manji HK. Reverse translational strategies for developing animal models of bipolar disorder. *Disease models & mechanisms*. 2009; 2:238–245. [PubMed: 19407332]
- Malkoff-Schwartz S, Frank E, Anderson B, Sherrill JT, Siegel L, Patterson D, Kupfer DJ. Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes: a preliminary investigation. *Archives of general psychiatry*. 1998; 55:702–707. [PubMed: 9707380]
- Mansell W, Pedley R. The ascent into mania: a review of psychological processes associated with the development of manic symptoms. *Clinical psychology review*. 2008; 28:494–520. [PubMed: 17825463]
- Mansour HA, Monk TH, Nimgaonkar VL. Circadian genes and bipolar disorder. *Annals of medicine*. 2005; 37:196–205. [PubMed: 16019718]
- McClung CA. Circadian rhythms and mood regulation: insights from pre-clinical models. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2011; 21(Suppl 4):S683–693. [PubMed: 21835596]
- McClung CA, Sidiropoulou K, Vitaterna M, Takahashi JS, White FJ, Cooper DC, Nestler EJ. Regulation of dopaminergic transmission and cocaine reward by the Clock gene. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102:9377–9381. [PubMed: 15967985]
- McInnes LA, Service SK, Reus VI, Barnes G, Charlat O, Jawahar S, Lewitzky S, Yang Q, Duong Q, Spesny M, Araya C, Araya X, Gallegos A, Meza L, Molina J, Ramirez R, Mendez R, Silva S, Fournier E, Batki SL, Mathews CA, Neylan T, Glatt CE, Escamilla MA, Luo D, Gajiwala P, Song T, Crook S, Nguyen JB, Roche E, Meyer JM, Leon P, Sandkuijl LA, Freimer NB, Chen H. Fine-scale mapping of a locus for severe bipolar mood disorder on chromosome 18p11.3 in the Costa Rican population. *Proceedings of the National Academy of Sciences of the United States of America*. 2001; 98:11485–11490. [PubMed: 11572994]
- Miczek KA, Maxson SC, Fish EW, Faccidomo S. Aggressive behavioral phenotypes in mice. *Behavioural brain research*. 2001; 125:167–181. [PubMed: 11682108]
- Miczek KA, O'Donnell JM. Intruder-evoked aggression in isolated and nonisolated mice: effects of psychomotor stimulants and L-dopa. *Psychopharmacology*. 1978; 57:47–55. [PubMed: 26933]
- Milhiet V, Boudebessé C, Bellivier F, Drouot X, Henry C, Leboyer M, Etain B. Circadian abnormalities as markers of susceptibility in bipolar disorders. *Frontiers in bioscience (Scholar edition)*. 2014; 6:120–137. [PubMed: 24389266]
- Mitchell PJ. Antidepressant treatment and rodent aggressive behaviour. *European journal of pharmacology*. 2005; 526:147–162. [PubMed: 16289453]

- Morden B, Mullins R, Levine S. Effects of REM deprivation on the mating behavior of male rats. *Psychophysiology*. 1968; 5:241–242.
- Moretti M, Valvassori SS, Varela RB, Ferreira CL, Rochi N, Benedet J, Scaini G, Kapczinski F, Streck EL, Zugno AI, Quevedo J. Behavioral and neurochemical effects of sodium butyrate in an animal model of mania. *Behavioural pharmacology*. 2011; 22:766–772. [PubMed: 21989497]
- Nakane H, Ooboshi H, Ibayashi S, Yao H, Sadoshima S, Fujishima M. Isradipine, a calcium channel blocker, attenuates the ischemia-induced release of dopamine but not glutamate in rats. *Neuroscience letters*. 1995; 188:151–154. [PubMed: 7609897]
- Nestler EJ, Hyman SE. Animal models of neuropsychiatric disorders. *Nature neuroscience*. 2010; 13:1161–1169. [PubMed: 20877280]
- O'Donnell KC, Gould TD. The behavioral actions of lithium in rodent models: leads to develop novel therapeutics. *Neuroscience and biobehavioral reviews*. 2007; 31:932–962. [PubMed: 17532044]
- Paszti-Gere E, Jakus J. Protein phosphatases but not reactive oxygen species play functional role in acute amphetamine-mediated dopamine release. *Cell biochemistry and biophysics*. 2013; 66:831–841. [PubMed: 23625176]
- Perez J, Tardito D, Mori S, Racagni G, Smeraldi E, Zanardi R. Abnormalities of cyclic adenosine monophosphate signaling in platelets from untreated patients with bipolar disorder. *Archives of general psychiatry*. 1999; 56:248–253. [PubMed: 10078502]
- Post RM. Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neurosci Biobehav Rev*. 2007; 31:858–373. [PubMed: 17555817]
- Post RM, Kalivas P. Bipolar disorder and substance misuse: pathological and therapeutic implications of their comorbidity and cross-sensitisation. *The British journal of psychiatry : the journal of mental science*. 2013; 202:172–176. [PubMed: 23457180]
- Post RM, Leverich GS, Xing G, Weiss RB. Developmental vulnerabilities to the onset and course of bipolar disorder. *Development and psychopathology*. 2001; 13:581–598. [PubMed: 11523849]
- Post RM, Susan R, Weiss B. Sensitization, kindling, and carbamazepine: an update on their implications for the course of affective illness. *Pharmacopsychiatry*. 1992; 25:41–43. [PubMed: 1579606]
- Post RM, Uhde TW, Putnam FW, Ballenger JC, Berrettini WH. Kindling and carbamazepine in affective illness. *J Nerv Ment Dis*. 1982; 170:717–731. [PubMed: 6754868]
- Post RM, Weiss SR. Sensitization, kindling, and anticonvulsants in mania. *J Clin Psychiatry*. 1989; 50(Suppl):23–30. [PubMed: 2689434]
- Post RM, Weiss SR. A speculative model of affective illness cyclicity based on patterns of drug tolerance observed in amygdala-kindled seizures. *Molecular neurobiology*. 1996; 13:33–60. [PubMed: 8892335]
- Post RM, Weiss SR. Sensitization and kindling phenomena in mood, anxiety, and obsessive-compulsive disorders: the role of serotonergic mechanisms in illness progression. *Biological psychiatry*. 1998; 44:193–206. [PubMed: 9693391]
- Powell SB, Young JW, Ong JC, Caron MG, Geyer MA. Atypical antipsychotics clozapine and quetiapine attenuate prepulse inhibition deficits in dopamine transporter knockout mice. *Behavioural pharmacology*. 2008; 19:562–565. [PubMed: 18690110]
- Prickaerts J, Moechars D, Cryns K, Lenaerts I, van Craenendonck H, Goris I, Daneels G, Bouwknecht JA, Steckler T. Transgenic mice overexpressing glycogen synthase kinase 3beta: a putative model of hyperactivity and mania. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2006; 26:9022–9029. [PubMed: 16943560]
- Queiroz AI, de Araujo MM, da Silva Araujo T, de Souza GC, Cavalcante LM, de Jesus Souza Machado M, de Lucena DF, Quevedo J, Macedo D. GBR 12909 administration as an animal model of bipolar mania: time course of behavioral, brain oxidative alterations and effect of mood stabilizing drugs. *Metabolic brain disease*. 2015
- Ralph-Williams RJ, Paulus MP, Zhuang X, Hen R, Geyer MA. Valproate attenuates hyperactive and perseverative behaviors in mutant mice with a dysregulated dopamine system. *Biological psychiatry*. 2003; 53:352–359. [PubMed: 12586455]

- Rao JS, Keleshian VL, Klein S, Rapoport SI. Epigenetic modifications in frontal cortex from Alzheimer's disease and bipolar disorder patients. *Translational psychiatry*. 2012a; 2:e132. [PubMed: 22760556]
- Rao JS, Kellom M, Reese EA, Rapoport SI, Kim HW. Dysregulated glutamate and dopamine transporters in postmortem frontal cortex from bipolar and schizophrenic patients. *Journal of affective disorders*. 2012b; 136:63–71. [PubMed: 21925739]
- Razafsha M, Behforuzi H, Harati H, Wafai RA, Khaku A, Mondello S, Gold MS, Kobeissy FH. An updated overview of animal models in neuropsychiatry. *Neuroscience*. 2013; 240:204–218. [PubMed: 23473749]
- Redrobe JP, Nielsen AN. Effects of neuronal Kv7 potassium channel activators on hyperactivity in a rodent model of mania. *Behavioural brain research*. 2009; 198:481–485. [PubMed: 19162078]
- Rezin GT, Furlanetto CB, Scaini G, Valvassori SS, Goncalves CL, Ferreira GK, Jeremias IC, Resende WR, Cardoso MR, Varela RB, Quevedo J, Streck EL. Fenproporex increases locomotor activity and alters energy metabolism, and mood stabilizers reverse these changes: a proposal for a new animal model of mania. *Molecular neurobiology*. 2014; 49:877–892. [PubMed: 24126971]
- Ricke AK, Snook RJ, Anand A. Induction of prolonged mania during ketamine therapy for reflex sympathetic dystrophy. *Biological psychiatry*. 2011; 70:e13–14. [PubMed: 21529780]
- Riegel RE, Valvassori SS, Elias G, Reus GZ, Steckert AV, de Souza B, Petronilho F, Gavioli EC, Dal-Pizzol F, Quevedo J. Animal model of mania induced by ouabain: Evidence of oxidative stress in submitochondrial particles of the rat brain. *Neurochem Int*. 2009; 55:491–495. [PubMed: 19447152]
- Riegel RE, Valvassori SS, Moretti M, Ferreira CL, Steckert AV, de Souza B, Dal-Pizzol F, Quevedo J. Intracerebroventricular ouabain administration induces oxidative stress in the rat brain. *International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience*. 2010; 28:233–237. [PubMed: 20153819]
- Robinson TE, Becker JB, Moore CJ, Castaneda E, Mittleman G. Enduring enhancement in frontal cortex dopamine utilization in an animal model of amphetamine psychosis. *Brain research*. 1985; 343:374–377. [PubMed: 4052758]
- Roybal K, Theobald D, Graham A, DiNieri JA, Russo SJ, Krishnan V, Chakravarty S, Peevey J, Oehrlin N, Birnbaum S, Vitaterna MH, Orsulak P, Takahashi JS, Nestler EJ, Carlezon WA Jr, McClung CA. Mania-like behavior induced by disruption of CLOCK. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104:6406–6411. [PubMed: 17379666]
- Ruktanonchai DJ, El-Mallakh RS, Li R, Levy RS. Persistent hyperactivity following a single intracerebroventricular dose of ouabain. *Physiology & behavior*. 1998; 63:403–406. [PubMed: 9469734]
- Rygula R, Szczech E, Kregiel J, Golebiowska J, Kubik J, Popik P. Cognitive judgment bias in the psychostimulant-induced model of mania in rats. *Psychopharmacology*. 2015; 232:651–660. [PubMed: 25116482]
- Saul MC, Gessay GM, Gammie SC. A new mouse model for mania shares genetic correlates with human bipolar disorder. *PloS one*. 2012; 7:e38128. [PubMed: 22675514]
- Schaeffer JC, Cho AK, Fischer JF. Inhibition of synaptosomal accumulation of 1-norepinephrine II: N-aryloxyalkylphentermines, quaternary d-amphetamines, and 3-aryloxypropylamines. *Journal of pharmaceutical sciences*. 1976; 65:122–126. [PubMed: 1255416]
- Schulze TG, Buervenich S, Badner JA, Steele CJ, Detera-Wadleigh SD, Dick D, Foroud T, Cox NJ, MacKinnon DF, Potash JB, Berrettini WH, Byerley W, Coryell W, DePaulo JR Jr, Gershon ES, Kelsoe JR, McInnis MG, Murphy DL, Reich T, Scheftner W, Nurnberger JI Jr, McMahon FJ. Loci on chromosomes 6q and 6p interact to increase susceptibility to bipolar affective disorder in the national institute of mental health genetics initiative pedigrees. *Biological psychiatry*. 2004; 56:18–23. [PubMed: 15219468]
- Scheuing L, Chiu CT, Liao HM, Chuang DM. Antidepressant mechanism of ketamine: perspective from preclinical studies. *Front Neurosci*. 2015; 9:249. [PubMed: 26257598]
- Serra G, Koukopoulos A, De Chiara L, Koukopoulos AE, Tondo L, Girardi P, Baldessarini RJ, Serra G. Three-year, naturalistic, mirror-image assessment of adding memantine to the treatment of 30

treatment-resistant patients with bipolar disorder. *The Journal of clinical psychiatry*. 2015; 76:e91–97. [PubMed: 25650685]

- Serretti A, Drago A, De Ronchi D. Lithium pharmacodynamics and pharmacogenetics: focus on inositol mono phosphatase (IMPase), inositol polyphosphatase (IPPase) and glycogen synthase kinase 3 beta (GSK-3 beta). *Curr Med Chem*. 2009; 16:1917–1948. [PubMed: 19442155]
- Shaldubina A, Einat H, Szechtman H, Shimon H, Belmaker RH. Preliminary evaluation of oral anticonvulsant treatment in the quinpirole model of bipolar disorder. *Journal of neural transmission* (Vienna, Austria : 1996). 2002; 109:433–440.
- Shaltiel G, Maeng S, Malkesman O, Pearson B, Schloesser RJ, Tragon T, Rogawski M, Gasior M, Luckenbaugh D, Chen G, Manji HK. Evidence for the involvement of the kainate receptor subunit GluR6 (GRIK2) in mediating behavioral displays related to behavioral symptoms of mania. *Molecular psychiatry*. 2008; 13:858–872. [PubMed: 18332879]
- Sharma AN, Bauer IE, Sanches M, Galvez JF, Zunta-Soares GB, Quevedo J, Kapczinski F, Soares JC. Common biological mechanisms between bipolar disorder and type 2 diabetes: Focus on inflammation. *Progress in neuro-psychopharmacology & biological psychiatry*. 2014; 54:289–298. [PubMed: 24969830]
- Sidor MM, Spencer SM, Dzirasa K, Parekh PK, Tye KM, Warden MR, Arey RN, Enwright JF 3rd, Jacobsen JP, Kumar S, Remillard EM, Caron MG, Deisseroth K, McClung CA. Daytime spikes in dopaminergic activity drive rapid mood-cycling in mice. *Molecular psychiatry*. 2015; 5
- Steckert AV, Valvassori SS, Mina F, Lopes-Borges J, Varella RB, Kapczinski F, Dal-Pizzol F, Quevedo J. Protein kinase C and oxidative stress in an animal model of mania. *Current neurovascular research*. 2012; 9:47–57. [PubMed: 22272765]
- Steckert AV, Valvassori SS, Varella RB, Mina F, Resende WR, Bavaresco DV, Ornell F, Dal-Pizzol F, Quevedo J. Effects of sodium butyrate on oxidative stress and behavioral changes induced by administration of D-AMPH. *Neurochemistry international*. 2013; 62:425–432. [PubMed: 23411414]
- Stertz L, Fries GR, Aguiar BW, Pfaffenseller B, Valvassori SS, Gubert C, Ferreira CL, Moretti M, Cereser KM, Kauer-Sant'Anna M. Histone deacetylase activity and brain-derived neurotrophic factor (BDNF) levels in a pharmacological model of mania. *Revista brasileira de psiquiatria* (Sao Paulo, Brazil : 1999). 2014; 36:39–46.
- Sui L, Song XJ, Ren J, Ju LH, Wang Y. Intracerebroventricular administration of ouabain alters synaptic plasticity and dopamine release in rat medial prefrontal cortex. *Journal of neural transmission* (Vienna, Austria : 1996). 2013; 120:1191–1199.
- Swerdlow NR, Halim N, Hanlon FM, Platten A, Auerbach PP. Lesion size and amphetamine hyperlocomotion after neonatal ventral hippocampal lesions: more is less. *Brain research bulletin*. 2001; 55:71–77. [PubMed: 11427340]
- Szabo ST, Machado-Vieira R, Yuan P, Wang Y, Wei Y, Falke C, Cirelli C, Tononi G, Manji HK, Du J. Glutamate receptors as targets of protein kinase C in the pathophysiology and treatment of animal models of mania. *Neuropharmacology*. 2009; 56:47–55. [PubMed: 18789340]
- Takuma K, Maeda Y, Ago Y, Ishihama T, Takemoto K, Nakagawa A, Shintani N, Hashimoto H, Baba A, Matsuda T. An enriched environment ameliorates memory impairments in PACAP-deficient mice. *Behavioural brain research*. 2014; 272:269–278. [PubMed: 25014004]
- Teixeira AL, Quevedo J. Animal models in psychiatry. *Revista brasileira de psiquiatria* (Sao Paulo, Brazil : 1999). 2013; 35(Suppl 2):S73–74.
- Toker L, Bersudsky Y, Plaschkes I, Chalifa-Caspi V, Berry GT, Buccafusca R, Moechars D, Belmaker RH, Agam G. Inositol-related gene knockouts mimic lithium's effect on mitochondrial function. *Neuropsychopharmacology*. 2014; 39:319–328. [PubMed: 23924600]
- Trevizol F, Roversi K, Dias VT, Roversi K, Pase CS, Barcelos RC, Benvegno DM, Kuhn FT, Dolci GS, Ross DH, Veit JC, Piccolo J, Emanuelli T, Burger ME. Influence of lifelong dietary fats on the brain fatty acids and amphetamine-induced behavioral responses in adult rat. *Progress in neuro-psychopharmacology & biological psychiatry*. 2013; 45:215–222. [PubMed: 23791617]
- Valvassori SS, Bavaresco DV, Budni J, Bobsin TS, Goncalves CL, de Freitas KV, Streck EL, Quevedo J. Effects of tamoxifen on tricarboxylic acid cycle enzymes in the brain of rats submitted to an

animal model of mania induced by amphetamine. *Psychiatry research*. 2014; 215:483–487. [PubMed: 24359811]

- Valvassori SS, Budni J, Varela RB, Quevedo J. Contributions of animal models to the study of mood disorders. *Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999)*. 2013; 35(Suppl 2):S121–131.
- van Enkhuizen J, Geyer MA, Kooistra K, Young JW. Chronic valproate attenuates some, but not all, facets of mania-like behaviour in mice. *The international journal of neuropsychopharmacology/ official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*. 2013; 16:1021–1031. [PubMed: 23164454]
- van Enkhuizen J, Henry BL, Minassian A, Perry W, Milienne-Petiot M, Higa KK, Geyer MA, Young JW. Reduced dopamine transporter functioning induces high-reward risk-preference consistent with bipolar disorder. *Neuropsychopharmacology*. 2014; 39:3112–3122. [PubMed: 25005251]
- Vassout A, Veenstra S, Hauser K, Ofner S, Brugger F, Schilling W, Gentsch C. NKP608: a selective NK-1 receptor antagonist with anxiolytic-like effects in the social interaction and social exploration test in rats. *Regulatory peptides*. 2000; 96:7–16. [PubMed: 11102646]
- Verwer RW, Van Vulpes EH, Van Uum JF. Postnatal development of amygdaloid projections to the prefrontal cortex in the rat studied with retrograde and anterograde tracers. *The Journal of comparative neurology*. 1996; 376:75–96. [PubMed: 8946285]
- Wang D, Corbett D. Cerebral ischemia, locomotor activity and spatial mapping. *Brain research*. 1990; 533:78–82. [PubMed: 2085736]
- Weeke A, Juel K, Vaeth M. Cardiovascular death and manic-depressive psychosis. *Journal of affective disorders*. 1987; 13:287–292. [PubMed: 2960722]
- Wilkinson LS, Mittleman G, Torres E, Humby T, Hall FS, Robbins TW. Enhancement of amphetamine-induced locomotor activity and dopamine release in nucleus accumbens following excitotoxic lesions of the hippocampus. *Behavioural brain research*. 1993; 55:143–150. [PubMed: 8395178]
- Willner P. The validity of animal models of depression. *Psychopharmacology*. 1984; 83:1–16. [PubMed: 6429692]
- Wolterink G, Daenen LE, Dubbeldam S, Gerrits MA, van Rijn R, Kruse CG, Van Der Heijden JA, Van Ree JM. Early amygdala damage in the rat as a model for neurodevelopmental psychopathological disorders. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2001; 11:51–59. [PubMed: 11226812]
- Wong P, Chang CC, Marx CE, Caron MG, Wetsel WC, Zhang X. Pregnenolone rescues schizophrenia-like behavior in dopamine transporter knockout mice. *PloS one*. 2012; 7:e51455. [PubMed: 23240026]
- Yang CR, Bai YY, Ruan CS, Zhou HF, Liu D, Wang XF, Shen LJ, Zheng HY, Zhou XF. Enhanced aggressive behaviour in a mouse model of depression. *Neurotox Res*. 2015; 27:129–142. [PubMed: 25367807]
- Yildiz A, Guleryuz S, Ankerst DP, Ongur D, Renshaw PF. Protein kinase C inhibition in the treatment of mania: a double-blind, placebo-controlled trial of tamoxifen. *Archives of general psychiatry*. 2008; 65:255–263. [PubMed: 18316672]
- Young JW, Henry BL, Geyer MA. Predictive animal models of mania: hits, misses and future directions. *British journal of pharmacology*. 2011a; 164:1263–1284. [PubMed: 21410454]
- Young JW, Minassian A, Paulus MP, Geyer MA, Perry W. A reverse-translational approach to bipolar disorder: rodent and human studies in the Behavioral Pattern Monitor. *Neuroscience and biobehavioral reviews*. 2007; 31:882–896. [PubMed: 17706782]
- Young JW, van Enkhuizen J, Winstanley CA, Geyer MA. Increased risk-taking behavior in dopamine transporter knockdown mice: further support for a mouse model of mania. *Journal of psychopharmacology (Oxford, England)*. 2011b; 25:934–943.
- Zarate CA Jr, Singh JB, Carlson PJ, Quiroz J, Jolkovsky L, Luckenbaugh DA, Manji HK. Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. *Bipolar disorders*. 2007; 9:561–570. [PubMed: 17845270]

- Zhuang X, Oosting RS, Jones SR, Gainetdinov RR, Miller GW, Caron MG, Hen R. Hyperactivity and impaired response habituation in hyperdopaminergic mice. *Proceedings of the National Academy of Sciences of the United States of America*. 2001; 98:1982–1987. [PubMed: 11172062]
- Zugno AI, Chipindo H, Canever L, Budni J, Alves de Castro A, Bittencourt de Oliveira M, Heylmann AS, Gomes Wessler P, da Rosa Silveira F, Damazio LS, Mastella GA, Kist LW, Bogo MR, Quevedo J, Gama CS. Omega-3 fatty acids prevent the ketamine-induced increase in acetylcholinesterase activity in an animal model of schizophrenia. *Life sciences*. 2015a; 121:65–69. [PubMed: 25498892]
- Zugno AI, Pacheco FD, Budni J, de Oliveira MB, Canever L, Heylmann AS, Wessler PG, da Rosa Silveira F, Mastella GA, Goncalves CL, Freitas KV, de Castro AA, Streck EL, Quevedo J. Maternal deprivation disrupts mitochondrial energy homeostasis in the brain of rats subjected to ketamine-induced schizophrenia. *Metabolic brain disease*. 2015b; 30:1043–1053. [PubMed: 25920483]

Highlights

- The pathophysiology of bipolar mania remains incompletely elucidated.
- Recently, new animal models for mania have been proposed.
- Herein, we review the validity of these models.
- Validity parameters of rodent models for mania are limited.
- Novel genetic models and adaptation of existing paradigms hold promise for modelling mania in animals.

Table 1

Validity criteria for the evaluation of animal models

Validity	Definition
Face validity	Similarity in the phenomenon between the model and the modeled condition (Einat, 2011). It corresponds to mimicking symptoms and diagnostic criteria of the psychiatric condition in the animal, including behavioral and cognitive features (Belzung and Lemoine, 2011). Most of the models mimic dimensions (endophenotypes) rather than the disorder as a whole.
Construct validity	Similarity in the pathophysiological mechanisms presented by the model and the modeled condition, or the similarity of the biological processes that lead to disease (Belzung and Lemoine, 2011). A validated model is expected to present biological alterations that are similar to those presented by patients.
Predictive validity	Similarity in the treatment response between the model and the modeled condition. Effective treatments for the condition should be able to reverse and/or prevent the behavioral and biological features presented by the model, ideally respecting the time frame observed in patients for the treatment effect.

These criteria are based on the classic proposal by (Willner, 1984), which were later developed to fit these three categories (i.e. face, construct, and predictive validities).

Table 2

Animal models of mania

Animal model of mania	References	Major benefits(s)	Major limitation(s)	Face validity	Predictive validity	Construct validity
Pharmacological models						
Psychostimulant-induced hyperactivity	(Frey et al., 2006b)	<ul style="list-style-type: none"> Mimics hyperlocomotion in rodents. Frequently used as an animal model of mania. Similarities in biomarkers between the model and humans. 	<ul style="list-style-type: none"> Does not simulate hypomanic states. Tolerance to psychostimulants Based on assumption that only selective neurotransmitter(s) are involved in manic illness. Nonspecific to mania. 	++	++	+++
Quinpirole-induced hyperactivity	(D'Aquila et al., 2001; Shalubina et al., 2002)	<ul style="list-style-type: none"> Mimics hyperactivity in rodents and resembles the oscillating nature of BD. A variation of this model can also mimic antidepressant-related mania. 	<ul style="list-style-type: none"> No evidence of behavioral features other than locomotor activity. No evidence of construct validity. 	+	++	
Ouabain-induced hyperactivity	(El-Mallakh et al., 2003; el-Mallakh et al., 1995; Riegel et al., 2009)	<ul style="list-style-type: none"> Mimics hyperactivity in rodents. Unlike psychostimulants, no apparent risk of tolerance. 	<ul style="list-style-type: none"> Cardiotoxic. Involves stressful surgeries such as intra-cerebroventricular (ICV) cannula implantation. 	++	++	+
Ketamine-induced hyperactivity	(Ghedim et al., 2012)	<ul style="list-style-type: none"> Mimics hyperactivity in rodents. 	<ul style="list-style-type: none"> Nonspecific to mania (ketamine administration is a classic animal model of schizophrenia). 	+	++	+
Environmental models						
Sleep deprivation	(Benedetti et al., 2008)	<ul style="list-style-type: none"> Simulate mania-like disturbances in diurnal rhythms. 	<ul style="list-style-type: none"> Sleep deprivation is significant stressor. 	++	++	++

Animal model of mania	References	Major benefit(s)	Major limitation(s)	Face validity	Predictive validity	Construct validity
			<ul style="list-style-type: none"> Lack of specificity for mania. 			
Resident-intruder test	(Miczek et al., 2001)	<ul style="list-style-type: none"> Significant predictive validity. Potential model of antidepressant-induced mania. 	<ul style="list-style-type: none"> Has been utilized as a model of depression. No evidence of construct validity. 	+	++	
Dominant-submissive behavior paradigm	(Malatynska and Knapp, 2005)	<ul style="list-style-type: none"> Mimics aggressive behavior resembling manic symptoms. 	<ul style="list-style-type: none"> Laborious and time consuming. Risk of injury to intruder animals. Lack of specificity for mania. 	+	+	
Genetic Models						
Dopamine transporter (DAT)	(Giros et al., 1996)	<ul style="list-style-type: none"> Presents hyperlocomotion and reduced hyperlocomotion and stereotypic behavior response following psychostimulants Hyperlocomotion is reversed by treatment with valproate. 	<ul style="list-style-type: none"> Lack of specificity for manic-like behavior. Limited data on construct validity (other than increased levels of dopamine). 	++	++	+
Circadian locomotor output cycle kaput (CLOCK)	(McClung, 2011; Roybal et al., 2007)	<ul style="list-style-type: none"> Strong behavioral characterization that resembles human mania. Evidence of construct and predictive validities. 	<ul style="list-style-type: none"> Limited data on predictive validity; lack of specificity for manic-like behavior. 	++	++	++
Circadian gene D-box binding protein (DBP)	(Le-Niculescu et al., 2008)	<ul style="list-style-type: none"> Model resembles switch from depression to mania. 	<ul style="list-style-type: none"> Limited data on all of the validities. 	+	+	+
Glutamate receptor 6 (GluR6)	(Shaltiel et al., 2008)	<ul style="list-style-type: none"> Rationale is based on linkage studies. 	<ul style="list-style-type: none"> Limited data on predictive and construct validities. 	++	+	+

Animal model of mania	References	Major benefit(s)	Major limitation(s)	Face validity	Predictive validity	Construct validity
Glycogen synthase kinase 3 β (GSK-3 β)	(Prickaerts et al., 2006)	<ul style="list-style-type: none"> Model is based on a well-established pathophysiological feature of BD. 	<ul style="list-style-type: none"> Limited data on all validity parameters. Overexpression of GSK-3β is compensated by other mechanisms, which reduces the effect of the initial stimulus. Not specific for mania. 	+		+
Pituitary adenylate cyclase-activating polypeptide (PACAP)	(Hattori et al., 2012)	<ul style="list-style-type: none"> Mimics hyperlocomotion and is based in genetic data showing an association between this the PACAP gene and BD. 	<ul style="list-style-type: none"> Not specific to mania. Lack of data on predictive validity. Limited face and construct validity. 	++		+
Extracellular signal-regulated kinase (ERK1)	(Engel et al., 2009)	<ul style="list-style-type: none"> Relevant behavioral symptoms. ERK1 pathway is central for the actions of mood stabilizers. 	<ul style="list-style-type: none"> Limited data on construct validity. Not specific for mania. 	++	+	+
Postsynaptic density protein SHANK3	(Han et al., 2013)	<ul style="list-style-type: none"> Multiple mania-like behavioral phenotypes, such as reduced immobility in tail suspension test, disrupted acoustic startle response, hyperphagia, reduction of social interaction and abnormal circadian rhythm. 	<ul style="list-style-type: none"> Lack of specificity for mania (as Shank3 overexpressing mice also exhibit pro-convulsive behavior). 	++	+	+
Neuron-specific α -3 subunit (ATP1A3)	(Krischenbaum et al., 2014)	<ul style="list-style-type: none"> This model may replace the pharmacological ouabain model of mania, providing a less laborious model. 	<ul style="list-style-type: none"> The degree of physiological dysfunction of Na⁺K⁺-ATPase coupled with the magnitude of stressors may determine the expression of both manic and depressive-like behaviors in rodents. 	++	++	++

Animal model of mania	References	Major benefits(s)	Major limitation(s)	Face validity	Predictive validity	Construct validity
B-cell lymphoma 2 (Bcl-2)	(Lien et al., 2008)	<ul style="list-style-type: none"> Developed based on studies suggesting the relevance of apoptosis in the pathophysiology of BD. 	<ul style="list-style-type: none"> Limited predictive and construct validities. 	++	+	+
Mice strains						
Black Swiss (BS) mice	(Flaisher-Grinberg and Einat, 2010)	<ul style="list-style-type: none"> Consistent face and predictive validities. No induction is needed. 	<ul style="list-style-type: none"> Limited construct validity. 	++	++	+
Madison (MSN) mice	(Saul et al., 2012)	<ul style="list-style-type: none"> Mimics multiple mania-like behaviors hyperlocomotion, hypersexuality, and increased forced swimming. 	<ul style="list-style-type: none"> Lack of specificity for mania (behavioral phenotypes overlap with schizophrenia and attention deficit hyperactivity disorder). 	+	+	++

Note: The columns on the right estimate face, predictive, and construct validity based on a 4-point scale (blank, +, ++, +++).