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Investigating the underlying mechanisms of aberrant behaviors in bipolar disorder from patients to models:

Rodent and human studies

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Abstract

Psychiatric patients with bipolar disorder suffer from states of depression and mania, during which a variety of symptoms are present. Current treatments are limited and neurocognitive deficits in particular often remain untreated. Targeted therapies based on the biological mechanisms of bipolar disorder could fill this gap and benefit patients and their families. Developing targeted therapies would benefit from appropriate animal models which are challenging to establish, but remain a vital tool. In this review, we summarize approaches to create a valid model relevant to bipolar disorder. We focus on studies that use translational tests of multivariate exploratory behavior, sensorimotor gating, decision-making under risk, and attentional functioning to discover profiles that are consistent between patients and rodent models. Using this battery of translational tests, similar behavior profiles in bipolar mania patients and mice with reduced dopamine transporter activity have been identified. Future investigations should combine other animal models that are biologically relevant to the neuropsychiatric disorder with translational behavioral assessment as outlined here. This methodology can be utilized to develop novel targeted therapies that relieve symptoms for more patients without common side effects caused by current treatments.

Keywords

Bipolar disorder; translational; animal model; dopamine transporter

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Introduction

Treatments for bipolar disorder (BD) have been very limited and no novel therapeutics specifically for BD have been developed in a long time. Treatments that target the neural circuitry specifically affected in BD patients are urgently required in order to ameliorate the symptoms of this disorder. BD is a major psychiatric disorder affecting approximately 2% of people worldwide (Merikangas et al., 2011). It is characterized by episodes of mania and depression, with periods of absence of symptoms that meet diagnostic criteria for mania or depression in-between (euthymic state). The symptomatology of BD is heavily dependent on the state in which patients present. Mania includes long periods of euphoria, reduced sleep, hypersexuality, extreme irritability, racing thoughts, aggression, hedonic behavior, and hyperactivity, which is a conspicuous feature during acute manic states (Perry et al., 2010; Cheniaux et al., 2014). Indeed, the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM V) states that changes in activity and energy are required for diagnosis of a manic episode in addition to an 'increase in goal-directed activity' or 'psychomotor agitation' (DSM-V, 2013). Symptoms of depression are largely the opposite and consist of long periods of dysphoria, reduced libido, increased sleep, feeling tired or 'slowed down', anhedonia, and greater risk of suicide. Bipolar depression is differentiated from unipolar depression or major depressive disorder (MDD) diagnostically by the requirement of at least one manic or hypomanic episode for BD diagnosis (DSM-V, 2013). In addition to mood and behavioral changes, patients with BD also suffer from a variety of neurocognitive deficits in domains such as executive functioning, vigilance, impulsivity, and decision-making (Sax et al., 1999; Fleck et al., 2003; Martinez-Aran et al., 2004; Savitz et al., 2005; Burdick et al., 2007; Goodwin et al., 2008). Although BD has typically been described as a mood disorder, these cognitive impairments are irrefutably important since they correlate closely with a patient's functional outcome (Green, 2006; Bearden et al., 2010; Torres et al., 2011). Hence, by understanding and improving cognitive function, the patient's quality of life will likely improve.

Untreated or poorly maintained BD can be devastating to the quality of life of patients and their families. Treatments that are commonly used include the mood stabilizer lithium, anticonvulsants such as valproate and lamotrigine, and several antipsychotics (Grunze et al., 2009). None of these treatments completely stabilize behavior nor improve cognitive functioning. In fact, current treatments, particularly lithium, can worsen cognitive functioning and ingenuity (Pachet and Wisniewski, 2003; Holmes et al., 2008). Hence, increased creativity and individuality felt by many people with BD are eroded by these treatments, limiting adherence compliance (Martinez-Aran et al., 2009). Instead of using generic 'band aid' treatments for subduing behavior, developing targeted treatments for problematic symptoms experienced by BD patients would likely generate better treatment outcomes and adherence. Indeed, none of the currently approved treatments were developed with BD as a target, but were in fact discovered serendipitously (Gould and Einat, 2007). Together with the symptoms suffered by patients, these poor treatment options contribute to an increased suicide mortality rate (Osby et al., 2001); recent estimates indicate that one in three BD patients attempt suicide (Novick et al., 2010). Novel therapies based on the

underlying mechanisms of abnormal behavior in BD patients are urgently required to improve quality of patient care.

Both *in vitro* and *in vivo* preclinical studies play essential roles in the discovery of novel targets to develop useful therapeutic outcomes. Modeling the abnormal behaviors present in people with BD across different species remains a challenging task (Malkesman et al., 2009). The complexity of the abnormal behaviors in patients both within and between bipolar states makes modeling BD extremely difficult. Even targeting a single behavioral abnormality can be challenging; for example, racing thoughts or hopelessness is measured using questionnaires in humans, which would be impossible to mimic in rodent studies. The limitations of mimicking psychiatric illnesses in non-human mammals has resulted in the frequent simplistic use of increased motor activity as a primary measure of animal models of BD mania (Frey et al., 2006; Kato et al., 2007). Besides activity, other relevant BD behaviors modeled in animals include aggression, hypersexuality, hedonia-like behavior, inattention, and risk-taking or decision-making (Gessa et al., 1995; Young et al., 2011c). The use of a comprehensive sequence of tests assessing different BD-like behaviors - instead of focusing on one aspect of the illness (e.g., hyperactivity) - can aid the identification of global mechanisms underlying symptoms as well as treatments (Einat, 2007). Combining this approach with the reverse-translational behavioral tasks that characterize behaviors from patients to rodents and *vice versa* would likely yield more relevant information (Young et al., 2007a; Geyer, 2008; Markou et al., 2009).

The majority of approaches used in the field still tend to focus on the assessment of relative basic behaviors in rodents. The observations of simple behaviors in rodents have limited validity with regards to modeling human behaviors often interpreted from self-report measures (e.g., hedonistic behavior and sweet solution preference or psychomotor agitation and hyperactivity). More elaborate tasks provide a high-quality method to quantify behaviors exhibited by BD patients in a laboratory setting and subsequently assess such behaviors in rodents. Therefore in this review, we will describe models of BD that specifically utilize translationally relevant tasks. While the use of basic tests with little specific relevance to abnormal patient behavior can be useful as a first pass in the screening of rodent models for BD, our focus will be placed on tasks that exist in both humans and animals from which direct comparisons of behavior performance can be made. Several lines of research have begun to utilize this methodology, resulting in promising behavioral paradigms in humans and rodents. Indeed, this translational approach is being used in other disorders as well, such as HIV and methamphetamine dependence (Henry et al., 2014), schizophrenia (Demeter et al., 2013), and other substance use disorders (Voon et al., 2014). Here, the quantification of abnormal behavior in BD and attempts to recreate these behaviors in etiologically relevant models will be discussed. This review provides an invited summary of research presented as a Keynote Lecture at the International Behavioral Neuroscience Society in 2014, highlighting our laboratory's approach toward delineating the neural mechanisms underlying BD.

Pathophysiology of BD

Mechanisms underlying the complex umbrella of symptoms in BD are as yet unresolved, complicating targeted treatment development. Nevertheless, several mechanisms have been elucidated that likely mediate both states of mania and depression in BD. The catecholaminergic-cholinergic balance hypothesis of BD states that functional levels of catecholamines are increased during manic states, whereas increased cholinergic functioning is more relevant to depression (Janowsky et al., 1972; van Enkhuizen et al., 2014c). Among the catecholamines, dysfunctional dopamine (DA) neurotransmission is recognized to be a central factor in the pathophysiology of BD (Vawter et al., 2000; Manji et al., 2003; Berk et al., 2007). The DA transporter (DAT) is the primary reuptake mechanism of extracellular DA by which homeostasis is maintained (Cooper et al., 1991). Polymorphisms in the gene encoding for DAT have been associated with BD (Greenwood et al., 2006; Pinsonneault et al., 2011; Vaughan and Foster, 2013), although these results have not been replicated in every genome wide association study (Network and Pathway Analysis Subgroup of Psychiatric Genomics, 2015). SNPs can reduce cell surface migration of DAT (Horschitz et al., 2005), down-regulating its functional expression. Subsequently, reduced striatal DAT levels have been observed in drug-free depressed and euthymic BD patients (Anand et al., 2011) and in the postmortem tissue of BD patients (Rao et al., 2012). On the other hand, higher DAT binding has also been observed in the striatum of medicated depressed (Amsterdam and Newberg, 2007) and unmedicated euthymic (Chang et al., 2010) BD patients. Another symptom associated with BD is an abnormal circadian rhythm (McClung, 2011). For instance, altered rhythms in physiological parameters such as body temperature, plasma cortisol, and melatonin have been observed in patients with depression and BD (McClung, 2007), who also often experience altered sleep-wake cycles. Altered circadian rhythms can influence the release, synthesis, and levels of neurotransmitters such as DA (McClung, 2007). Taken together, these mechanistic findings provide targets which can be used to aid the development of animal models as well as treatments for BD.

Altered exploratory behavior in BD mania

Previously, we described how increased motor activity and exploratory behavior described in patients with BD could be characterized using a multivariate translational approach called the human behavioral pattern monitor (BPM) (Young et al., 2007a; Henry et al., 2010). In brief, the human BPM consists of a room that is novel to the test subjects and contains furniture and several items placed around the room to encourage exploration (Fig. 1A). Subjects are asked to wait in the room with no specification of the duration, unaware of simultaneously being tested on several ambulatory parameters. By measuring exploratory behavior of patients in this novel environment, a unique pattern of activity and exploration of manic (Perry et al., 2009) and euthymic BD patients (Henry et al., 2013) was identified. This abnormal exploratory pattern exhibited by BD patients included hyperactivity, increased specific exploration, and more linear patterns of movement, which importantly differed from control subjects (Perry et al., 2009), adult attention deficit hyperactivity (ADHD) subjects (Paulus et al., 2007), and patients with schizophrenia (Perry et al., 2009). Because the human BPM was developed using a “reverse-translational” approach based on the BPM originally designed for testing rats (Geyer et al., 1986) or mice (Risbrough et al.,

2006), it has been possible to examine mechanisms that underlie this specific pattern of exploration using the same manner of assessment of locomotor exploration in rodents. In brief, the BPM for rodents consists of a Plexiglas arena containing both floor and wall holes (Fig. 1A). Infrared beams attached along all four walls and in each hole detect and record holepokes, rearing, and the location of the animal. Using these data, the BPM is able to quantify activity, exploration, and the structural patterns of motor activity of rodents (Henry et al., 2010).

Previously, the rat and mouse BPM systems have proven useful to differentiate between pharmacological stimulants such as 3,4-methylenedioxy-*N*-methylamphetamine (MDMA), scopolamine, and apomorphine (Geyer et al., 1986; Paulus et al., 1990; Lehmann-Masten and Geyer, 1991; Risbrough et al., 2006). None of these stimulants recreated the abnormal exploratory profile observed in BD patients however. Furthermore, treatment with the mixed DAT / norepinephrine transporter (NET) inhibitor amphetamine, a manipulation often used to model BD in rodents, also failed to recreate this pattern in mice (Perry et al., 2009). When mice with selectively reduced DAT functioning were tested in the mouse BPM however, both constitutive knockdown (KD) of the DAT and pharmacological inhibition with the selective DAT inhibitor GBR12909 induced a behavioral profile similar to that of BD patients (Perry et al., 2009; Young et al., 2010b). These test animals were hyperactive, exhibited increased exploration as indicated by increased rearing and holepoking, and moved in straighter, more direct patterns compared to wild-type (WT) mice. This hyper-exploratory profile was attenuated with environmental familiarity, but was reinstated with environmental novelty (Young et al., 2010a). Such observations are consistent with environmental familiarity aiding the transition from patients in a manic to a euthymic state (Minassian et al., 2011). Moreover, the hypersensitivity of these mice to psychostimulants (Young et al., 2010a) is consistent with the sensitivity of BD patients to stimulants (Wingo and Ghaemi, 2008). Besides the selective DAT inhibitor GBR12909, mice treated with the atypical stimulant modafinil also exhibited a similar mania-like profile in the BPM (Young et al., 2011b). These data are consistent with evidence that modafinil exerts its primary effects by blocking the DAT (Volkow et al., 2009; Zolkowska et al., 2009). Modafinil may also exert downstream effects on the DA D₁ and D₄ receptors (Young and Geyer, 2010; Young et al., 2011b), although a wide array of other receptors may also be involved in the effects of modafinil (Minzenberg and Carter, 2008). Studies investigating whether modafinil in healthy humans mimics the exploratory profile of BD patients are currently ongoing.

Complete knockout (KO) of the DAT gene also results in hyperactivity and similar movement disorganization, characterized by predominantly straight path patterns (Ralph et al., 2001b). Since these DAT KO mice were tested using a video-tracker system, no information on specific exploration (holepoking or rearing) was assessed. Another study did investigate exploratory behavior and observed no difference in rearing and less object interactions exhibited by DAT KO compared to WT mice (Spielewoy et al., 2000). Interestingly, treatment with the DA D₁ antagonist SCH23390 attenuated the animals' hyperactivity and altered their movement into more meandering behavior similar to control mice (Ralph et al., 2001b). Stimulant treatment attenuates the hyperactive profile of DAT KO mice however (Trinh et al., 2003), mimicking treatment effects of ADHD, not BD

(Pataki and Carlson, 2013). In fact, stimulants often exacerbate symptoms of BD mania and therefore complete KO of the DAT gene may not be suitable as a model for BD mania. Another mouse model of BD mania, created with a mutation in the *Clock* gene, exhibited similarities with the behavioral phenotype of patients in the BPM, but failed to mimic the pattern completely (van Enkhuizen et al., 2013b). In contrast to patients with BD, these *Clock*¹⁹ mice exhibited more circumscribed, small-scale movements instead of direct, more linear paths (van Enkhuizen et al., 2013b). Hence, while circadian machinery linked to BD, although not this particular gene, and *Clock*¹⁹ mice exhibiting altered sleep patterns (McClung, 2013), these mice do not recreate the pattern of altered exploration observed in BD mania patients (Minassian et al., 2011). Furthermore, these mice have yet to be tested in domains of neurocognition relevant to BD. Similarly to *Clock*¹⁹ mice, a mouse model of schizophrenia, the chakragati strain, also exhibited hyperactivity combined with more meandering, small-scale movements in the BPM (Young et al., 2014). The increased small-scale movements of these mice are likely due to unilateral increases of DA in the brains of these mice. Other mechanisms involved could include the serotonin system as psilocin (the active metabolite of psilocybin) and the non-selective serotonin receptor agonist 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) also induced circumscribed behavior in mice, an effect mediated by the 5-HT_{2C} and 5-HT_{1A} receptors respectively (Halberstadt et al., 2011). Importantly however, these hallucinogens reduced activity and exploration in mice, resulting in a profile different from that of BD patients. It therefore seems that selectively reducing DAT functioning in mice specifically recreates the behavioral phenotype of BD mania patients in the BPM. Thus, while the mouse BPM has face validity for the human BPM, the prediction that reduced, but not completely lost, DAT functioning in mice recreates the hyper-exploratory profile of mania patients further supports the translational validity of the BPM.

Going beyond these face and predictive validities, the effects of pharmacological treatments on the exploratory profile of these models were also investigated. Acute treatment with the mood-stabilizing agent valproate attenuated hyperactivity of DAT KD mice (Ralph-Williams et al., 2003) but not that of GBR12909-induced activity (Douma et al., 2011). Chronic treatment is needed before the Young Mania Rating Scale (YMRS) score of patients drop to the point they are considered euthymic (Cipriani et al., 2011), as does their degree of hyperactivity (Minassian et al., 2011), supporting the premise that the pharmacological predictive validity of a model of mania may be more suitably assessed using chronic treatments (Harrison-Read, 2009; Young et al., 2011a). Encouragingly, chronic valproate treatment via the rodents' chow at 15 g/kg resulted in serum concentrations within the human therapeutic range for BD (van Enkhuizen et al., 2013c). This treatment attenuated the hyperactivity of both DAT KD mice and mice administered GBR12909. The hyper-exploration and abnormal behavioral organization were unaffected in these models however, supporting the premise that valproate does not fully treat every aspect of mania, and that measurements beyond hyperactivity alone are required for the development of fully efficacious treatments (van Enkhuizen et al., 2013c). Interestingly, mania patients treated largely with valproate also exhibited a reduced effect size difference of hyperactivity compared with healthy subjects, yet their hyper-exploratory or abnormal behavioral organization was unaffected (Minassian et al., 2011) consistent with animal studies (van

Enkhuizen et al., 2013c). The positive effects of chronic valproate treatment on models involving reduced DAT functioning may be explained by chronic valproate increasing neuronal DAT levels (Wang et al., 2007). Hence, reducing synaptic DA levels by increasing DAT expression may be a viable treatment for BD mania. This possibility is consistent with evidence of hyperdopaminergic states of manic BD patients (Sjostrom and Roos, 1972; Gerner et al., 1984), which are also seen in the DAT KD animal model (Zhuang et al., 2001). Another putative treatment would therefore include directly reducing DA availability, which was also studied in these models. In humans, treatment with alpha-methyl-*p*-tyrosine (AMPT), a competitive inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of catecholamines, reduced symptoms in manic patients and increased depression in BD depressed subjects (Brodie et al., 1971; Bunney et al., 1971). In another study however, AMPT did not affect mood during treatment of euthymic subjects, but resulted in hypomanic relapses post-treatment (Anand et al., 1999). When administered to DAT KD mice, AMPT attenuated the mania-like activity levels and disordered movement organization, without affecting control mice (van Enkhuizen et al., 2014a), consistent with reduced symptoms in mania patients (Brodie et al., 1971). Exploration however, was not attenuated by AMPT in DAT KD mice, but was instead increased. Hence, consistent with BD mania patients, chronic valproate treatment lowered hyperactivity in reduced DAT function models but not other aspects of exploratory behavior. Furthermore, AMPT treatment reduced hyperactivity, but increased exploration, in these mice and reduced mania symptoms in mania patients. To a certain extent, these data therefore support the pharmacological predictive validity of reduced DAT functioning as a model for BD mania.

In summary, abnormal exploration of patients with BD was characterized using a translational paradigm that enabled comparison with the locomotor profile of potential animal models for BD (see Table 1). Based on putative etiological mechanisms of reduced DAT functioning, we identified that selectively reducing DAT functioning induced an abnormal exploratory profile similar to that of patients with BD mania patients, supporting the construct and predictive validity of these models. Additionally, these DAT models meet the pharmacological predictive validity criterion since their hyperactive profiles were attenuated by treatment with valproate or AMPT. Similarities of behaviors observed between the reduced DAT functioning animal models and *Clock*⁻¹⁹ mice may provide important future directions. Because *Clock*⁻¹⁹ mice have increased DA release and turnover (Spencer et al., 2012), the relationship between the DA system and aberrant circadian rhythms may be fundamentally important in the biological mechanisms of BD. Investigating the effects of catecholamine depletion with AMPT in *Clock*⁻¹⁹ mice may further demonstrate the contribution of hyperdopaminergia being responsible for the animals' mania-like behavior.

Altered prepulse inhibition in BD mania

A more traditional and commonly used translational test is the assessment of sensorimotor gating of the startle reflex. Across organisms, sensorimotor gating serves to filter out excessive stimuli in order to focus on the relevant features of the environment (Braff et al., 2001). In normal individuals, a weak prepulse before a subsequent startling stimulus will inhibit the startle response, termed prepulse inhibition (PPI; Fig. 1B). In the context of

psychiatric research, PPI of the eye blink response was first assessed in patients with schizophrenia (Braff et al., 1978) and afterwards translated to assess similar measures in animals, particularly rodents in which the startle response is measured by a whole-body flinch (Swerdlow et al., 1986; Geyer and Swerdlow, 2001; Geyer et al., 2002; Weber and Swerdlow, 2008). Reduced sensorimotor gating as measured by lower PPI is observed in several psychiatric disorders such as Huntington's disease (Swerdlow et al., 1995), obsessive-compulsive disorder (Ludewig et al., 2002), schizophrenia (Braff et al., 2001), panic disorder (Ludewig et al., 2002), and is also observed in acutely manic (Perry et al., 2001) and remitted BD patients (Giakoumaki et al., 2007), although other studies failed to report deficits in remitted adult and pediatric BD patients (Barrett et al., 2005; Rich et al., 2005) or in manic/mixed episode BD patients (Carroll et al., 2007). A more recent study reported PPI deficits in male euthymic BD patients, but increased PPI in female BD patients (Gogos et al., 2009). Additionally, normal PPI is observed in unipolar depressed individuals (Perry et al., 2004; Quednow et al., 2006), suggesting that active manic symptoms and/or acute psychosis may be necessary to exhibit PPI deficits (Kohl et al., 2013). Whether dysfunctional PPI is truly state-dependent is unclear, since PPI has yet to be studied in depressed bipolar patients. Since abnormal PPI has also been observed in the relatives of BD patients (Giakoumaki et al., 2007), impaired PPI may indicate a genetic predisposition to BD (perhaps a mania/psychosis vulnerable type). Because PPI is observable across different species and measures a central component of information processing, it is a useful behavioral phenotype to investigate in animal models related to neuropsychiatric disorders. Since PPI deficits are most characterized and replicated in patients with schizophrenia (Braff et al., 2001; Swerdlow et al., 2008), the majority of preclinical PPI studies focus on this disease (Powell et al., 2012). Nevertheless, sensorimotor gating has also been studied in animal models related to BD.

The PPI paradigm in rodents has been used extensively in pharmacological studies, elucidating the mechanisms underlying PPI as well as searching for potential new antipsychotics (Geyer et al., 2001). For instance, DA agonists impair PPI in both humans and animal models, effects that can be blocked by DA antagonists (Braff et al., 2001; Geyer et al., 2001). Increased DA is often noted in the pathophysiology of BD and it is worth mentioning that elevating DA impairs PPI in rodents. For instance, the selective DAT inhibitor GBR12909 that recreates the behavioral profile of BD patients in mice in the BPM (see above) also impairs PPI of mice (Kwek and van den Buuse, 2013). Furthermore, modafinil also impaired PPI in mice, an effect that was reversed by co-treatment with the DA D₂ receptor antagonist haloperidol (Kwek and van den Buuse, 2013). These data support the premise that the effect of modafinil was likely mediated by an interaction with the DA system. Hence, agents that recreate the mania-like BPM profile in mice also disrupt PPI, an effect that can be attenuated using BD mania-approved treatments.

In addition to antipsychotic treatments, the effects of mood-stabilizing agents on PPI have also been investigated. In rats, lithium attenuated PPI deficits induced by amphetamine (Zheng et al., 2013), supporting a possible interaction between lithium and the DA / noradrenergic system. We have observed that chronic lithium treatment resulting in low therapeutic serum concentrations blocked the GBR12909-induced PPI deficits in mice (van Enkhuizen et al., Accepted). Treatment with the anticonvulsant topiramate, occasionally

used off-label for BD, increased PPI in rats and potentiated the PPI-increasing effects of haloperidol and clozapine (Frau et al., 2007). Indeed, improvements of baseline PPI in normal animals or models with naturally low PPI are observed with certain antipsychotics (Geyer, 2008) and mood stabilizers (Flood et al., 2009). Similarly, healthy humans with low baseline PPI often exhibit increases in PPI after treatment with antipsychotics (Holstein et al., 2011; Csomor et al., 2014). PPI deficits induced by the DA agonist apomorphine in rats were also prevented by topiramate (Frau et al., 2007), asenapine (Marston et al., 2009), a novel antipsychotic in the treatment of SCZ and BD, and the mood stabilizers valproate, carbamazepine, and lithium (Umeda et al., 2006), suggesting an interaction with the DA system for these treatments. Hence, pharmacological PPI studies may prove useful in elucidating putative treatments that may not obviously interact with the DA system.

In search for BD animal models with greater etiological validity, the translational PPI paradigm has also been used to evaluate numerous genetic animal models. Potential susceptibility genes associated with BD or genes encoding for proteins that are likely involved in the pathogenesis of BD have been modified in rodents, after which the sensorimotor gating of these mice is tested (Powell et al., 2012). For instance, deletion at the 22q11 locus is associated with SCZ and BD (Papoulos et al., 1996; Berrettini, 2000). Mice that model the 22q11 deletion syndrome were genetically engineered and displayed PPI impairments (Paylor et al., 2006). Because redoxdysregulation and allelic variants of the genes coding for the rate-limiting glutathione synthesizing enzyme glutamate-cysteine-ligase modifier (GCLM) have also been implicated in BD, mice with this GCLM knocked out were tested and exhibited PPI deficits (Kulak et al., 2012). In a genome-wide association study, a relationship between the NCAN gene and BD was observed. Ncan KO mice were subsequently tested and displayed decreased PPI levels, together with a range of other mania-like behaviors (e.g., hyperactivity, increased saccharine preference, and amphetamine hypersensitivity), which were normalized after lithium treatment (Miro et al., 2012). In another recent study, treatment with valproate reversed PPI deficits observed in transgenic mice overexpressing corticotropin-releasing factor, which is implicated in the etiology of BD (T et al., 2014). Finally, PPI deficits observed in BD have been recapitulated in other animal models that exhibit mania-like behavior such as the Na⁺, K⁺-ATPase $\alpha 3$ mutant mice (Kirshenbaum et al., 2012) or *Clock* 19 mutant mice (van Enkhuizen et al., 2013b), but not in other animal models such as the N-ethyl-N-nitrosourea (ENU)-generated mutant mouse strain (Umemori et al., 2013). Furthermore, Black Swiss mice have often been reported as a model for mania (Hannah-Poquette et al., 2011) yet they exhibited better PPI compared to C57BL/6 mice (Ralph et al., 2001a). Given the observed PPI deficits across numerous disorders, investigating the exploratory and/or other relevant behaviors of these genetic mutants will prove useful for BD research in the future.

As previously mentioned, DAT KO mice have also been suggested as a model for mania and their sensorimotor gating capacities have also been assessed. Significant PPI deficits were observed in these mice, which were attenuated by pretreatment with the DA D₂ antagonist raclopride (Ralph et al., 2001b) and the antipsychotics clozapine and quetiapine (Powell et al., 2008). DAT KD mice, that have approximately 10% expression of the DAT gene compared to WT mice, initially appeared to have normal PPI levels (Ralph-Williams et al.,

2003). More recently however, we have observed PPI deficits in these DAT KD mice (van Enkhuizen et al., Accepted). Interestingly, the COMT Val allele, which contributes to slower DA clearance in the prefrontal cortex, is associated with reduced PPI in Caucasian healthy humans (Roussos et al., 2008; Quednow et al., 2009). Therefore, a link between reduced DA clearance and PPI deficits has been established.

Together, these pharmacological and genetic studies can be helpful in the screening of valid animal models for BD and development of novel therapeutics (see Table 2), although the PPI paradigm by itself is not selective for assessing BD mania treatment efficacy. Furthermore, it is clear that the circuitry underlying PPI is diverse and complex (Swerdlow et al., 2001), yet it is unclear whether deficits in models described here are a result of alterations in different circuitry, or whether they exert an effect that converges on one particular circuit. Comparing these manipulations for this convergence would be useful in order to establish whether novel treatments could be elucidated from this work. Importantly, the strength of high-quality translational research is the capacity to assess a battery of different behaviors relevant to the disorder across species (Young et al., 2011a; Powell et al., 2012). Measurements of PPI can be a great additional tool in this multivariate approach. In the case of PPI and BD, mixed results are observed across both models and patients.

Impaired cognitive behaviors in BD mania

Neurocognitive capabilities closely correlate with a patients' functional outcome (Green, 2006). Developing treatments targeted at the neurocognitive deficits of patients should therefore enhance their quality of life. Impaired cognition as a quantifiable symptom of BD should be included in the multivariate assessment of screening animal models for BD. Working memory, vigilance, inhibitory control, decision-making under risk, and processing speed can all be affected in BD patients (Martinez-Aran et al., 2004; Savitz et al., 2005; Burdick et al., 2011). Some of the cognitive deficits that can be quantified in both humans and rodents include impaired attentional performance, disinhibition, and impaired risk-based decision-making (Young et al., 2013b; van Enkhuizen et al., 2014d), but further studies in other cognitive domains are required. Translational paradigms assessing such behavior in a similar fashion across species can help bridge the gap between cognitive difficulties in BD and their assessment in animal models for BD.

Decision-making and risk-preference

Decision-making performance in a clinical setting is most often measured using a task called the Iowa gambling task (IGT) (Bechara et al., 1994). The IGT (Fig. 1C) is based on repeatedly making choices between four different card decks in order to maximize gains in the long-term (100 choices total). Unknown to the test subject, two options will deliver high monetary gains but with occasionally large losses (disadvantageous), while the other two options pay smaller amounts of money but also incur smaller penalties (advantageous). Initially, healthy individuals will sample all decks but as the task progresses they preferentially choose the advantageous options significantly more as they deliver the highest gains in the long-term. Patients with BD however, choose more disadvantageous or risky choices and learn slower (Adida et al., 2011; Ibanez et al., 2012; van Enkhuizen et al., 2014d). Hence, BD patients make poorer decisions under risk in a laboratory-based task.

In order to study biological mechanisms behind decision-making in more detail, several different rodent versions of the IGT have been developed (de Visser et al., 2011). One procedure uses an operant-based chamber in which the rodent chooses from four different light cues (Fig. 1C). Each option is associated with a specific reward/punishment schedule similar to the one used in human IGT. One technique uses such an IGT but trains the rodents on the reinforcement schedules over many (>20) sessions with decision-making assessed after contingency acquisition. Using this procedure, the effects of pharmacological manipulations of DA, serotonin, and norepinephrine (Zeeb et al., 2009; Baarendse et al., 2013) as well as lesions in the orbitofrontal cortex and amygdala (Zeeb and Winstanley, 2011) on decision-making for learned contingencies could be studied. When this multiple-sessions IGT paradigm was adopted for use in mice, it was discovered that the DAT KD mouse model for BD tended to exhibit an increased risk-preference compared to WT mice after 25 training sessions (Young et al., 2011c). Furthermore, secondary measures indicated elevated levels of motivation and motor impulsivity in these mice. Using the same IGT procedure, the effects of selective DAT inhibition was also studied in mice. GBR12909 and modafinil both increased measures of motor impulsivity and motivation significantly, but affected risk-preference only subtly (van Enkhuizen et al., 2013a). In contrast, the mixed DAT/NET inhibitor amphetamine induced a more conservative strategy in both mice (van Enkhuizen et al., 2013a) and rats (Zeeb et al., 2009), resulting in a risk-averse preference without affecting motor impulsivity. Hence, in this between-sessions IGT, amphetamine reduced risk preference in rodents (opposite to BD mania patients), while selective DAT inhibition only subtly increased risk preference.

Importantly however, the human IGT requires subjects to learn to select the advantageous options over a single session. BD patients learn more slowly in this single task. Thus, a similar time-course of this decision-making process in a rodent IGT may more accurately reflect human decision-making. When tested within a single session, it was possible for rats to learn to select the advantageous options over time in a single 60 min session (Rivalan et al., 2009) consistent with healthy humans. This single-session IGT test was successfully adopted for use in mice, resulting in a single-session IGT more analogous to the human IGT (van Enkhuizen et al., 2014d). Using this procedure, it was established that both GBR12909-treated and DAT KD mouse models of BD exhibited poor learning of reward contingencies over a single session consistent with what was observed in manic BD patients performing the human IGT. Additionally, DAT inhibition also increased motivation and motor impulsivity in mice consistent with earlier observations (van Enkhuizen et al., 2013a). Perhaps most striking was that using *post-hoc* choice analyses, it was discovered that decision-making deficits of the BD mania patients and both mouse models were driven by increased sensitivity to rewards, specifically a preference to shift to high reward options. Such findings in patients are consistent with previous reports for mania patients and differ by state of BD, with depressed patients being more sensitive to punishment (Adida et al., 2011; Must et al., 2013). Combined, these data indicate that selectively reducing DAT functioning induces a behavioral profile that resembles the impaired decision-making and hedonia behaviors observed in BD mania (Cassidy et al., 1998). These data also highlight that species-specific versions of the IGT provide another useful translational tool that can be

used to investigate the biological underpinnings of poor risk-based decision-making in patients with BD (see Table 3).

Attentional functioning

Another typical neuropsychological test that is often used to quantify attention and inhibitory deficits - another core aspect of cognitive dysfunction in BD - is the continuous performance test (CPT; Fig. 1D). Different versions of the CPT exist, but all include both target and non-target stimuli with which attentional processes such as vigilance and response inhibition can be quantified. When patients with BD are tested in the CPT, several studies have demonstrated impaired attentional performance and inhibitory processing deficits compared to healthy subjects (Harmer et al., 2002; Bora et al., 2006). Because vigilance deficits present in BD can be measured this way, vigilance may be another potential target to assess across species (Young et al., 2009a). Using the same operant chambers as utilized for the rodent IGT, a 5-choice (5C)-CPT was developed for mice (Young et al., 2009b), and is also being used in rats (Barnes et al., 2012b). Hence, several measures of vigilance and response inhibition processes can successfully be measured with the 5C-CPT in both mice and rats wherein improved performance was observed in healthy mice and rats (Barnes et al., 2012a; Young et al., 2013a), and PCP impaired performance in rats (Barnes et al., 2012b). Subsequently, the 5C-CPT was reverse-translated for use in humans with recent reports describing the first translational assessment of vigilance wherein patients with schizophrenia exhibit impaired performance (Young et al., 2013b) in the 5C-CPT that is also fMRI compatible (McKenna et al., 2013). Hence, the human task is clinically sensitive while also demonstrating translational predictive validity.

In support of the translational predictive validity of the 5C-CPT, both mice and healthy humans displayed impaired attentional functioning after 36 hours of sleep deprivation (van Enkhuizen et al., 2014b). Using the mouse 5C-CPT, it was discovered that DAT KD mice exhibited inhibitory deficits and poor vigilance similar to that of patients with BD mania performing the human 5C-CPT (Young et al., In preparation). This translational paradigm could therefore prove useful when assessing attention in rodent models for BD and comparing it with that of patients. These studies are also of importance for future BD research given that sleep deprivation can induce mania in BD patients. While some have therefore suggested that sleep deprivation induces mania-like behavior in rodents, e.g., hyperactivity, increased aggression, hypersexuality, and stereotypy (Hicks et al., 1979; Gessa et al., 1995), this premise is somewhat flawed since healthy humans are not 'manic' as a result of sleep deprivation. Rather, because sleep deprivation can precipitate (hypo)manic states in patients (Salvadore et al., 2010), sleep deprivation could be combined with genetic susceptibility models related to BD (Malkesman et al., 2009) and tested in the 5C-CPT in an attempt to more closely relate to clinical findings. Since patients with bipolar depression can actually benefit from sleep deprivation (Bunney and Bunney, 2013), the same procedure may also be used to validate predictive treatment models of BD depression because if in a 'depressed' state, mice should recover from sleep deprivation. Thus, the 5C-CPT provides an additional instrument to the behavioral toolset with which behaviors relevant to BD can be screened and associations between environmental manipulations and genetic susceptibility for BD can be studied (see Table 3).

Links between behaviors for treatment development

Selective inhibition of the DAT recreates several behavioral profiles of BD mania (Fig. 2). Perhaps most importantly, risk-preference in the mouse IGT correlated modestly with specific exploration in the mouse BPM (Young et al., 2011c). In human studies, a relationship was observed between specific exploration in the BPM and poor performance in the frontal-mediated Wisconsin card-sorting test (WCST) (Henry et al., 2011). In other words, the higher the specific exploration, the more likely subjects (mice or humans) were to exhibit impaired cognitive functioning. It is therefore feasible that developing treatments that would attenuate the pervasive specific exploration profile of BD patients seen in mania and euthymic phases may also positively affect a number of cognitive functions. To date, no such attenuation has been observed in published studies in which AMPT or VPA was administered to the DAT mice in the mouse BPM (van Enkhuizen et al., 2013c; van Enkhuizen et al., 2014a). Instead, both treatments increased levels of specific exploration even further, reflective perhaps of a deleterious effect on cognition. AMPT treatment can indeed impair cognitive functioning as was previously assessed by reward processing and probabilistic learning in human patients with MDD (Hasler et al., 2009b; Hasler et al., 2009a) and bulimia nervosa (Grob et al., 2012). The mood stabilizer VPA, just as lithium, has also been associated with cognitive deficits in healthy subjects and BD patients (Senturk et al., 2007; Holmes et al., 2008). These data highlight the difficulty in studying the predictive pharmacological validity of animal models for BD without a ‘gold standard’ treatment that is efficacious for all symptoms and underscore the need to develop novel treatments that benefit cognition in the already negatively affected BD population.

Limitations and future studies

The current review has focused on efforts made to determine what neural mechanisms might contribute to abnormal behaviors that are relevant to BD, particularly mania. This review has focused on translational tests of behavior that are sensitive to deficits in BD patients and in which an equivalent task exists in rodents (Fig. 1). Significant progress has been made, but a great deal of work is still required in this field. Reduced DAT functioning appears key to recreating many aspects of behavioral abnormalities seen in BD mania patients (Fig. 2). This idea stemmed in part from observations that a DAT polymorphism reduces DAT expression and lower DAT levels are observed in drug-free patients with BD, although these genetic observations in humans are inconsistent. Future studies should determine if patients with genetic polymorphisms exhibit reduced DAT levels and abnormal behaviors in these translational paradigms. Furthermore, other aspects of cognitive functioning rarely tested in animal models of BD such as working memory have not been tested in the DAT model animal. Most animal working memory paradigms utilize delays while human paradigms manipulate the number of information items (Dudchenko, 2004), limiting their translational validity. Some rodent span tasks do exist (Young et al., 2007b; Davies et al., 2013), and models of BD should also be tested in these paradigms as well as tasks that investigate other cognitive domains, e.g., executive functioning in the attentional set-shifting task (Birrell and Brown, 2000; Gilmour et al., 2013).

Another shortcoming of the presented work is the focus of studies on the (hypo)manic phase of BD. For instance, the reduced DAT functioning models lack any depression-relevant behaviors, limiting their utility for BD individuals who experience both mania and depression. Future studies should conduct longitudinal and cross-sectional studies of BD patients across the mood state spectrum in translationally relevant paradigms to establish patient behavioral profiles as targets for animal models. For instance, although both depressed and manic patients exhibit impaired IGT performance, depressed subjects seem to be more sensitive to punishment compared to reward hypersensitivity exhibited by manic subjects (Adida et al., 2011; van Enkhuizen et al., 2014d). Such data could provide clues as to what behavior should be exhibited by the model animal and what mechanisms should be explored for each phase of the disorder. From a biological perspective, there is renewed evidence that suggests that impaired cholinergic mechanisms play a key role during bipolar depression (Janowsky et al., 1994; van Enkhuizen et al., 2014c), which may be restored during euthymic phases (Hannestad et al., 2013) and switch to aberrant dopaminergic signaling during mania (Manji et al., 2003). Thus ideally, future research should focus on the cyclical nature of BD when attempting to model the disease and discover novel treatments. It is possible that the molecular clock machinery in BD is susceptible to internal and external stimuli such as stress or daylight lengths (Dulcis et al., 2013; Wang and Chen, 2013), which subsequently can change the homeostasis of the DA / acetylcholine systems, resulting in a shift to either mania or depression. As reviewed elsewhere (Young and Dulcis, 2015), it has been reported that: 1) mania onset appears to be linked to long periods of daylight, while depression onset is associated with short daylight durations; 2) concomitant neurotransmitter switching occurs whereby elevated dopamine is apparent during long-daylight-length and corticotropin releasing factor (CRF) in short daylight-length; and 3) that increased CRF expression elevates ACh levels in a manner that may predispose to depression. Accordingly, experiments that manipulate the durations of daylight periods in animal models prior to tests using cross-species paradigms relevant to both mania and depression could help to elucidate mechanisms related to the disparate phases of BD and the switching between states that is so characteristic of the disorder.

The relevance of particular models for other disorders should also receive attention. DAT KD/KO mice have also been described as models for ADHD (Leo and Gainetdinov, 2013), and indeed hyperactivity, inattention, and impaired decision-making are present in both ADHD and BD populations. Moreover, reduced striatal DAT levels have also been observed in ADHD subjects (Fusar-Poli et al., 2012). However, ADHD subjects tested to-date display a different BPM profile from BD subjects and DAT KD mice (Paulus et al., 2007). Furthermore, DAT KD mice are also hypersensitive to psychostimulants similar to stimulant-induced mania. In contrast, the hyperactivity of DAT KO mice is attenuated by such stimulants (Trinh et al., 2003) consistent with ADHD treatments. Because ADHD and BD presents with similar clinical symptoms and comorbidity is high (Klassen et al., 2010), elucidating differences between these disorders in order to avoid potentially harmful treatment of wrongly diagnosed ADHD with stimulants will be important future research. The overlap of affected behaviors in BD and ADHD (as well as in other disorders) for which reduced DAT functioning recreates, may also relate more to the cognitive/behavioral domains affected as opposed to a specific disease state. The National Institute of Mental

Health (NIMH) has proposed and promoted the Research Domain Criteria (RDoC) initiative, which bypasses diagnostic categories and focuses instead on classifying psychopathology based on dimensions of functioning in patients (see Table 4 for relevance to bipolar disorder across species) (Cuthbert and Insel, 2010; Morris and Cuthbert, 2012; Insel, 2014). Such an approach may prove to show that reduced DAT activity affects these domains of functioning irrespective of disease state, and that patients with BD simply have lower DAT expression during a manic episode. The reduced DAT models we present here therefore address key aspects of increased dopaminergic transmission. Hence, examining DAT levels and the behavior of patients across diagnostic categories using these translationally relevant paradigms could be a useful RDoC approach.

Another avenue of research could include investigating the highly prevalent cannabis usage among BD patients (Lev-Ran et al., 2013). Although substance abuse in general is high in psychiatric populations, there is evidence that suggests BD patients may be using cannabis as a means to self-medicate (Leweke and Koethe, 2008). Importantly, interactions exist between the (endo)cannabinoid and DA systems, hence future research should investigate their relationship with BD. While the effects of cannabidiol have been investigated on amphetamine-induced oxidative stress (Valvassori et al., 2011), no attempts to measure a behavioral profile were made and, as described above, selective DAT inhibition may better recreate what occurs in BD patients. More research is therefore required in clinical and model behavioral studies. Finally, other neurotransmitter systems relevant to BD besides the catecholamines should be studied, e.g., the involvement of glutamate and NMDA receptors.

Summary and conclusions

Advances in scientific discoveries for mental health disorders have been vast in recent years and are increasing in pace. Unfortunately, the research to market success rate for drug development is merely 1 in 1000 compounds. To develop a BD-targeted treatment, it will be important to use a model animal for BD based on etiological and predictive validity. The application of translational approaches will likely reduce the risk of conducting expensive late-phase clinical trials for novel drugs that prove ineffective (Markou et al., 2009). A broad range of behaviors across species should be assessed, and the labeling of stimulant-induced hyperactivity as 'mania-like' should be reconsidered. Utilizing models with altered mechanisms that potentially underlie BD (etiological validity) and exposing them to a set of translational tests used to characterize deficits in patients fills a crucial gap between preclinical and clinical research. This work would then provide preliminary evidence for targeted mechanistic (PET or EEG)/cognitive studies in patients during illness states to link preclinical evidence to the clinical state (Figure 3). This translational approach will benefit both the understanding of mechanisms implicated in BD pathology and the opportunity to test novel therapeutics. Importantly, despite having been neglected for BD research in the past, this approach includes assessing neurocognitive deficits in patients. Combining relevant environmental manipulations with genetic susceptibility models that contribute to switching (Malkesman et al., 2009; Blumberg, 2012) may improve our knowledge about the oscillatory nature of BD. Although few models of the switching between states in BD exist, some have been proposed and would benefit from translational assessment, as has previously been thoroughly reviewed (Young and Dulcis, 2015). Ultimately, using

translational approaches as described in this review may eventually yield novel therapies that specifically target the biological circuitry of BD, thus improving the lives of patients.

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Highlights

- Bipolar mania patients exhibit a unique behavioral profile
- This profile includes hyperexploration, risk-preference, and inattention
- This profile can be quantified using reverse-translated tasks
- Reducing dopamine transporter function recreates this profile
- Mice with reduced dopamine transporter can be used to assess novel treatments

Figure 1.

Illustration of the translational behavioral paradigms outlined in this review used to assess similar behaviors in patients with bipolar disorder and animal models. The behavioral pattern monitor (BPM) can be used to quantify ambulatory behavior of both humans and rodents, utilizing similar computational measures of activity, exploration, and behavioral organization (A) [see (Henry et al., 2010)]. Deficits of prepulse inhibition (PPI) are used in the sensorimotor gating assessment of humans as well as rodents (B). In humans, reactivity to the startling stimulus is often assessed using the eye-blink response, while in rodents a whole-body flinch is measured [see (Geyer et al., 2002)]. Poor decision-making of bipolar patients can be assessed with the human Iowa gambling task (IGT), while impaired risk-taking behavior of mice can be observed with the mouse IGT (C). The subject is required to learn to pick the "safe" cards / nosepoke the "safe" cue lights in order to gain the most reward over time [see (de Visser et al., 2011)]. Impaired vigilance and loss of inhibitory control are present in patients with bipolar disorder and can be successfully measured with both human and rodent 5-choice continuous performance tests (5C-CPT; D). Subjects are required direct a joystick / nosepoke at a target whenever one cue lights up or inhibit from responding whenever all cues light up [see (Young et al., 2013b)].

Figure 2.

Translational behavioral assessment of the dopamine transporter (DAT) model animal for bipolar disorder (BD) mania based on altered DAT functioning observed in patients with BD. Polymorphisms in the gene encoding for the DAT and reduced cell surface expression of DAT, the primary reuptake mechanism of free dopamine (DA) from the synaptic cleft, have been associated with BD. Lower striatal DAT levels have also been observed in patients by using positron emission tomography (PET). Mice with reduced functioning of the DAT, through either genetic knockdown (KD) or pharmacological inhibition, displayed a range of behaviors consistent with that of BD mania patients in human analogues. These behaviors include hyper-exploration in the behavioral pattern monitor (BPM), reduced prepulse inhibition in the acoustic startle test, high-reward risk-preference in the Iowa gambling task (IGT), and inattention in the 5-choice continuous performance test. Risk-preference of both wild-type (WT) and KD mice in the IGT correlated with specific exploration (holepokes) in the BPM.

Figure 3. Schematic of process for developing targeted therapeutic for psychiatric disorders

In order to develop novel treatments for patients with psychiatric disorders such as bipolar disorder, a greater understanding of the neural mechanisms underlying the disorder is required. Initially, clinical behavioral observations can be quantified using behavioral tools. If tools with translational relevance are used, animal studies assessing mechanisms underlying these behaviors can be conducted. Moreover, in combination with the etiology/mechanisms of the disorder, model organisms targeted at these mechanisms will have increased relevance to these abnormal behaviors. These model organisms could then be tested in similar translational tests to confirm the mechanistic relevance of manipulating these organisms. If confirmed, such findings would then support more invasive and costly techniques such as positron emission tomography (PET) to confirm *in vivo* relevance of altered mechanisms linked to that behavior. Meanwhile, compounds targeting that mechanism can be developed. These compounds could then be combined with behavioral testing in conjunction with biomarkers to confirm target efficacy. These studies can be first conducted in healthy subjects, particularly if behavioral effects in normal animals are observed, then moved into the patient population. Finally, once target engagement is demonstrated, the compound can be tested in large clinical trials required for evidence for treatment efficacy. \$ denotes the time and funding required for each aspect of this schematic. Because studies on biomarker confirmation/compound testing in humans are so expensive, generating evidence for target relevance using model organisms would greatly reduce the cost, effort, and burden on patients.

Table 1

Observations from studies focusing on exploratory behavior across patients with bipolar disorder and animal models.

Humans	Paradigm	Manipulations	Observations	References
BD manic / euthymic	BPM		↑ activity, ↑ exploration, ↓ circumscribed	Perry et al., 2009; Henry et al., 2013
BD manic	BPM	Environmental familiarity; chronic treatment	↓ exploration over time	Minassian et al., 2011
BD		Stimulant treatment	mania / hypomania	Wingo et al., 2008
BD manic / depressed		AMPT treatment	↓ manic symptoms; ↑ depression	Brodie et al., 1971; Bunney et al., 1971
BD		AMPT treatment cessation	↑ hypomanic relapses	Anand et al., 1999
Rodents				
Mice	BPM	Amphetamine	↑ activity, ↔ exploration, ↓ circumscribed	Perry et al., 2009
Mice	BPM	DAT KD; GBR12909; modafinil	↑ activity, ↑ exploration, ↓ circumscribed	Perry et al., 2009; Young et al., 2010a; 2011a
DAT KD mice / GBR12909	BPM	Environmental familiarity; stimulant treatment	↓ exploration; hypersensitivity	Young et al., 2010b
Mice		DAT KD; acute valproate	↓ hyperactivity	Ralph-Williams et al., 2003
Mice		GBR12909; acute valproate	↔ hyperactivity	Douma et al., 2011
DAT KD / GBR-treated mice	BPM	Chronic valproate in chow	↓ hyperactivity	Van Enkhuizen et al., 2013c
DAT KD mice	BPM	Sub-chronic AMPT	↓ hyperactivity, ↓ disordered organization, ↑ exploration	Van Enkhuizen et al., 2014a
Mice		DAT KO	↑ activity, ↓ exploration, ↓ circumscribed; attenuated by D ₁ antagonist; ↓ activity by stimulant	Ralph et al., 2001; Spielesoy et al., 2000; Trinh et al., 2003
Mice	BPM	<i>Clock</i> 19 mutation	↑ activity, ↑ exploration, ↑ circumscribed	Van Enkhuizen et al., 2013b
Mice	BPM	Serotonin agonism	↓ activity, ↓ exploration	Halberstadt et al., 2011

BD = bipolar disorder, BPM = behavioral pattern monitor, AMPT = alpha-methyl-para-tyrosine, DAT = dopamine transporter, KD = knockdown, KO = knockout, ↑ = increased, ↓ = decreased, ↔ = no effect

Table 2

Observations from sensorimotor gating studies assessing prepulse inhibition across patients with bipolar disorder and animal models.

Humans	Manipulations	Observations	References
BD manic; remitted BD, relatives of BD; male euthymic BD		↓ PPI	Perry et al., 2001; Giakoumaki et al., 2007; Gogos et al., 2009
Remitted adult / pediatric BD		↔ PPI	Barret et al., 2005; Rich et al., 2005
Mixed episode BD; female euthymic		↔ PPI	Carrol et al., 2007; Gogos et al., 2009
Unipolar depressed		↔ PPI	Perry et al., 2004; Quednow et al., 2006
Healthy subjects	COMT polymorphism (Val allele)	↓ PPI	Quednow et al., 2009
Rodents			
Mice	DA agonists; modafinil	↓ PPI, blocked by D ₂ antagonist haloperidol	Geyer et al., 2001; Kwek et al., 2013
Mice	GBR12909	↓ PPI	Kwek et al., 2013
Rats	Amphetamine	↓ PPI; attenuated by lithium	Zheng et al., 2013
Rats	Topiramate, haloperidol, clozapine	↑ PPI	Frau et al., 2007
Rats	DA agonist apomorphine	↓ PPI; attenuated by topiramate, asenapine, valproate, carbamazepine, lithium	Frau et al., 2007; Marston et al., 2009; Umeda et al., 2006
Mice	DAT KO	↓ PPI, attenuated by D ₂ antagonist raclopride, clozapine, quetiapine	Powell et al., 2008
Mice	DAT KD	↔ PPI; ↓ PPI	Ralph-Williams et al., 2003; Van Enkhuizen et al., Accepted
Mice	22q11 mutation	↓ PPI	Paylor et al., 2006
Mice	GCLM KO	↓ PPI	Kulak et al., 2012
Mice	Ncan KO	↓ PPI, attenuated by lithium	Miro et al., 2012
Mice	Overexpressing CRF	↓ PPI, attenuated by valproate	T. et al., 2014
Mice	Na ⁺ , K ⁺ -ATPase α3 mutation	↓ PPI	Kirshenbaum et al., 2012
Mice	<i>Clock</i> 19 mutation	↓ PPI	Van Enkhuizen et al., 2013b

BD = bipolar disorder, PPI = prepulse inhibition, COMT = catechol-O-methyl transferase, DA = dopamine, DAT = dopamine transporter, KO = knockout, KD = knockdown, GCLM = glutamate-cysteine-ligase modifier, CRF = corticotropin-releasing factor, ↑ = increased, ↓ = decreased, ↔ = no effect

Table 3

Observations from translational paradigms assessing cognitive behaviors across patients with bipolar disorder and animal models.

Humans	Paradigm	Manipulations	Observations	References
BD	CPT		↓ vigilance, ↓ inhibitory control	Bora et al., 2006; Harmer et al., 2002
BD	WCST, Stroop color and word test		↓ executive function	Martinez-Aran et al., 2004
BD	CVLT, WMS-R		↓ working memory	Martinez-Aran et al., 2004
BD	Single-session IGT		↓ risk-based decision-making	Adida et al., 2011; Ibanez et al., 2012; Van Enkhuizen et al., 2014d
Healthy subjects	5C-CPT	36 hour sleep deprivation	↓ vigilance	Van Enkhuizen et al., 2014b
Rodents				
Mice	Multiple-session IGT	DAT KD	↑ risk-preference, ↑ motivation, ↑ motor impulsivity	Young et al., 2011c
Mice	Multiple-session IGT	GBR12909, modafinil	↑ motivation, ↑ motor impulsivity, ↔↑ risk-preference	Van Enkhuizen et al., 2013a
Mice, rats	Multiple-session IGT	Amphetamine	↓ risk-preference, ↔ motor impulsivity, ↔ motivation	Van Enkhuizen et al., 2013a; Zeeb et al., 2009
Mice	Single-session IGT	DAT KD, GBR12909	↑ risk-preference; ↑ motivation; ↑ motor impulsivity	Van Enkhuizen et al., 2014d
Mice	5C-CPT	DAT KD	↓ vigilance	Young et al., In preparation
Mice	5C-CPT	36 hour sleep deprivation	↓ vigilance	Van Enkhuizen et al., 2014b

BD = bipolar disorder, CPT = continuous performance test, WCST = Wisconsin card sorting test, CVLT = California verbal learning test, WMS-R = Wechsler memory scale – revised, IGT = Iowa gambling task, 5C = 5-choice, DAT KD = dopamine transporter knockdown, ↑ = increased, ↓ = decreased, ↔ = no effect

Table 4

RDoC-relevant dimensions related to quantified behavior of bipolar mania patients and mice with reduced DAT functioning

Domain	Construct	Subconstruct	Quantification method
Positive Valence	Approach Motivation	Effort valuation / willingness to work	Progressive ratio
		Action selection / Preference-based decision making	Iowa Gambling Task
Cognitive	Cognitive Control	Response selection, inhibition or suppression	False Alarms in the 5C-CPT
	Perception	Auditory perception	Prepulse Inhibition
Arousal and Regulatory	Arousal	None	Vigilance measure in the 5C-CPT
			Activity in the BPM