

REVIEW

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Animal models for bipolar disorder: from bedside to the cage

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Abstract

Bipolar disorder is characterized by recurrent manic and depressive episodes. Patients suffering from this disorder experience dramatic mood swings with a wide variety of typical behavioral facets, affecting overall activity, energy, sexual behavior, sense of self, self-esteem, circadian rhythm, cognition, and increased risk for suicide. Effective treatment options are limited and diagnosis can be complicated. To overcome these obstacles, a better understanding of the neurobiology underlying bipolar disorder is needed. Animal models can be useful tools in understanding brain mechanisms associated with certain behavior. The following review discusses several pathological aspects of humans suffering from bipolar disorder and compares these findings with insights obtained from several animal models mimicking diverse facets of its symptomatology. Various sections of the review concentrate on specific topics that are relevant in human patients, namely circadian rhythms, neurotransmitters, focusing on the dopaminergic system, stressful environment, and the immune system. We then explain how these areas have been manipulated to create animal models for the disorder. Even though several approaches have been conducted, there is still a lack of adequate animal models for bipolar disorder. Specifically, most animal models mimic only mania or depression and only a few include the cyclical nature of the human condition. Future studies could therefore focus on modeling both episodes in the same animal model to also have the possibility to investigate the switch from mania-like behavior to depressive-like behavior and vice versa. The use of viral tools and a focus on circadian rhythms and the immune system might make the creation of such animal models possible.

Keywords: Translational, Human condition, Circadian rhythm, Dopamine, Immune system, Stress

Background

Bipolar disorder (BD) is characterized by recurrent episodes of manic and depressive states with intervening episodes of euthymia (normal mood) (Merikangas et al. 2007; Anderson et al. 2012; Phillips and Kupfer 2013). The symptomatology of BD is very heterogenic and heavily depends on the patient's state. Throughout manic episodes, people undergo euphoria, aggression, reduced need for sleep, high reward seeking, hypersexuality, and hyperactivity (Perry et al. 2010; Anderson et al. 2012; Cheniaux et al. 2014). In contrast, a state of depression includes anhedonia, increased sleep, reduced libido, feeling tired, and a greater risk of suicide among other symptoms (American Psychiatric Association 2013; Anderson

et al. 2012). In addition, BD patients suffer from various cognitive deficits (Martínez-Arán et al. 2004; Savitz et al. 2005; Burdick et al. 2007; Goodwin et al. 2008). Established treatments for BD include mood stabilizers, such as lithium, anticonvulsants, like valproate, and antipsychotics. Current treatments, however, are not able to completely stabilize behavioral aberrations or to recover cognitive deficits (Grunze et al. 2013; van Enkhuizen et al. 2015a). Lithium, the first line medication for BD, is furthermore suspected to cause negative side effects, including cognitive impairment (Pachet and Wisniewski 2003; Holmes et al. 2008; Grunze et al. 2013). Besides the lack of novel developed therapeutics (Mallesman et al. 2009), current clinical criteria fail to diagnose milder symptoms of BD and therefore it can take years to finally diagnose this psychiatric disorder (Merikangas et al. 2011). Improvement of treatment and diagnosis options is crucial, particular given the high rate of

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suicide attempts in patients with BD (Novick et al. 2010). A better understanding of cause and pathophysiology of the disease is needed to archive these improvements. Adequate animal models for BD will provide a useful tool to advance the knowledge on the underlying neurobiology of BD. Establishing animal models for psychiatric disorders, however, is a difficult task (Malkesman et al. 2009). Not only are the symptoms in patients with one disorder often quite broad and variable between patients, some symptoms used to diagnose psychiatric disorders in humans are not even possible to assess in animals, such as feelings of worthlessness or guilt (Malkoff-Schwartz et al. 1998; Nestler and Hyman 2010). Given its cyclical nature, BD is thereby especially hard to model (Gould and Einat 2007, 2014). So far BD is mainly investigated in separated animal models for either mania or depression (Einat 2014; van Enkhuizen et al. 2015a). The animal models mostly mimic some behavioral characteristics of BD, which are more or less easy to measure, such as overall locomotor activity, sexual behavior, aggression, risk taking, and decision making (Einat 2014; van Enkhuizen et al. 2015a; Harrison et al. 2016; Sharma et al. 2016). An animal model of BD in rodents, which models the whole complexity of symptoms, might never be possible. Nonetheless, it is still crucial to create and characterize new models for BD, which consistently tighten the gap between human pathophysiology and BD-like symptoms in animals. Animal models are an indispensable tool and a critical component in the preclinical research field. They allow developing new treatment and diagnosis options and therewith improving the lives of BD patients and can therefore not be replaced. Ideally, an adequate animal model of BD should include elements of the three axes of validity: face, predictive, and construct validity. Face validity indicates to which extent the model reflects characteristics of the human disease. Predictive validity refers to which degree the model will respond to an efficient treatment in humans. Construct validity reflects to which extent the model measures what it claims to be measuring (Einat 2014; Malkesman et al. 2009). The ideal animal model should therefore comply with the following requirements: (i) model BD-specific behavioral abnormalities with ideally all its facets; (ii) consider the cyclical nature of BD; (iii) be able to spontaneously switch between both episodes (all face validity); (iv) respond to current established treatment; and (v) due to the fact that not all BD patients respond to medications (Cipriani et al. 2011), reflect a distribution of responders and nonresponders (both predictive validity) (Einat 2014). This division would represent the result of clinical trials and therefore a group effect of treatment should still be observed. Additional prior determination of individual, untreated baseline measurements will be required

to compare intra-individual differences before and after treatment of the animals to later successfully separate responders from nonresponders. It should furthermore (vi) be affected by pharmacological, environmental, or genetically manipulations in regard to the same mechanisms that are involved in human patients (face validity).

To date, no such animal model for BD exists. However, within the last couple of years several models were able to at least address some of the above-mentioned requirements and have therewith been able to improve our understanding of the neurobiology underlying BD. In this review, we will discuss various aspects that are affected in patients with BD, namely circadian rhythm, neurotransmitters focusing on the dopaminergic system, environment, and immune system. Disruptions and influences regarding these topics in patients will be compared to findings in animal models and we will illustrate how these findings have been used to develop animal models for the disorder.

Circadian rhythm

Aberrations of the sleep–wake cycle and circadian rhythms belong to primary symptoms of patients suffering from BD and are used as diagnostic criteria (Gonzalez 2014; Kripke et al. 2009; McCarthy and Welsh 2012; Wirz-Justice 2006). Patients display irregularities in daily biological rhythms including sleep, activity, body temperature, hormonal secretions, cell regeneration, and eating behavior (Bunney and Potkin 2008; Goetze and Tölle 1987; McClung 2007; Salvatore and Tohen 2007; Souetre et al. 1988; Takahashi et al. 2008). In addition, psychotherapeutic treatment (interpersonal and social rhythm therapy) with the aim of stabilizing and structuring daily routines and thereby enabling a normalized sleep–wake cycle is an effective therapeutic tool for mood stabilization and can reduce the number of manic and depressive episodes (Frank et al. 2000, 2007; Miklowitz et al. 2007). At the same time, mania can be induced by disruption of circadian rhythms (Bunney and Bunney 2000; McClung 2013). Circadian disruptions present in humans suffering from BD suggest an involvement of circadian clock genes in the pathogenesis of the disease (Cosgrove et al. 2016; Etain et al. 2011; Wirz-Justice 2006; McClung 2007; Frank et al. 2000). Indeed, BD symptoms are correlated with disruptions of the circadian rhythm and associated with a polymorphism of the *circadian locomotor output cycles kaput (Clock)* gene (Benedetti et al. 2003; Logan and McClung 2016; Serretti et al. 2003).

Targeting circadian rhythm genes to disrupt mechanisms regulating the circadian rhythm has been widely used to create animal models for BD (McClung et al. 2005; Mukherjee et al. 2010; Roybal et al. 2007). The master pacemaker of the circadian rhythm is localized

in the suprachiasmatic nuclei and interconnects a complex network of transcriptional–translational activation and repression, resulting in an oscillating expression of clock genes over a period of 24 h (Takahashi et al. 2008). Several diverse preparations of *Clock* manipulation were used as animal models to study BD. The most common model is the *Clock* Δ 19 mutant mouse. These mice carry a deletion at exon 19 of the *Clock* gene, resulting in a dominant-negative protein, unable to activate transcription (King et al. 1997). Mutant mice exhibit mania-like behavior (Roybal et al. 2007) and altered sleep patterns (McClung 2013). The disruption of CLOCK resulted in lower immobility in the forced swim test, a greater preference for rewarding stimuli, such as sucrose solution and cocaine, a lower threshold within intra-cranial self-stimulation at lower drug doses, lowered anxiety levels, and less depressive-like behavior (McClung et al. 2005; Roybal et al. 2007). In addition, the *Clock* mutant mice exhibited deficits within the paired pulse inhibition paradigm (van Enkhuizen et al. 2013b). *Clock* Δ 19 mutant mice were also tested in the behavioral pattern monitor (BPM), a test to pattern and level of locomotor activity, exploratory behavior, and novelty seeking in humans and rodents (Perry et al. 2009; Young et al. 2007). While BD patients show increased exploration and goal-directed behavior, illustrated through linear and direct movements (Logan and McClung 2016; Minassian et al. 2011; Perry et al. 2009, 2010), the *Clock* Δ 19 mutant mice do not represent this specific exploration and goal-directed behavior. They exhibit more circumscribed, small-scale movements (Perry et al. 2009; van Enkhuizen et al. 2013b). In summary, the *Clock* Δ 19 mutant mice resemble various but not all behavioral aspects of BD mania in humans to its full extent. Another manipulation of *Clock*, which resulted in BD-relevant behavior, is the knock-down of CLOCK specifically in the ventral tegmental area (VTA) of mice (Mukherjee et al. 2010). The knock-down of *Clock* expression resulted in abnormal circadian rhythms, indicated by less robust activity in dark phases and enhanced activity in resting phases, less anxiety behavior, and increased locomotor activity in a novel environment. Despite the observed hyperactivity in a novel environment, the overall locomotor activity over a period of 24 h, however, was reduced (Mukherjee et al. 2010). In contrast to the previously observed less-depression-like behavior of the *Clock* Δ 19 mutant mice (Roybal et al. 2007), the CLOCK knock-down mice exhibited increased depression-like behavior in the forced swim and learned helplessness test and thereby express a mixed state of mania- and depression-like behavior (Mukherjee et al. 2010). Mukherjee and colleagues postulated, therefore, that CLOCK's functioning in the VTA is required for the regulation of mood-related behavior. This

hypothesis is supported by the fact that over-expression of CLOCK in the VTA reduces hyperactivity and restores anxiety-related behavior almost to wild-type level in the *Clock* Δ 19 mutant mice (Roybal et al. 2007). Disrupted circadian rhythm in these animal models might create a vulnerable state with a greater sensitivity for addiction and mood disorders (Logan et al. 2014; Logan and McClung 2016). Commonly found in both *Clock* mice models is an enhanced dopamine (DA) release from neurons in the VTA, which is reflected, for example, in an increased dopaminergic cell firing rate (Coque et al. 2011; McClung et al. 2005; Mukherjee et al. 2010; Roybal et al. 2007). This functional linkage between the dopaminergic system (see “Dopaminergic pathways”) and aberrant circadian rhythms connects two major pathways, which may be involved in the pathogenesis of BD and are often used as targets for the development of genetic or environmental animal models for BD. This involvement of the dopaminergic system supports the dopamine hypothesis (Berk et al. 2007) that hyper-dopaminergic transmission might be responsible for mania in humans and therefore also for mania-like behavior in animals.

Chronic lithium treatment was able to normalize various aspects of aberrant behavior in the *Clock* Δ 19 mutant mice (Coque et al. 2011; Roybal et al. 2007). Lithium's therapeutic efficacy might be due to its properties to lengthen the circadian period, which was observed across several species (Klemfuss 1992; Kripke et al. 1978). One well-studied potential target of lithium's action is the inhibition of glycogen synthase kinase-3 beta (GSK-3 β) (Klein and Melton 1996; Serretti et al. 2009; but see also Agam and Azab 2016). GSK-3 β is involved in various cell functions, like gene transcription, neurogenesis, and apoptosis (Doble and Woodgett 2003). GSK-3 β is also able to regulate the circadian clock through phosphorylation of CLOCK and nuclear receptor subfamily1, group D, member1 (REV-ERB α) (Bellet and Sassone-Corsi 2010; Besing et al. 2015; Martinek et al. 2001; Yin et al. 2006) and thereby modulates the circadian rhythm (Besing et al. 2015). Synthetic inhibition of GSK-3 β was able to mimic the effects of lithium and to prevent mania-like behavior, such as amphetamine-induced hyperactivity, in male C57BL/6J mice (Kozikowski et al. 2007). In addition, *gsk-3 β* haploinsufficient mutant mice, lacking one copy of the gene coding for GSK-3 β , show the same behavioral effects as lithium-treated mice (O'Brien et al. 2004). *gsk-3 β* haploinsufficiency reduces exploratory behavior and immobility time in the forced swim test, comparable to treatment with lithium in wild-type mice, without affecting overall activity (O'Brien et al. 2004). Both manipulations of GSK-3 β suggest that lithium's therapeutic effect as a mood stabilizer depends on inhibiting GSK-3 β activity (O'Brien et al. 2011). Once again a manipulation

of the circadian rhythm through transgenic mice over-expressing GSK-3 β resulted in mania-like behavior (Prickaerts et al. 2006). The GSK-3 β over-expressing mice exhibited hyperactivity, reduced immobility in the forced swim test, reduced habituation in the open field test, and increased acoustic startle response (Prickaerts et al. 2006). Patients in manic episodes opposingly exhibit reduced startle responses (Perry et al. 2001). Due to the nonspecific alterations of the dopaminergic system in the GSK-3 β over-expressing mice, which are also recognizable in other psychiatric disorders, such as schizophrenia and attention-deficit hyperactivity disorder (ADHD), this animal model, however, lacks specificity for mania (Sharma et al. 2016).

An additional target of the circadian rhythm, which can be used to model BD-relevant behavior, is the extracellular-signal-regulated kinase (ERK) (Engel et al. 2008). The ERK pathway mediates proliferation, differentiation, and plasticity of neurons in the central nervous system (Thomas and Huganir 2004). ERKs are also involved in resetting the master pacemaker in the suprachiasmatic nucleus via photic input (Butcher et al. 2002; Coogan and Piggins 2004). Infusion of ERK inhibitor into the suprachiasmatic nucleus of mice prevents the activity rhythms shift, which is usually observed between light and dark phases (Butcher et al. 2002). A knock-out of the gene coding for ERK1 resulted in hyperactivity, enhanced goal-directed activity, increased risk taking or impulsivity, and increased reward-motivated behavior (Engel et al. 2008). In addition, the ERK1 pathway can be activated by lithium and valproate, but only valproate, not lithium, was able to reduce the behavioral abnormalities (Engel et al. 2008). The ERK pathway can in turn be activated by neurotrophins. One of these neurotrophins might play a role in the pathophysiology of BD, namely the brain-derived neurotrophic factor (BDNF) (Frey et al. 2013; Södersten et al. 2014). *BDNF* haploinsufficient mice indeed exhibit mania-like behavior, including hyperactivity, increased aggressive behavior, and appetite (Kernie et al. 2000; Lyons et al. 1999). Interestingly, even untreated *BDNF* haploinsufficient mice show reduced hippocampal volume and their CA3 dendritic arborizations resembled stressed wild-type mice, suggesting a role of BDNF in hippocampal dendritic remodeling (Magariños et al. 2011).

One downstream target of the ERK signaling pathway is B-cell lymphoma 2 (Bcl-2), which is involved in neuronal development, plasticity, and degeneration (Akhtar et al. 2004) through inhibition of apoptosis (Bold et al. 1999; Campani et al. 2001). Interestingly, lithium affects the Bcl-2 levels, with chronic lithium treatment increasing Bcl-2 levels in the brain of rats (Chen et al. 1999; Manji et al. 2000). Consistent with this effect of lithium is that transgenic over-expression of Bcl-2 in mice prevents

neuronal death (Bonfanti et al. 1996) and acts protective against deleterious stress-induced neuronal endangerment (DeVries et al. 2001). Although BD is rather associated with neuroplasticity deficits than neurodegenerative events (Rajkowska 2002), cell death might play a role in the pathogenesis of BD (Lee et al. 2002). Bcl-2 manipulation might also be related to anxiety as mice with an additional *Bcl-2* transgene, and therefore elevated Bcl-2 levels, exhibited less anxiety behavior (Rondi-Reig et al. 1997; Rondi-Reig and Mariani 2002). On the other hand, mice with a heterozygous knock-out of the *Bcl-2* gene exhibit Bcl-2 deficiency and increased anxiety behavior (Einat et al. 2005). In addition, Bcl-2 heterozygous knock-out mice show some behaviors similar to mania, including increased reward seeking and amphetamine sensitization, and lithium pretreatment attenuated sensitization in these animals (Lien et al. 2008).

Another gene heavily involved in the regulation of circadian rhythms is *Dbp*. It encodes for the albumin D element-binding protein, a transcription factor that is regulated by the CLOCK protein (Ripperger et al. 2000; Wuarin et al. 1992). *Dbp* expression is affected in patients with BD and can furthermore be influenced by lithium treatment (Kittel-Schneider et al. 2015). A heterozygous knock-out of DBP in mice induces a depressive-like phenotype indicated by reduced locomotor activity and diminished response to amphetamine. When exposed to environmental stress (see “[Environment: stressors](#)”), DBP knock-out mice show a switch in behavior and become hyperactive. This switch, which to some extent resembles the switch from depression to mania in BD patients, can be prevented by the administration of valproate (Le-Niculescu et al. 2008).

But even stressors alone (e.g., sleep deprivation) can disrupt the circadian clock resulting in changes of mood and even the induction of mania in BD patients (Colombo et al. 1999; Malkoff-Schwartz et al. 1998; Wright 1993). It is therefore possible that sleep deprivation paradigms can induce mania-like behavior in rodents. Indeed, wild-type rats after typically 72 h of sleep deprivation exhibited mania-like behavior, such as enhanced aggressive behavior and hypersexuality (Gessa et al. 1995; Hicks et al. 1979; Morden et al. 1968). But this behavioral phenotype lasted only for about 30 min. In addition, chronic lithium can reverse the mania-like behavior (Gessa et al. 1995). However, it should be noted that the disruption of regular sleep requires the usage of techniques that cause additional stress (i.e., immobilization, isolation, and the fear and experience of falling into water) (Logan and McClung 2016). Benedetti and colleagues used an improved protocol to minimize these additional stressors and still found mania-like behavior, such as increased locomotor activity and aggressive behavior (Benedetti et al. 2008). These

results indicate that sleep deprivation alone is a sufficient stressor to induce BD-relevant behavior.

An additional possibility to affect the sleep–wake cycle is the high-frequency stimulation of the lateral hypothalamus, which resulted in mania-like behavior in rats (Abulseoud et al. 2014). The hypothalamic stimulated rats exhibited hyperactivity, such as increased grooming, and reduced resting phases, as well as hypersexuality, i.e., increased rearing and sexual self-stimulation. These behavioral characteristics could be attenuated through chronic lithium treatment.

Apart from the cycle of day and night, the changing of seasons and the associated photoperiod length can trigger changes in mood (Young and Dulcis 2015). Indeed, a seasonal pattern of the episodes of BD was identified in a proportion of patients (Schaffer et al. 2003), whereas depressive symptoms are more prevalent during winter months (Meesters and Gordijn 2016; Rosenthal et al. 1984). This seasonal effect might be due to shortening or lengthening of the day-lengths and the associated received illumination. Modified illumination in rats induced a switch in neurotransmitter expression. A long day period of 19 h of light resulted in a switch from DA to somatostatin expression in hypothalamic neurons after 1 week. The contrary effect was observed with a short day period of 5 h light (Dulcis et al. 2013). In addition, a matching pattern of receptor expression was observed: an increased expression of postsynaptic dopamine D2 receptors (D2R) was accompanied by the presynaptic increase in dopaminergic interneurons (Dulcis et al. 2013). Rats in the long day period exhibited more anxiety behavior in the elevated plus maze and more depressive-like behavior measured by increased immobile time in the forced swim test, whereas animals in the short day period displayed decreased anxiety-related behavior and less immobile time (Dulcis et al. 2013).

Disruption of the circadian rhythms has been widely used to induce BD-like behavior, mainly mania-like behavior (Table 1). Here it is to consider that the manipulations have been mainly conducted in nocturnal animals and results might not be comparable to mechanisms in diurnal humans (Challet 2007). Using diurnal rodent animal models could be beneficial in this field of research (Ashkenazy et al. 2009; Bilu et al. 2016; Einat et al. 2006; Leach et al. 2013). Nevertheless, effects are quite robust as various disruptions of one gene (i.e., *Clock*) as well as targeting related pathways or environmentally influence sleeping behavior result in similar effects (McClung et al. 2005; Mukherjee et al. 2010; Prickaerts et al. 2006; Roybal et al. 2007). Observations of depressive-like behavior after manipulations of circadian rhythms are rare. We see mixed behavior, some aspects of mania- and at the same time depressive-like behavior, in the *ClockΔ19* mutant

mouse (Mukherjee et al. 2010). Similarly, manipulation of *Bcl-2*, a gene that has indirect connections with circadian rhythm pathways, can induce both behavioral states (Lien et al. 2008). Here it is important to note that elevated levels of *Bcl-2* are associated with decreased anxiety (Rondi-Reig et al. 1997; Rondi-Reig and Mariani 2002), while *Bcl-2* deficiency increases anxiety (Einat et al. 2005). The most promising model in terms of the cyclic characteristic of BD is the manipulation of length of day. Here we see depressive-like behavior when extending the day period and (at least) less depressive-like behavior when decreasing the day period (Dulcis et al. 2013).

Sensitization models and neurotransmitters in general

Nearly 100 years ago, Kraepelin made the observation that with an increasing number of episodes the course of the illness worsens, the so-called sensitization model of BD (Kraepelin 1909; Post 1992). Later on behavioral sensitization to psychostimulants in rodents was used to resemble the shortening of interepisodic intervals during the progression of BD in humans (Post 1990). Repeated administration of the same dose of cocaine induced hyperactivity and elevated stereotypy responses in rats (Kilbey and Ellinwood 1977; Post 1990). A drug-high state after the administration of psychostimulants was furthermore associated with increased aggression (Borison et al. 1978; Davies et al. 1974), a declined cognitive performance (Fries et al. 2015; Rygula et al. 2015) and deficits in prepulse inhibition (PPI) (Zheng et al. 2013). Several different psychostimulants were administered to induce mania-like behavior. Apart from cocaine, the used substances were amphetamine (Frey et al. 2006), lisdexamfetamine dimesylate (Macêdo et al. 2013), and fenproporex in rats (Rezin et al. 2014), and alpha-lipoid acid (Macêdo et al. 2012) and GBR12909 in mice (Queiroz et al. 2015). All these substances resulted in mania-like behavior, which could be attenuated by mood stabilizers like valproate or lithium (Sharma et al. 2016).

Withdrawal from psychostimulants is accompanied by depressive-like behavior or at least an anhedonic state measured as reduced sexual behavior (Barr et al. 1999), elevated thresholds in self-stimulation (Markou and Koob 1991; Wise and Munn 1995), reduced activity (Paulson et al. 1991), decreased sucrose consumption (Barr and Phillips 1999), increased negative contrast (Barr and Phillips 2002), and increased anxiety (Mutschler and Miczek 1998). Immobility time in the forced swim test, however, depends on the administered doses of amphetamine as well as the training procedure and was reported to be reduced during amphetamine withdrawal (Schindler et al. 1994) but also to be increased (Marszalek-Grabska et al. 2016). Withdrawal furthermore induces supersensitivity of serotonergic neurons (Baumann and

Table 1 Summary of manipulable risk factors for BD and their influence on BD-relevant behavior

Manipulation	BD-relevant behavior	Neurobiology	References
<i>Circadian rhythm</i> <i>ClockΔ19</i> mutant mice	Hyperactivity Altered sleep pattern Greater preference for rewarding stimuli Decreased anxiety behavior Less depressive-like behavior Impaired PPI Abnormal circadian rhythms Less anxiety	Altered sleep pattern Enhanced DA release	(Coque et al. 2011; van Enkhuizen et al. 2013b; McClung 2013; McClung et al. 2005; Mukherjee et al. 2010; Roybal et al. 2007)
CLOCK knock-down mice	Hyperactivity in novel environment but decreased overall hyperactivity Increased depression-like behavior and helplessness		
GSK-3β haploinsufficient mutant mice	Reduced exploration Less helplessness Normal overall activity	Affect gene transcription, neurogenesis, and apoptosis	(Besing et al. 2015; O'Brien et al. 2004, 2011; Prickaerts et al. 2006)
GSK-3β over-expression mice	Hyperactivity Less helplessness Reduced habituation Increased acoustic startle response	Alterations of dopaminergic system	
ERK1 knock-out mice	Hyperactivity Enhanced goal-directed activity Increased risk taking and impulsivity Increased reward seeking	Shift of activity rhythm	(Engel et al. 2008)
BDNF haploinsufficient mutant mice	Hyperactivity Increased aggression Elevated appetite	Decreased BDNF level following DA overactivity	(Kernie et al. 2000; Lyons et al. 1999; Magariños et al. 2011)
Bcl-2 heterozygous knock-out mice	Increased anxiety Increased reward seeking Increased amphetamine sensitization	Decreased hippocampal volume CA3 dendritic arborizations resemble stressed wild-type mice Decreased <i>Bcl-2</i> level	(DeVries et al. 2001; Einat et al. 2005; Lien et al. 2008; Rondi-Reig et al. 1997; Rondi-Reig and Mariani 2002)
DBP heterozygous knock-out mice	Hypoactivity Diminished response to amphetamine Environmental stress induce hyperactivity	Acts protective against deleterious stress-induced neuronal endangerment	(Le-Niculescu et al. 2008)

Table 1 continued

Manipulation	BD-relevant behavior	Neurobiology	References
Sleep deprivation	Hyperactivity Increased aggression Increased exploratory behavior Hypersexuality Hyperactivity Increased grooming Hypersexuality Reduced resting phases Anxiety behavior Helplessness	Affects sleep–wake cycle	(Benedetti et al. 2008; Gessa et al. 1995; Hicks et al. 1979; Malkoff-Schwartz et al. 1998; Morden et al. 1968) (Abulseoud et al. 2015; Abulseoud et al. 2014)
High-frequency stimulation of the lateral hypothalamus			
Photoperiod lengths		Neurotransmitter switching (DA ↔ somatostatin)	(Dulcis et al. 2013)
<i>Sensitization models</i>			
Administration of psychostimulants (amphetamine, cocaine)	Hyperactivity Increased aggression Stereotypes Increased hedonic behavior Disturbed sleep–wake cycle Declined cognitive performance Deficient PPI response	Increased synaptic DA and NE levels Disturbance of homeostatic mechanisms Alterations in BDNF level	(Borison et al. 1978; Davies et al. 1974; Frey et al. 2006; Fries et al. 2015; Gould et al. 2001; Kilbey and Ellinwood 1977; Macêdo et al. 2012, 2013; Post 1992; Post 1990; Queiroz et al. 2015; Rezin et al. 2014; Rygula et al. 2015; Seiden et al. 1993; Zheng et al. 2013)
Withdrawal following chronically psychostimulant administration	Hypoactivation Increased anxiety Anhedonia Increased negative contrast Decreased motivation	Supersensitivity of serotonergic neurons a decrease in NE Reduced DA responsiveness	(Barr et al. 1999; Barr and Phillips 1999, 2002; Baumann and Rothman 1998; Markou and Koob 1991; Marszalek-Grabaska et al. 2016; Mutschler and Miczek 1998; Paulson et al. 1991; Schindler et al. 1994; Schwartz et al. 1982; Wise and Munn 1995)
<i>Dopaminergic pathways</i>			
Increased D1R expression in the prefrontal cortex	Increased impulsivity Increased sexual behavior Hedonic behavior Addictive behavior	Decreased D2R in nucleus accumbens	(Freund et al. 2016; Sonntag et al. 2014)
Termination of previous D1R over-expression	Hypoactivity Anhedonic behavior Helplessness	Increased CREB in nucleus accumbens	(Freund et al. 2016)

Table 1 continued

Manipulation	BD-relevant behavior	Neurobiology	References
DAT knock-down mice	Hyperactivity in novel environments Increased risk behavior Hyperexploratory behavior Less anxiety Impaired decision making with a preference for high reward combined with high risk	Hyperdopaminergia	(Dulcis et al. 2013; van Enkhuizen et al. 2014b; van Enkhuizen et al. 2014a; Giros et al. 1996; Ralph et al. 2001; Ralph-Williams et al. 2003; Young et al. 2010, 2011; Zhuang et al. 2001)
DAT knock-out mice	Hyperactivity Sensorimotor deficits within PPI		
GluR6 knock-out mice	Hyperactivity Increased risk taking Elevated aggression Heightened responsivity to amphetamine Less anxiety		(Shaltiel et al. 2008)
<i>Environmental stressors</i>			
Prenatal stress	Hyperactivity in novel environment Hypersensitivity to amphetamine Anhedonia Increased helplessness Increased anxiety Impaired cognition including working memory deficits Decreased exploratory behavior	Incomplete development of hippocampus and reduced weight of the prefrontal cortex and nucleus accumbens Alterations in HPA axis and neurotransmitter levels in early development Reduced BDNF levels Decreased Bcl-2 level Diminished neurogenesis Increased mGluR1 and mGluR2 Altered immune system Stimulating dopaminergic transmission	(Clarke and Schneider 1993; Coe et al. 2003; Diz-Chaves et al. 2012; Fatima et al. 2017; Frye and Wawrzycki 2003; Guan et al. 2013; Hao et al. 2010; Jia et al. 2015; Koehl et al. 1999; Lemaire et al. 2000; Lin et al. 2012; Lin and Wang 2014; Uno et al. 1990; Wakshlak and Weinstock 1990)
Postnatal stress	Social withdrawal Hypoactivity Increased stereotypes Increased anxiety behavior Heightened response to acute stressor Elevated PPI response	Hippocampal development, memory, spatial and social learning, response to stress of the HPA axis Decreased BDNF level Neuronal atrophy Stimulating dopaminergic transmission	(Caldji et al. 2000b; Duman et al. 2016; Duman and Monteggia 2006; Huot et al. 2002; Huot et al. 2001; Kalinichev et al. 2002; Ladd et al. 2000, 2004; Lippmann et al. 2007; Magariños et al. 2011; McIntosh et al. 1999; Wigger and Neumann 1999)

Table 1 continued

Manipulation	BD-relevant behavior	Neurobiology	References
Chronic stress (through, e.g., repeated social defeat)	Depressive-like behavior Hypoactivity Reduced exploration Reduced aggression Hyposexuality Elevated anxiety Submissive behavior Social avoidance	Disrupted circadian rhythms and immune function	(Berton et al. 1998; Crawford et al. 2013; Hollis et al. 2010; Hollis and Kabbaj 2014; Leuner et al. 2014; Maier and Seligman 1976; Meerlo et al. 1996; Porsolt et al. 1977; Ruis et al. 1999; Steru et al. 1985; Tidey and Miczek 1997; Tomatzky and Miczek 1993; Wulsin et al. 2016)
<i>Immune system</i>			
Maternal immune activation	Increased locomotor response to amphetamine Increased repetitive and stereotypic behavior Increased anxiety Helplessness Disrupted sensorimotor gating Impaired working memory	Increased inflammation Increased striatal DA release	(Bakos et al. 2004; Cotter et al. 1995; Eßlinger et al. 2016; Fernández de Cossío et al. 2017; Kneeland and Fatemi 2013; Meyer et al. 2005; Remus and Dantzer 2016; Ronovsky et al. 2017; Rose et al. 2017; Shi et al. 2003; Wachholz et al. 2017; Zuckerman et al. 2003)

Rothman 1998), a transient decrease in norepinephrine (NE) in the hypothalamus, and a reduction in responsiveness to amphetamine in terms of DA concentrations in caudate-putamen and nucleus accumbens (Paulson et al. 1991). Even a switch in behavior has been shown in the same animal model. Anhedonic symptoms after withdrawal stabilize after a while (Paulson et al. 1991; Wise and Munn 1995). Morphine pretreated rats, furthermore, show a switch in β -endorphin-induced locomotor activity from being hyper-responsive to hypo-responsive when going through withdrawal (Schwartz et al. 1982).

The administration of psychostimulants affects several neurotransmitter systems which is in line with the fact that a number of neurotransmitters are affected in patients with BD (Barchas and Altemus 1999; Schildkraut 1965). Similarly, other pathways, e.g., the phosphoinositide cycle have been reported to be involved in BD and are targeted by treatment options for the disorder (Agam et al. 2002). A comprehensive overview of all these neurotransmitters and pathways would go beyond the scope of this review; therefore, we will give a brief overview on neurotransmitters and then focus on the dopaminergic system in “[Dopaminergic pathways](#).”

The cholinergic system seems to be predominantly involved in depressive-like symptoms in humans and animals. Manipulation of the cholinergic system through administration of arecoline, a direct agonist of cholinergic receptors, induced depression in both healthy controls and unmedicated euthymic BD patients (Nurnberger et al. 1983). Furthermore, affective disorder patients undergo exaggerated depressive responses to cholinergic agents compared to control groups. This hypersensitivity to cholinergic manipulations supports the hypothesis of a cholinergic imbalance during depressive episodes (van Enkhuizen et al. 2015b; Janowsky et al. 1994). Further evidence for the involvement of acetylcholine in BD comes from neuroimaging studies, where physostigmine, a cholinesterase inhibitor, resulted in elevated acetylcholine levels in the brain, counteracted mania, and induced depressive-like symptoms in both control and patients with affective disorders (Hannestad et al. 2013; Janowsky et al. 1972; Janowsky et al. 1974). Also reduced β_2 nicotinic acetylcholine receptor availability was observed in depressed BD patients compared to healthy and euthymic individuals (Hannestad et al. 2013). The brains of depressed patients contain elevated levels of choline, the precursor of acetylcholine (Steingard et al. 2000), supporting a hypercholinergic state during depressive episodes (van Enkhuizen et al. 2015b).

Animal models confirm the involvement of the cholinergic system in depression. The $\alpha 7$ nicotinic acetylcholine receptor agonist SSR180711 shows antidepressant-like effects in mice, indicated by reduced immobility time in

the forced swim test (Andreasen et al. 2012). Interestingly, behaviorally effective doses of SSR180711 inhibited in part the serotonin reuptake (Andreasen et al. 2012). Another subtype-selective nicotinic acetylcholine receptor agonist acts antidepressant-like by reversing the escape deficits in the learned helplessness paradigm in rats (Ferguson et al. 2000). Furthermore, nicotine attenuates anhedonia-like behavior in rats (Andreasen et al. 2011) and depressive-like behavior in mice (Andreasen and Redrobe 2009). The withdrawal of chronic nicotine administration induces depressive-like behavior in mice, measured as increased immobility time in the force swim test (Roni and Rahman 2014). Another manipulation of the cholinergic system is the inhibition of acetylcholinesterase, which is degrading acetylcholine. This inhibition induces depressive- and anxiety-like behavior in mice (Mineur et al. 2013). Interestingly, both lithium and valproate increase the activity of acetylcholinesterase in the brain of rats (Varela et al. 2013).

The catecholaminergic system on the other hand is mainly involved in mania-like symptoms in humans as well as in animals. Elevated levels of both DA and NE could be observed in BD rapid cycling (Juckel et al. 2000) and normal cycling patients (Berk et al. 2007). Several antidepressants increase synaptic catecholamine (Salvi et al. 2008; Tanda et al. 1994) levels. Furthermore, as already mentioned above the psychostimulant amphetamine increases synaptic DA and NE levels through inhibition or reversing the corresponding reuptake mechanisms or elevated DA efflux (Berk et al. 2007; Raiteri et al. 1975; Schaeffer et al. 1976; Sulzer et al. 2005). Amphetamine not only induces mania-like behavior in animals but also causes manic symptoms in healthy humans and BD patients, such as decreased need for sleep, elevated mood, drive and energy and attention, sleep, sexual behavior, sensorimotor function, learning and memory are affected (Asghar et al. 2003; Berk et al. 2007; Corp et al. 2014; Cousins et al. 2009; Jacobs and Silverstone 1986; Nurnberger et al. 1982; Peet and Peters 1995; Seiden et al. 1993). These behavioral effects of amphetamine administration are not only a simple consequence of increased neurotransmitter levels but it is more likely that a disturbance of the homeostatic mechanisms, controlling the catecholamine levels, plays a key role for this dramatic mood shift (Anand et al. 1999; van Enkhuizen et al. 2015b; Young and Dulcis 2015). Comparable to the animal models psychotherapeutics, such as lithium and valproate, can also attenuate the amphetamine mania-relevant behavior in humans (Flemlbaum 1974; Silverstone et al. 1980; Van Kammen and Murphy 1975).

Several neurotransmitters are affected in BD and together with the high comorbidity of BD with substance

abuse disorders (Kessler et al. 1997; Regier et al. 1990; Salloum et al. 2005) sensitization models have some face validity. They have for a long time also been the only BD animal models that show both phases, mania and depression, in the same animal model (Kato et al. 2007). On the other hand, the fact that psychostimulants act on numerous pathways hampers the investigation of the neurobiology underlying the observed behavioral changes. Therefore, more recent models for BD try to focus on one neurotransmitter system, primarily the dopaminergic system. Its involvement in BD and manipulations in animal models will be discussed in “[Dopaminergic pathways](#).”

Another limitation of the psychostimulant induced animal models for BD mania is that only a few simple aspects of human mania, like hyperactivity, are mimicked and even the amphetamine-induced hyperactivity is not specific for BD (Logan and McClung 2016; Rygula et al. 2015).

Dopaminergic pathways

Evidence from both human and animal studies suggests that BD is caused by an impaired neurotransmitter homeostasis (Berk et al. 2007). Clinical observations revealed that DA is altered in both episodes of BD. Thus, the dopamine hypothesis, claiming that dopaminergic transmission is disturbed depending on the mood phase, is one of the most promising hypotheses for the pathophysiology of BD (Berk et al. 2007). Manic episodes are associated with hyperdopaminergia. Increased dopaminergic transmission then induces homeostatic regulation mechanisms, which in a next step downregulate the post- and presynaptic sensitivity of receptors among other mechanisms. This downregulation results in an episode of decreased dopaminergic transmission, which is associated with the depressive episode of BD. This hypodopaminergic state activates then again the same homeostatic mechanisms, which now upregulate the key elements, resulting in another manic episode and thereby explaining the cyclic nature of the disease. A desynchronization of receptors and other key elements in different brain regions might be a possible explanation for euthymic episodes (Berk et al. 2007).

The dopaminergic system is involved in experiencing pleasure, mediating motivation (Bressan and Crippa 2005), impulsivity, risk behavior, and cognitive processes (Seamans and Yang 2004). Manipulation of the dopamine D1 receptor (D1R) in several species results in working memory deficits (Floresco and Phillips 2001; Goldman-Rakic 1999; Paspalas et al. 2013; Puig et al. 2014). Furthermore, increased D1R expression in the prefrontal cortex plays a role in impulsivity (Loos et al. 2010), cocaine addiction, sucrose preference, and high-risk

behavior (Sonntag et al. 2014). All these behaviors are to a certain extent detectable in patients of BD, including increased risk for substance abuse (Messer et al. 2017), increased impulsivity in manic episodes (Logan and McClung 2016), or cognitive deficits (Cope et al. 2016). Indeed, elevations in D1R have been observed in BD patients via positron emission tomography and single-photon emission computed tomography (Gonul et al. 2009; Suhara et al. 1992; Yao et al. 2013). Also other dopamine receptors are altered in BD patients and might therefore play a role in the pathogenesis of the disease. The D2R density is elevated in the nucleus accumbens in bipolar patients with psychotic symptoms (Pearlson et al. 1995). Elevated DA levels in the urine were additionally observed in BD patients within manic episodes (Joyce et al. 1995). Alterations in the dopaminergic system through administration of psychostimulants result in a shift of neurotransmitter levels and manic behavior in humans (Cousins et al. 2009). DA levels can be affected through administration of L-DOPA, the precursor of DA, which is an established medication for Parkinson's disease (Berk et al. 2007). L-DOPA administration induced behavior similar to BD mania in these patients, such as increased sexual behavior, impulsivity, and risk taking (Berk et al. 2007; Claassen et al. 2011; van Praag and Korf 1975; Raja and Bentivoglio 2012). Not all, but some BD patients treated with different DA agonists, such as bromocriptine, also experienced manic episodes (Fisher et al. 1991; Gerner et al. 1976). BD depression can be treated with such agonists and resulted in an improvement of depressive symptoms (Goldberg et al. 2004; Zarate et al. 2004). On the other hand, manic symptoms of BD patients can be attenuated through administration of DA antagonists (Christie et al. 1989; Tohen et al. 2003; Vieta et al. 2005). Furthermore, antidepressants increase the dopaminergic transmission in the prefrontal cortex and nucleus accumbens as shown in rodents (Tanda et al. 1994). Alterations of functional DA transporter (DAT) levels, particularly reduced availability, were confirmed in BD patients via positron emission tomography (Anand et al. 2011), in postmortem tissue (Rao et al. 2012; Young and Dulcis 2015) and cell culture experiments (Horschitz et al. 2005).

A knock-down of DAT in mice with reduced DAT functioning to approximately 10% of wild-type level resulted in mania-like behavior, such as hyperactivity in novel environments (Zhuang et al. 2001), increased risk behavior in the Iowa Gambling Task (IGT) (Young et al. 2011), impaired decision making with a preference for high reward combined with high risk in the IGT (van Enkhuizen et al. 2014b), and a similar hyperexploratory behavior in the BPM as observed in humans but with less straight movements compared to BD patients (van Enkhuizen

et al. 2014a; Perry et al. 2009; Young et al. 2010). But DAT knock-down mice fail to mimic the observed sensorimotor deficits in PPI observed in humans (Ralph-Williams et al. 2003). Alpha-methyl-*p*-tyrosine induced depletion of DA and was able to attenuate some of the behavioral abnormalities of the DAT knock-down mice (van Enkhuizen et al. 2014a), similar to the effect of chronic valproate treatment (van Enkhuizen et al. 2013a), whereas both treatments did not affect the exploration behavior. To sum up, this animal model is able to resemble various behavioral aspects of human BD mania (Cassidy et al. 1998; van Enkhuizen et al. 2015a). Interestingly, photoperiod length can influence the DAT level in the brain of rats (Dulcis et al. 2013), thereby again connecting the dopaminergic system and the circadian rhythm (see “[Circadian rhythm](#)”) with the pathophysiology of BD. Possible critiques of the DAT knock-down mice are the clearly too low *DAT* expression compared with unmedicated BD patients, which is approximately 80% of healthy subjects (Anand et al. 2011; Young and Dulcis 2015) and that this animal model mimics only BD mania and not depression (van Enkhuizen et al. 2015a). Mania-like behavior, such as hyperactivity (Giros et al. 1996; Ralph et al. 2001) and sensorimotor deficits in PPI (Ralph et al. 2001), can also be induced through a complete knock-out of the *DAT* gene in mice. The pointed hyperactivity of these mice could be attenuated through the D1R antagonist SCH23390 (Ralph et al. 2001). PPI deficits could be diminished through clozapine and quetiapine, which are atypical antipsychotics used as an effective treatment for BD mania and schizophrenia (Powell et al. 2008), acting as antagonists of the D2R (Brust et al. 2015; Masri et al. 2008). However, the DAT knock-down and knock-out mice were also used as animal models for ADHD (Leo and Gainetdinov 2013) and schizophrenia (Gainetdinov et al. 2001). This is no surprise considering the fact that DA transmission is also involved in the pathogenesis of these disorders (Gainetdinov et al. 2001; Giros et al. 1996; Leo and Gainetdinov 2013; Sharma et al. 2016; Zhuang et al. 2001). Nevertheless, we want to point out that it is important to create specific animal models, which are able to model more facets of the complex behavior of each of these disorders and the cyclical nature of BD especially.

One different approach to recreate the cyclical nature of BD within one animal through manipulating the dopaminergic system was realized by Freund and colleagues, using an inducible lentiviral vector system. Over-expression of D1R in the medial prefrontal cortex of rats resulted in increased sexual behavior, increased sucrose preference, impulsivity, and increased drug-related behavior (Sonntag et al. 2014). The increased D1R expression in the medial prefrontal cortex was accompanied by decreased D2R expression in the nucleus

accumbens. Even more interestingly, just the termination of this viral over-expression was sufficient enough to induce depressive-like behavior in the triadic paradigm of learned helplessness, reduced activity, and diminished sucrose preference (Freund et al. 2016). Termination of D1R over-expression furthermore increased levels of cAMP response element-binding protein (CREB) in nucleus accumbens (Freund et al. 2016). This animal model is therewith one of the few models, which is able to recreate the cyclical nature of BD. It furthermore supports the hypothesis that the homeostatic regulation of DA transmission plays a key role in the pathogenesis of BD (Berk et al. 2007).

Animal models that manipulate dopaminergic pathways mainly increased dopaminergic transmission and therewith induced mania-like behavior (Table 1). Inducible viral over-expression of D1R allowed investigating behavior after the termination of the over-expression (Freund et al. 2016). Results indicate that while increased dopaminergic transmission is associated with mania-like behavior the termination of increased dopaminergic transmission induces depressive-like behavior. Exact mechanisms leading to the observed behavioral changes are still unclear. Autoregulatory mechanism might have downregulated D1R expression during the viral over-expression causing reduced dopaminergic transmission after the termination of the over-expression. This explanation would be in line with Berk's dopamine hypothesis of BD (Berk et al. 2007). While this approach might be a promising new way to create an animal model for BD, further studies, e.g., on the models' susceptibility to treatment like lithium are necessary for better understanding of the underlying mechanisms.

Environment: stressors

Stressful life events in combination with genetic factors are a risk factor for the onset of psychiatric disorders (Afifi et al. 2009; Bebbington et al. 1984; Costello 1982; Kendler et al. 1999; Paykel 1978; Schmitt et al. 2014; Surtees et al. 1986). Environmental risk factors, causing these stressful experiences, are for example neglect during childhood, maternal loss, economic problems, family violence, abuse, sexual maltreatment, and many more (Bernstein et al. 2003; Brown et al. 2009; Kaufman and Charney 2001; Marangoni et al. 2016; Mullen et al. 1996). In fact almost two-third of BD patients sustained at least one negative or goal-attainment life event 6 months prior to the index or first occurred episode (Simhandl et al. 2015). Especially the first period of life plays an important role in the development of children (Vetulani 2013). Different types of maltreatment including physical, sexual, and emotional abuse or neglect in the early period of life (i.e., early life stress, ELS) are associated with mood

disorders (Affi et al. 2009; Green et al. 2010; Hovens et al. 2010; Leverich et al. 2002; McLaughlin et al. 2010). ELS in humans can lead to impaired cognitive functioning, exemplified in worse academic performance, impaired intellectual ability, language difficulties, and lower IQ (Cohen et al. 2008; De Bellis et al. 2009; van den Dries et al. 2010; Loman et al. 2009; Nelson et al. 2007). The risk to develop anxiety, depression, and psychoses in adulthood is particularly increased through ELS (Bebbington et al. 2004; Gilbert et al. 2009; Kaufman and Charney 2001; Mullen et al. 1996) and it is more likely that these illnesses are treatment resistant (Bryer et al. 1987; Nemeroff et al. 2003; Vetulani 2013). These long-lasting effects can occur through high or chronic levels of stress, because they might affect brain development and thereby mental health (Anda et al. 2006; De Bellis et al. 1999a; De Bellis et al. 1999b; Lupien et al. 2009; Maniglio 2009; McLaughlin et al. 2010; Pechtel and Pizzagalli 2011; Pirkola et al. 2005; Spataro et al. 2004; Teicher 2002). 32 percent of psychiatric disorders can be explained by childhood adverse experiences (Green et al. 2010; Pechtel and Pizzagalli 2011). These experiences influence also the overall lifespan, because humans, who experienced more than six traumatic events in their childhood, have an increased risk of dying approximately 20 years earlier (Anda et al. 2009; Brown et al. 2009).

The mother–infant interaction is very important not only for humans, but also for primates, rodents, or mammals in general for the development of the offspring and includes much more than just supply with nutrition (Gutman and Nemeroff 2002; Harlow and Zimmermann 1959; Heim and Nemeroff 2002; Kaffman and Meaney 2007; Mason and Berkson 1975; Meaney 2001; Tractenberg et al. 2016). Stressful events in the early period of life produce long-lasting effects on brain development in rodents (Caldji et al. 1998, 2000a; Francis and Meaney 1999; Romeo et al. 2003; Tractenberg et al. 2016), comparable to the effects observed in humans.

ELS in rodents can be induced as early as the prenatal period by stressing the pregnant dam, e.g., by restraint. Observed behavioral consequences of adult rats, which were prenatally stressed, can be identified as depressive-like, namely anhedonia, increased helplessness, indicated through increased immobility time in the forced swim test, increased anxiety behavior in the open field test, impaired cognition, decreased exploratory behavior, and social withdrawal (Fatima et al. 2017; Frye and Wawrzcki 2003; Hao et al. 2010; Jia et al. 2015; Lin et al. 2012; Lin and Wang 2014; Wakshlak and Weinstock 1990). Similar long-lasting effects on social behavior could be observed in prenatally stressed rhesus macaques (Clarke and Schneider 1993).

Prenatal stress is associated with alterations in the immune system (Diz-Chaves et al. 2012, see “Immune system”) and HPA axis (Koehl et al. 1999), decreased neurogenesis in the hippocampus (Fatima et al. 2017; Lemaire et al. 2000; Lin and Wang 2014), and reduced BDNF levels (Jia et al. 2015; Lin and Wang 2014). In addition, the metabotropic glutamate receptor 1 (mGluR1) is increased in the hippocampus and prefrontal cortex and mGluR5 is increased in the striatum of prenatally stressed rats (Jia et al. 2015). Glutamate transporter expression is increased in adult prenatally stressed rats and therefore affects the whole glutamate neurotransmission long term, but only in the frontal cortex and hippocampus (Adrover et al. 2015). The glutamatergic system plays a critical role in the regulation of synaptic plasticity (D’Sa and Duman 2002; Manji et al. 2001). Chronic lithium and valproate treatment can down-regulate the synaptic expression of ionotropic glutamate receptors in hippocampal neurons of rats (Du et al. 2004; Gray et al. 2003) and the antidepressant imipramine has the opposite effect (Einat and Manji 2006; Gray et al. 2003). In addition, pharmacological inhibition of ionotropic glutamate receptors via several competitive and noncompetitive inhibitors attenuated amphetamine-induced hyperactivity in mice (Vanover 1998). Interestingly, a contrary effect occurs through manipulating the GluR6. Knock-out mice for the *GluR6* gene exhibited mania-like behavior, indicated through hyperactivity, heightened responsivity to amphetamine, increased risk-taking behavior, more aggressive, less immobility time in the forced swim test, and less anxiety behavior (Shaltiel et al. 2008). Lithium was able to attenuate these behavioral abnormalities (Shaltiel et al. 2008). Prenatal stress is in addition able to alter the circadian rhythm and corticosterone secretion through disturbance of the HPA axis in adult prenatally stressed rats (Koehl et al. 1999). One function of the HPA axis is the synthesis of cortisol, a glucocorticoid; especially, maternal glucocorticoid is crucial for fetal development, because it affects synaptic connections, density, and differentiation of postnatal development of the fetal hippocampus (Fatima et al. 2017; Trejo et al. 2000). An overall decrease in the number of neurons and overall size could be observed in fetal hippocampus of rhesus macaques, whose mothers were administered excessive amounts of glucocorticoids during pregnancy (Uno et al. 1990). Similar effects of inhibited hippocampal neurogenesis, decreased hippocampal volume, and elevated cortisol levels were observed in juvenile rhesus macaques prenatally stressed via environmental alterations of the photoperiod (Coe et al. 2003). Hippocampal *Bcl-2* expression is also affected, namely decreased, in juvenile prenatally stressed offspring rats,

exhibiting depressive-like behavior (Guan et al. 2013). Interestingly lithium, which attenuates mania-like behavior in animal models, increases the Bcl-2 level (Chen et al. 1999; Manji et al. 2000), indicating one way of lithium's therapeutic effects. In return, chronic stress during pregnancy affects not only the unborn pup, but also the mother. Stressed mother rats exhibit depressive-like behavior in the forced swim test, less maternal care, and a decrease in spine density in the medial prefrontal cortex (Leuner et al. 2014).

Not only prenatal but also postnatal stress, for example, induced through maternal separation of the pups from their mother for a defined amount of time (e.g., 2–4 h per day for up to 3 weeks) can result in long-lasting behavioral alterations. Early maternal separation (EMS) results in ELS and induces a conserved neural response, including a protest response and the feeling of despair in humans and animals (Hofer 2005). The mother's behavior has an influence on the brain development of the neonate. Hippocampal development, memory, spatial and social learning, and the response to stress of the HPA axis is affected by maternal licking and grooming of the offspring (Lévy et al. 2003; Lippmann et al. 2007; Liu et al. 1997, 2000; Vetulani 2013). This mother infant interaction has as well a physiological effect in rats and an interruption can result in alterations of the heart rate, hormone levels, and interestingly the circadian rhythm (Hofer 1970, 1975, 1976; Kuhn et al. 1990; Meaney et al. 1991; Stahl et al. 2002; Stanton and Levine 1990; Vetulani 2013). Rats exposed to chronic EMS exhibited hypoactivity, increased stereotypic behavior, abnormal anxiety behavior, abnormal HPA axis functioning, and heightened response to an acute stressor and an elevated acoustic startle response in adulthood (Caldji et al. 2000b; Huot et al. 2001; Kalinichev et al. 2002; Ladd et al. 2000, 2004; Lippmann et al. 2007; McIntosh et al. 1999; Wigger and Neumann 1999). Antidepressant treatment can attenuate these depressive-like behaviors induced by EMS (Cotella et al. 2013; Couto et al. 2012; El Houry et al. 2006; Huot et al. 2001; MacQueen et al. 2003). The BDNF levels were decreased over a long period of time in the hippocampus of adult rats exposed to EMS (Lippmann et al. 2007), as well as in rats that were chronically stressed (Smith et al. 1995). Prolonged stress experiments indicate that inhibition of BDNF could cause neuronal atrophy or that BDNF is required for neuronal remodeling (Duman et al. 2016; Magariños et al. 2011). Indeed, long-lasting reduced BDNF levels in the hippocampus were associated with learning and memory deficits, as well as depressive-like behavior (Duman and Monteggia 2006; Huot et al. 2002; Lippmann et al. 2007). Furthermore, BDNF expression can be increased through chronic antidepressant treatment in rat hippocampus (Nibuya et al. 1995;

Russo-Neustadt et al. 2000). In return, a single direct injection of BDNF into the hippocampus led to an antidepressant effect, indicated through comparable performances in the forced swim test and learned helplessness paradigm of rats chronically treated with antidepressants (Shirayama et al. 2002). This behavioral effect could not be recapitulated in mice with reduced BDNF expression (Saarelainen et al. 2003), suggesting that BDNF signaling is necessary for the antidepressant effect.

Interestingly, stress affects the dopaminergic system through stimulating dopaminergic transmission in the VTA of stressed rats (Di Chiara et al. 1999; Horger and Roth 1996; Nieoullon and Coquerel 2003; Yadid et al. 2001), which again links alterations in the dopaminergic system and stress to BD. In addition, humans and rodents are not only in these early stages of life highly vulnerable to stress, but also in adolescence. During this important time of brain development, neuroplasticity in stress regulatory circuits and HPA axis functioning are formed (Andersen 2003; Andersen and Teicher 2008; Eiland and Romeo 2013; Wulsin et al. 2016). Therefore, chronic stress exposure to rats in the late adolescence results in depressive-like behavior in adulthood (Wulsin et al. 2016). But the effects of environmental stressors can be so powerful to induce depressive-like phenotypes even in adult, normally raised rats. These stressors can be provided through several behavioral paradigms, such as the forced swim test (Porsolt et al. 1977), tail suspension test (Steru et al. 1985), and learned helplessness (Maier and Seligman 1976). Similar behavioral abnormalities, which can be described as depressive-like behavior, such as reduced locomotor and exploratory behavior, aggression, sexual behavior, elevated anxiety and submissive behavior, social avoidance, disrupted circadian rhythms, and immune function, can be induced through repeated exposure to social defeat in rats (Berton et al. 1998; Crawford et al. 2013; Hollis et al. 2010; Hollis and Kabbaj 2014; Meerlo et al. 1996; Ruis et al. 1999; Stefanski 2000; Tidey and Miczek 1997; Tornatzky and Miczek 1993). Another prominent stressor, sleep deprivation, was already discussed in “Circadian rhythm” and can result in mania-like behavior in rodents (Malkoff-Schwartz et al. 1998).

Environmental stress has been widely used to create animal models for depression. Paradigms like maternal separation (Tractenberg et al. 2016) or social defeat (Toyoda 2017) are well-established models that have revealed several neurobiological mechanisms that connect stress and the onset of depression. It is to mention, however, that we cannot distinguish between uni- and bipolar depressive-like behavior in these models. The administration of antidepressants in these models provides mixed results (Harrison and Baune 2014) but to our knowledge it did not result in the induction of mania-like behavior

as sometimes seen in patients with BD. Lithium was able to prevent ELS-associated changes in the brain (Husum and Mathé 2002).

Environmental stressors can also induce mania-like behavior, e.g., by affecting circadian rhythms (Malkoff-Schwartz et al. 1998). A combination of circadian rhythm manipulation and environmental stressors (comparable to Le-Niculescu et al. 2008; see “[Circadian rhythm](#)”) might therefore be useful to create a switch between both behavioral phases in animal models.

Immune system

During the past few years, it became more and more evident that the immune system plays an important role in psychiatric disorders including BD. First speculations started after epidemiological studies revealed that BD occurs more often in people born between December and March (Fuller Torrey et al. 1996), indicating that an infection of the mother during the winter months could contribute to the risk to develop BD. Indeed, several years later it was confirmed that an influenza infection during pregnancy increases the risk for the offspring to develop BD by fourfold (Parboosing et al. 2013). BD patients furthermore show an increased cerebrospinal fluid-to-serum ratio, which could be an indicator for a dysfunctional blood–brain barrier (Patel and Frey 2015; Zetterberg et al. 2014). However, not only the immune system predisposed to develop BD, but also changes in the immune system have been shown in patients diagnosed with BD. A persistent and low-grade pro-inflammatory state, which is more intense during mood episodes, especially manic episodes, and less intense in depressive episodes (Brietzke et al. 2009b; Modabbernia et al. 2013) has been revealed in these patients. Even euthymia has been associated with detectable peripheral pro-inflammatory activity (Brietzke et al. 2009a, 2009b). In support of these findings is the increased mortality rate of BD patients (Anda et al. 2009; Brown et al. 2009; Crump et al. 2013). Apart from suicide, this elevated mortality rate can be explained by additional natural causes of death associated with increased inflammation (Crump et al. 2013; Hoang et al. 2011; Kupfer 2005). Furthermore, the immunological response to stress is altered in patients with BD (Wieck et al. 2014). There are some findings showing that the number of past episodes could even be a key factor to understand the evolution of immunological changes in BD. In a study conducted by Maes and colleagues, they have found that the number of past depressive episodes positively correlates with pro-inflammatory cytokines (Maes et al. 2012). Indeed, elevated levels of pro-inflammatory cytokines were reported in BD patients (Goldstein et al. 2009; Haarman et al. 2014; Stertz et al. 2013). Interestingly, lithium is able

to attenuate pro-inflammatory cytokines (Boufidou et al. 2004; Green and Nolan 2012; Himmerich et al. 2013; Patel and Frey 2015; Rowse et al. 2012; Wang et al. 2009; Zhang et al. 2009).

In animal models, maternal immune activation (MIA) and its consequences for the offspring has been intensively studied in the last two decades (Meyer 2014). Thereby, the immune system of the pregnant dam has mainly been stimulated with the human influenza virus (Cotter et al. 1995; Kneeland and Fatemi 2013), the immunostimulant Polyinosinic:polycytidylic acid (poly I:C) (Eßlinger et al. 2016; Rose et al. 2017; Shi et al. 2003), or bacterial lipopolysaccharide (Bakos et al. 2004; Fernández de Cossío et al. 2017) during different gestational stages. In adult animals that had been exposed to MIA sensorimotor gating, i.e., latent inhibition and the US-preexposure effect are disrupted, impairments in working memory are evident and the locomotor response to amphetamine is increased (Meyer et al. 2005). Furthermore, a reduction in social interactions in addition to increased repetitive and stereotypic behavior has been reported (Fernández de Cossío et al. 2017; Rose et al. 2017). Even depressive-like behavior including increased anxiety and helplessness (Meyer et al. 2005; Ronovsky et al. 2016) has been shown. Thereby, depressive-like behavior has also been reported in the second generation after MIA (Ronovsky et al. 2017). Taken together, MIA results in the development of several behavioral deficits that are associated with psychiatric disorders. Given the strong effect on sensorimotor gating and deficits in social behavior, MIA in animal models has mainly been associated with a schizophrenia-like phenotype (Meyer et al. 2005) or autism-related characteristics (Fernández de Cossío et al. 2017). An animal model for BD using MIA has never been proposed. At the same time, deficits in sensory gating have been implicated in patients with BD (Cheng et al. 2016), specifically during the acute mania phase (Kohl et al. 2013). Similarly, impairments in working memory (Dickinson et al. 2017) and social cognition (Hoertnagl et al. 2014) have been reported in patients with BD and animals after MIA (Fernández de Cossío et al. 2017; Meyer et al. 2005). Further findings on an increased striatal DA release following MIA (Zuckerman et al. 2003) are in line with the hypothesis that dopaminergic pathways are disrupted in BD (see “[Dopaminergic pathways](#)”) and further support the fact that MIA might be useful to also create animal models for BD. Less research on disrupted behavior after an acute or chronic activation of the immune system in adult animals has been conducted. Nevertheless, there is evidence that even in adulthood activation of the immune system can induce depressive-like behavior and anxiety (Remus and Dantzer 2016; Wachholz et al. 2017). So far no reports on

adult immune activation and mania-associated behaviors in animal models exist. An animal model of mania (induced by amphetamine; see “[Sensitization models and neurotransmitters in general](#)”), however, showed increased cytokine levels in plasma and brain, which could together with the mania-like behavior be reversed by lithium treatment (Valvassori et al. 2015). Even adult animals therefore show depressive-like behavior when manipulating the immune system and a mania-like phenotype in adult animals is associated with increased inflammation.

Taken together, there is growing evidence that the immune system plays an important role in BD. Animal models with an immune activation early in development (i.e., prenatally) show several behavioral changes that are associated with depression and mania. So far, however, no cycling between these two behavioral states has been shown after manipulation of the immune system and MIA has never been considered as a manipulation to create an animal model for BD.

Conclusions

BD was to some extent already described by ancient Greek scholars like Hippocrates and Aristoteles (Angst and Marneros 2001). Nevertheless, our current knowledge in the 21st century about the disorder is still limited. Given the fact that lithium, one of the top choice treatment options (Sani et al. 2017), was discovered by animal research (Cade 1949), animal models for the disorder can be a very useful tool to advance our knowledge. Indeed, several models have either confirmed findings from patients or even extended these findings by explaining the underlying neurobiological mechanisms. In this review, we could confirm that several affected areas and risk factors can be found in human patients as well as animal models for BD. Thereby, it can be noticed that all sections described here are connected with each other. Disruptions of circadian rhythms influence the dopaminergic system (Coque et al. 2011; McClung et al. 2005; Mukherjee et al. 2010; Roybal et al. 2007). DA in turn is well known as a key player in reward behavior and therewith drug use (Cooper et al. 2017). Substance abuse disorder is correlated with a stressful environment and stress increases the risk for relapse (Goldstein et al. 2008). Furthermore, stress and addiction induce similar epigenetic and neurobiological modifications (Cadet 2016; Moonat and Pandey 2012; Palmisano and Pandey 2017; Spanagel et al. 2014). Stress has an influence on the immune system (Stefanski 2000) and the immune system on the other hand is connected with pathways related to circadian rhythm (Dumbell et al. 2016). Manipulation in animal models therewith often results in an interplay of several affected

factors. It therewith resembles the human condition and it strengthens the model. At the same time, when several mechanisms are affected, the exact mechanism underlying BD is hard to investigate. It is clear that BD is not caused by a single factor. Therefore animal models that cover a broad range of the disruptions observed in human patients might need manipulations in several areas. At the same time, single-factor manipulations would be the best way to confirm correlations between observed changes and the manipulation. Due to the complex etiology, biology and disease pattern of psychiatric diseases, animal models with targeted mutations involve some limitations. Therefore, it is unlikely that one genetic alteration within an animal model will be able to recapitulate all facets of human DSM-defined disorder symptomatology (Kaiser and Feng 2015). DSM-defined disorders often contain similar phenotypical features, which can be based on diverse biological factors. Nevertheless, most established animal models for BD use one manipulation to model just a partial list of symptoms (concentrating on either mania or depressive-like symptoms). This approach facilitates to connect behavioral outcomes to specific pathways and is an important tool to advance our knowledge of certain aspects. Nevertheless, the diverse character of behavior and even switch of behavior observed in patients is not considered in these models. Specifically for the investigation of this switch and its neurobiology, it is crucial to create animal models presenting mania- as well as depressive-like behavior (Nestler and Hyman 2010). So far, very few models were able to show a switch between mania- and depressive-like behaviors. Sensitization models show mania-like behavior following repeated administration of psychostimulants (see “[Sensitization models and neurotransmitters in general](#)”) and depressive-like behavior during withdrawal (Antelman et al. 1998; Barr et al. 1999; Baumann and Rothman 1998; Marszalek-Grabska et al. 2016; Persico et al. 1995; Schwartz et al. 1982). However, psychostimulants target several neurotransmitter systems and therefore information on the neurobiology of BD we got from these models is limited. New techniques, namely the use of viral vector to induce genetic material into specific cells, might be promising for the development of new BD animal models reproducing the cyclic character of the disorder. D1R over-expression on glutamatergic cells in the medial prefrontal cortex induces mania-like behavior, while the single termination of this over-expression was sufficient enough to result in depressive-like behavior. It has to be noted, however, that this switch in behavior is not spontaneous as reported in BD patients. Apart from manipulating the dopaminergic system, circadian rhythms and the immune system seem to be promising targets for the development of animal models for BD. Investigating

the neurobiology behind the induction of mania- or depressive-like behavior by extending or shortening the length of day might provide us with the switch between the two phases and will induce both phases one after the other in one animal. Similarly, inducing an increased state of inflammation followed by a decreased state of inflammation might reveal an animal model for BD showing the characteristic switch between mood phases.

As always, further research is needed. New technology, however, either in the field of animal research as well as for examining human patients is being established. Combining these techniques with new insights especially in the fields of immunology and circadian rhythms provides us with new tools to develop better models.

Abbreviations

ADHD: attention-deficit hyperactivity disorder; Bcl-2: B-cell lymphoma 2; BD: bipolar disorder; BDNF: brain-derived neurotrophic factor; BPM: behavioral pattern monitor; Clock: circadian locomotor output cycles kaput; CREB: cAMP response element-binding protein; D1R: dopamine D1 receptor; D2R: dopamine D2 receptor; DA: dopamine; DAT: dopamine transporter; ELS: early life stress; EMS: early maternal separation; ERK: extracellular-signal-regulated kinase; GSK-3 β : glycogen synthase kinase-3 beta; HPA: hypothalamic–pituitary–adrenal; IGT: Iowa Gambling Task; mGluR: metabotropic glutamate receptor; MIA: maternal immune activation; NE: norepinephrine; poly I: C: polyinosinic:polycytidylic acid; PPI: prepulse inhibition; REV-ERBa: nuclear receptor subfamily1, group D, member1; VTA: ventral tegmental area.

Authors' contributions

NF and DKEB both contributed equally in writing this review. Both authors read and approved the final manuscript.

Competing interests

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