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Publication Date
2015-07-01

DOI
10.1016/j.ejphar.2015.03.019

Peer reviewed

European Journal of Pharmacology 759 (2015) 151–162

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Investigating the mechanism(s) underlying switching between states in bipolar disorder

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ARTICLE INFO

Article history:
Received 19 January 2015
Received in revised form
3 March 2015
Accepted 12 March 2015
Available online 23 March 2015

Keywords:
Bipolar disorder
Seasonality
Switching
Mania
Depression
Catecholamines
Triggers

ABSTRACT

Bipolar disorder (BD) is a unique disorder that transcends domains of function since the same patient can exhibit depression or mania, states with polar opposite mood symptoms. During depression, people feel helplessness, reduced energy, and risk aversion, while with mania behaviors include grandiosity, increased energy, less sleep, and risk preference. The neural mechanism(s) underlying each state are gaining clarity, with catecholaminergic disruption seen during mania, and cholinergic dysfunction during depression. The fact that the same patient cycles/switches between these states is the defining characteristic of BD however. Of greater importance therefore, is the mechanism(s) underlying cycling from one state – and its associated neural changes – to another, considered the 'holy grail' of BD research. Herein, we review studies investigating triggers that induce switching to these states. By identifying such triggers, researchers can study neural mechanisms underlying each state and importantly how such mechanistic changes can occur in the same subject. Current animal models of this switch are also discussed, from submissive- and dominant-behaviors to kindling effects. Focus however, is placed on how seasonal changes can induce manic and depressive states in BD sufferers. Importantly, changing photoperiod lengths can induce local switches in neurotransmitter expression in normal animals, from increased catecholaminergic expression during periods of high activity, to increased somatostatin and corticotrophin releasing factor during periods of low activity. Identifying susceptibilities to this switch would enable the development of targeted animal models. From animal models, targeted treatments could be developed and tested that would minimize the likelihood of switching.

Contents

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http://dx.doi.org/10.1016/j.ejphar.2015.03.019
0014-2999/

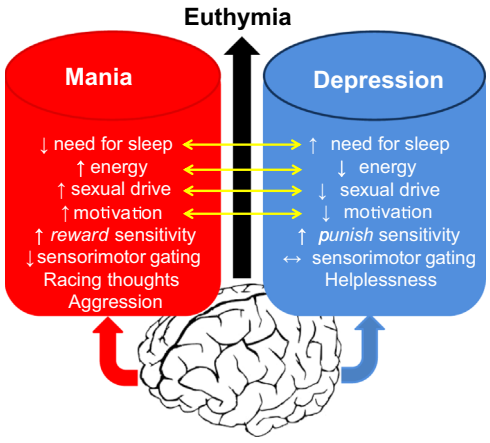


Fig. 1. Symptoms of the extreme states of bipolar disorder, mania and depression. Bipolar disorder is a unique disorder that transcends domains of function because the same patient can exhibit depression or mania at different points in their life. Periods when they exhibit symptoms of neither state are referred to as euthymia. Some symptoms are on a scale (yellow arrows) whereby the symptoms of each state are on the opposite ends of the spectrum. Some symptoms do not link with each other, where deficits seen in a manic state are normal during depression (*e.g.*, sensorimotor gating as measured by prepulse inhibition). Importantly, identifying triggers that change the neural circuitry of the brain toward mania or depressive symptoms is a vital step toward delineating the key circuitry that allows for a hypersensitivity to such triggers.

1. Introduction

Bipolar disorder (BD) is a life-long neuropsychiatric disorder affecting approximately 2–5% of the world's population (Akiskal et al., 2000; Judd et al., 2003; Merikangas et al., 2007). BD sufferers have a markedly increased suicide mortality rate (Osby et al., 2001) where one in three patients attempt suicide (Novick et al., 2010). The lifetime cost from treatment and lost productivity from people suffering from BD amounts to approximately $24 billion (Begley et al., 2001). BD is the sixth leading cause of disability among physical and psychological disorders worldwide (Murray and Lopez, 1996). BD is so-called because patients exhibit states of mania or depression, states that have polar opposite symptoms. Periods between extreme states where behavior is not as extreme (relatively normal) are referred to as a euthymic states. During a state of mania, people exhibit symptoms of euphoria, aggression, irritation, increased physical activity, racing thoughts, high reward-seeking behavior, and reduced need for sleep. In contrast, during a state of depression, people exhibit symptoms of reduced sense of self, helplessness, reduced energy, punish sensitivity, and increased sleep (Fig. 1). Importantly, *BD is a unique disorder that transcends domains of function because the same patient can exhibit depression or mania*. Hence, the fact that sufferers cycle/switch between states is the preeminent defining characteristic of BD (Goodwin and Jamison, 1990).

BD therefore, is an extremely complex neuropsychiatric condition. Beyond switching between mood states, subgroups of BD also exist. In BD type I, sufferers exhibit aspects of mania and depression, in type II patients exhibit aspects of hypomania and depression (Belmaker, 2004). Other subgroups of BD exist, including sufferers that exhibit rapid cycling between states (Fountoulakis et al., 2013; Zupancic, 2011), which may not be stable (Carvalho et al., 2014), or some sufferers that exhibit mixed states (McIntyre et al., 2012; Ouanes et al., 2014; Price and Marzani-Nissen, 2012). In addition, juvenile-onset of BD is being documented (Luckenbaugh et al., 2009), adding another aspect of sufferers of BD. Importantly, all sufferers exhibit mania and depressive symptoms in varying degrees. In addition to these subgroups, the differing neurobiological substrates that likely underlie depressed *vs.* manic states (Brady Jr. et al., 2014; Janowsky et al., 1983; Savitz et al., 2014; van Enkhuizen et al., 2014b) is the likely reason that the only approved treatments for BD have been discovered serendipitously or first for other disorders (Gould and Einat, 2007; Young et al., 2011). To develop treatments targeted for BD, the mechanism (s) underlying switching between states – described as the 'holy grail of BD research' (Blumberg, 2012) – needs to be discovered.

In order to test hypotheses on potential mechanism (s) underlying such switching, animals that are manipulated by such mechanisms would be extremely beneficial. In combination with such manipulations, testing the behavioral output with relevance to cognitive and behavioral states using tests relevant to those affected in mania and depression will prove vital (Young et al., 2011; (Geyer et al., 2012; Keeler and Robbins, 2011; Malkesman et al., 2009; Markou et al., 2008; van Enkhuizen et al., 2014b; Young and Geyer, 2014; Young et al., 2011). There is a dearth of animal manipulations targeting the etiologies of BD (Malkesman et al., 2009; Young et al., 2011), and what manipulations exist, few utilize cross-species tests relevant to mania or depression (van Enkhuizen et al., 2014b; Young et al., 2011). In fact, the vast majority of current models only attempt to model the mania aspect of BD (Einat, 2007; Gessa et al., 1995; Gould and Einat, 2007; Kara and Einat, 2013; Machado-Vieira et al., 2004; Malkesman et al., 2009; van Enkhuizen et al., 2014b; Young et al., 2007). Those studies that attempt to recreate depression do not do so as a form of depression relevant to bipolar disorder (Abelaira et al., 2013; Belzung, 2014; Berton et al., 2012; Carboni, 2013; Kreiner et al., 2013; O'Leary and Cryan, 2013; Pryce and Klaus, 2013). Even fewer studies attempt to model the switching between states of BD.

This review will bring into focus: (1) current models of cycling in BD; (2) the extant literature detailing causes of switching between states in BD; (3) how switching between states can also switch neurotransmitter mechanisms, underlying the varied behavior between states; and (4) how future models of switching between states will have to be tested in order to determine their relevance to that state.

2. Current attempts at modeling switching between states

Some attempts have been made to create animal models relevant to cycling in BD. These models range from *in vitro* to *in vivo* studies. Naturally, *in vivo* studies offer the opportunity to study the behavioral effects of the manipulation, especially behaviors with relevant to mania or depression depending on the time of manipulation.

Price (1967) proposed an evolutionary dominance hierarchy theory for developing mental illness. Briefly, this theory proposed that the maintenance of a hierarchy is essential for a social groups well-being, and since changes in the hierarchy are inevitable, certain behavioral characteristics during these changes make such transitions smoother. For example, the transition of defeated alpha male to a lower rank would be smoother if they exhibited low energy, disinterest, and reduced sexual drive – behaviors associated with depression. Based on this premise, Malatynska and Knapp (2005) have used dominant-submissive behaviors of rats as models of mania and depression [respectively]. Similarities of submissive behavior to depression include increased defensive behaviors, weight loss, sleep disturbances (Price et al., 1994). Dominant and submissive behaviors can be induced when resources are made scarce [*e.g.*, social competition model; (Cumming et al., 2014; Pucilowski et al., 1990; Taylor and Moore, 1975)]. Interestingly, such dominant and submissive behaviors are heritable (Nesher et al., 2013). Importantly for modeling switching in BD, antidepressants can attenuate submissive behaviors (Koolhaas et al., 1990; Mitchell

and Redfern, 1992). Treatments for anxiety can also attenuate submissive behavior however (Nesher et al., 2013; Piret et al., 1991), which are not used as treatments for depression in BD. Furthermore, lithium did not affect such submissive behavior (Nesher et al., 2013), despite being a treatment depression in BD. Additional support for this model comes however, from evidence that dominant behaviors are sensitive to reversal due to anti-manic treatments such as lithium and valproate (Malatynska et al., 2002; Nesher et al., 2013). The use of single doses as opposed to chronic treatment is in contrast with their efficacy in human treatment studies however (Young et al., 2011). When investigating potentially novel treatments, clonidine (an alpha2 adrenergic antagonist) reversed the dominance of rats (Malatynska et al., 2002). Clonidine has since received some support as a potential treatment for mania (Chou, 1991; Hardy et al., 1986; Jouvent et al., 1988; Maguire and Singh, 1987; Zubenko et al., 1984), although it – nor any mechanism of its type – has not been approved for treating mania. Additional concerns of this model include evidence that anxiogenic treatments attenuate dominant behavior of rats in social competition settings (Joly and Sanger, 1992), which are not used as treatments for mania. Another concern is that amphetamine attenuates the dominant behavior of rats (Malatynska and Kostowski, 1984; Miczek and Gold, 1983), yet can induce a manic state in patients with BD (see Section 3.1). Additionally, dominant males become submissive when they encounter a more dominant male (Willner et al., 1995), which hardly equates to a treatment for mania. Most importantly for this review, the behavior of these animals were rarely tested beyond their submissive or dominant behaviors, where neurocognitive and mood-related testing would be useful. Furthermore, the animals used in these behaviors are consistently submissive or dominant, not switching between the two states. Hence, the suitability of this dominant/submissive behavior as a model of switching relevant to BD is likely limited.

Another model of switching in BD resulted in the kindling hypothesis. Kindling refers to a progressive decline in the strength of electrical current required to elicit seizure activity. Although a strong current is needed initially, the electrical threshold required diminishes over time until a point of 'spontaneous epilepsy' develops. It was hypothesized that this kindling process could be elicited by introducing repetitive stimuli or psychomotor stimulant presentation (Post et al., 1982), although of some concern is that the mechanisms underlying each may be distinct (Weiss and Post, 1987). Post and Weiss (1989) suggested that since repeated treatment with cocaine can induce mania-like episodes, animals receiving different dosing regimens of cocaine can produce differing effects from motoric hyperactivity to convulsions. Moreover, anticonvulsant treatments such as carbamazepine are effective at inhibiting this 'kindling'. In part from this work, Post (1992) postulated the kindling hypothesis of mood disorders, whereby major psychological stressors play a greater role in the initial – as opposed to later – episodes of a mood disorder. While the initial hypothesis was to cover both unipolar depression and BD, most work has focused on evidence from unipolar depression (Monroe and Harkness, 2005). The utility of this model as a hypothesis for BD was reviewed recently, whereby only 1 in 3 retrospective human studies have provided support for such a hypothesis (Bender and Alloy, 2011). Numerous animal studies related to this kindling hypothesis have been conducted.

Antelman et al. (1998) investigated the effects of different numbers of cocaine treatment on oscillatory changes of dopamine efflux in response to amphetamine from rat slices from the nucleus accumbens and striatum. They also investigated the ability of lithium to block any observed effects. It was observed that a single treatment with cocaine reduced dopamine efflux, two treatments (1 week apart) had no effect, while 3 treatments also reduced dopamine efflux (2 weeks apart). When co-treated with lithium without cocaine, or 1 or 3 treatments, an increase in dopamine efflux was observed. Similar findings were observed for efflux from the striatum, although lithium did not increase efflux alone. A hypoalagesic response to shocks were seen when some multiple treatments of cocaine were given (1, 2, and 4 pretreatments) that was not reversed by lithium treatment. The authors claim that this effect is appropriate for evaluating the switching between states that occurs in BD. It remains unclear what relevance a hypoalagesic effect has to behaviors seen in BD sufferers however. Evaluating the behavioral outcomes of these models using BD-relevant tests for mania or depression would prove more useful. Furthermore, it is clear that repeated cocaine treatment in humans does not result in a cycling state consistent with BD and so these effects may simply relate to the pharmacological effect of cocaine/amphetamine/lithium treatment. Ultimately, this model may be more relevant to seizures since anticonvulsants such as topiramate, gabapetin, and tiagabine are effective in this model but not for treating BD mania or depression (Weiss, 2004). Such studies have also been related to the modeling of disease progression in epilepsy, pain syndrome, and post-traumatic stress disorder (Grillon et al., 1996; McFarlane et al., 2002; Post, 2002). Hence, these studies ultimately support the assertion of Bender and Alloy (2011) that the kindling hypothesis is not fully supported for switching in BD and that other hypotheses, such as the social rhythm disruption theory – that led to social rhythm therapies (SRT; see Section 3.2) – may fit better.

Testing manipulations in whole animals would allow their behavioral testing in cross-species tasks that are relevant to mania and depression (Fig. 1). Such studies will be vital to testing hypotheses underlying switching in BD. Ideally, these manipulations should be taken from etiological studies in BD patients identified as inducing a transition into another state.

3. Key studies investigating cycling/switching into other states in BD

There have been numerous studies/reports on triggers that can induce switches of BD sufferers into other affective states (*e.g.*, mania or depression). Although there are many methodological issues surrounding the definition of what constitutes a switch, (Salvadore et al., 2010), attempts have been made to review mechanisms that underlie switching to hypomania and mania (Chen et al., 2010; Salvadore et al., 2010) as well as switches to depression (Blumberg, 2012; Salvadore et al., 2010).

In a prospective 10 year study, it was observed that gender, a positive family history of BD, nor age were positive predictors of switching (Maj et al., 2002). This study focused on previous hospitalizations on switching, indicating that a higher number of hospitalizations was associated with switching. In another study, a mixed manic episode was more likely to predict a switch to a depressed state compared to exhibitions of mania symptoms alone (Zarate Jr. et al., 2001). While of importance for current treatment of sufferers, this clinical information may not prove useful for identifying mechanisms or specific triggers that could identify mechanisms. Other, more specific triggers, have been identified however.

3.1. Pharmacological triggers of switching between states in BD

One area of clinical importance that can also be informative for understanding mechanisms and model testing is that of antidepressant treatment-induced switching to a hypomanic or manic state in BD. Chronic treatment with tricyclic antidepressants have consistently been linked with producing a switch at rates ranging from 9% to 69% (Bunney Jr. et al., 1970; Lewis and Winokur, 1982;

Peet, 1994). Tricyclic antidepressants largely act to block both serotonin and norepinephrine re-uptake from the synaptic cleft, although there are a variety of effects at other receptors, notably in the serotonergic system. These combined inhibitors induce mania/hypomania at higher rates than from selective serotonin reuptake inhibitors (Bottlender et al., 2001; Peet, 1994). Treatment with bupropion – a combined dopamine/norepinephrine reuptake inhibitor – also induces switches in rates up to 19% (Sachs et al., 2007), although many studies focused on its use as an adjunctive therapy to mood stabilizing treatment (Salvadore et al., 2010). Ultimately, it appears that elevating norepinephrine or dopamine levels *via* blockade of their reuptake site likely induce switches from a depressed to a hypomanic or manic state, even during mood stabilizing co-treatment.

Direct treatment resulting in elevated dopamine/norepinephrine levels also induce mania-like states. For some time it was clear that treatment with the dopamine precursor L-dopa induced a hypomanic state of mood (Murphy et al., 1971). This treatment effect is consistent with observations that treating Parkinson's disease patients with L-dopa can induce mania-relevant behavior such as gambling and risk-taking (Claassen et al., 2011; Djamshidian et al., 2011; Raja and Bentivoglio, 2012). Indirect dopamine/norepinephrine stimulation by/the combined reuptake inhibitor amphetamine induces manic/hypomanic episodes in patients and mania-like behaviors in healthy subjects (Asghar et al., 2003; Corp et al., 2014; Jacobs and Silverstone, 1986). Conformation of the importance of reuptake sites to this mood-elevating effect of amphetamine comes from studies demonstrating that polymorphisms of these transporter sites can alter the effects of amphetamine (Dlugos et al., 2007; Lott et al., 2005). Interestingly however, it is not simply elevation of levels of these neurotransmitters, because reducing levels of tyrosine hydroxylase (TH; the precursor to dopamine/norepinephrine) *via* α-methyl-*p*-tyrosine (AMPT) treatment also induced hypomanic mood elevation (Anand et al., 1999). Although it is unclear whether AMPT would reduce mania behaviors in people undergoing a manic episode, this study makes it clear that it is the homeostatic control of catecholamines that are important for switching to mania/hypomania (Anand et al., 1999; van Enkhuizen et al., 2014b).

Manic episodes can be induced in BD patients using treatments beyond pharmacological-induced neurotransmitter manipulation. In particular, manipulation of the hypothalamic–pituitary–adrenal (HPA) axis can induce switching of mood states in 30–80% of cases in a dose-related fashion (Janowsky et al., 1983; Lewis and Smith, 1983; Phelan, 1989; Wada et al., 2000). Specifically, prednisone treatment can induce manic episodes in BD sufferers (Wada et al., 2000), while steroidal-based treatments for asthma can also induce a switch to a manic state (Phelan, 1989). Furthermore, HPA hyperactivity has been reported in rapid switching from mania to depression in case studies (Bunney Jr. et al., 1965; Fries et al., 2014). Hence, altered HPA function, or hypersensitivity to glucocorticoids, may represent a viable trigger related to switching between mood states.

Little is known about pharmacological treatments that can induce switching to a depressive state. One treatment used to improve memory in Alzheimer's disease is physostigmine, an acetylcholinesterase inhibitor (inhibits the breakdown of acetylcholine, hence indirectly elevates acetylcholine). Physostigmine treatment can reduce mania symptoms in BD patients (Janowsky et al., 1972). In healthy subjects, and euthymic patients with BD, physostigmine can also induce a state of depression (Risch et al., 1981; Shopsin et al., 1974). More recently, this work has been followed-up with observations that elevated acetylcholine levels are observed in patients with BD and unipolar depression (Hannestad et al., 2013) as well as altered cholinergic receptor levels in BD sufferers (Saricicek et al., 2012). Hence, elevating acetylcholine levels likely induces a depressed state in BD patients.

Other neurotransmitter systems have been investigated that may underlie switching in patients with BD. Neither lamotrigine nor riluzole, which inhibit glutamate release, do not increase switching in depressed BD patients (Calabrese et al., 1999; McIntyre et al., 2013; Zarate Jr. et al., 2005). Other novel treatments for depression – including BD depression – includes intravenous treatment with NMDA receptor antagonists such as ketamine (Lally et al., 2014; McGirr et al., 2015; Villasenor et al., 2014). No reports of ketamine-induced switching of BD depressed patients to mania have been reported. Hence, glutamatergic links to switching in BD appear unlikely.

3.2. Environmental factors that induce switching between states in BD

Other environmental factors of switching are important to take into consideration beyond pharmacological treatments however. Disturbed sleep patterns have been observed at the time of the switch to mania in euthymic unmedicated patients with BD, including increases in catecholamine release (Goodwin et al., 2007). Full sleep deprivation can induce a manic episode in up to 30% of BD patients (Colombo et al., 1999; Leibenluft et al., 1996; Wright, 1993), and mania-like behavior in healthy subjects (Aydin et al., 2013; McKenna and Eyler, 2012; van Enkhuizen et al., 2013a). Sleep deprivation-induced changes in mood supports the social rhythm disruption (SRD) (social zeitgeber) theory of affective disorders (Grandin et al., 2006; Malkoff-Schwartz et al., 2000). This SRD theory posits that a disruption in social/biological rhythm can induce changes in mood in vulnerable individuals. Such disruption can take the form of stressful live events stressors (Ellicott et al., 1990; Hirschfeld and Cross, 1982; Post, 1992), but can also include positive events (Bender and Alloy, 2011). Further support includes that the sleep-wake cycle and biological rhythms are altered in BD (Gonzalez, 2014; Robillard et al., 2013) and likely play a role in the pathophysiology of BD (Kripke et al., 2009; McCarthy et al., 2012; McCarthy and Welsh, 2012; McClung, 2007). Hence, BD sufferers may have a susceptibility to SRD that underlies shifting moods. Although the mechanism(s) underlying this theory have yet to be determined, it has resulted in efficacious treatment development called social rhythm therapy (SRT) designed to maintain a stable lifestyle (Bouwkamp et al., 2013; Frank et al., 2008; Harvey, 2011; Hlastala et al., 2010; Sachs, 2008). Hence, beyond pharmacological challenges, changes in the environment of the sufferer can induce switches in mood.

One of the greatest environmental triggers of changes in mood has been the changing of seasons. Seasonal variations effecting mood in BD have been recognized for over 2000 years when Hippocrates described the correlation between seasonal changes and the occurrence of mania in BD. This premise has been

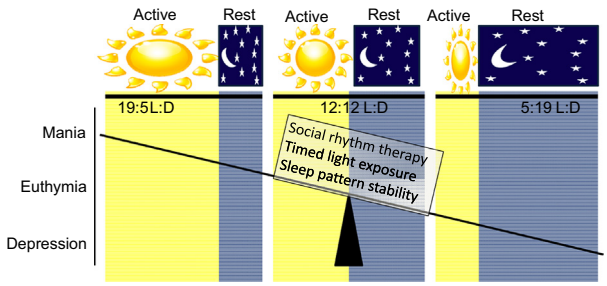


Fig. 2. Photoperiod length-induced changes of mood. As sufferers of bipolar disorder enter spring/summer, where longer light-induced active periods are present, they are more likely to exhibit mania symptoms. During shorter light-induced inactive periods however, bipolar sufferers are more likely to exhibit depressive symptoms. Maintaining stability of photoperiod supports a euthymic, non-clinical state, consistent with psychosocial social rhythm therapy, timed light exposure, and sleep pattern stabilization treatments.

supported by numerous studies reporting more mania episodes during the spring and summer (Barbini et al., 1995; Lee et al., 2007; Mulder et al., 1990; Parker and Walter, 1982; Sayer et al., 1991; Takei et al., 1992; Volpe and Del Porto, 2006), although this has not always been seen (Silverstone et al., 1995; Whitney et al., 1999). Changing seasons do not only affect sufferers of BD, but also people experiencing depression. Seasonal affective disorder is now a widely recognized condition wherein which people entering periods of seasons of short sunlight experience depressive symptoms (Jacobsen et al., 1987; Knapen et al., 2014; Rosenthal et al., 1984) and has been reviewed extensively (Gupta et al., 2013; Niemegeers et al., 2013). Light therapy (exposure to ultraviolet light at set times of the day) is used to treat seasonal affective disorder (Golden et al., 2006; Niemegeers et al., 2013) and is also used as an antidepressant in patients with BD (Postolache and Oren, 2005; Wu et al., 2009). Shortening day-lengths may represent one of the more consistent environmental triggers inducing a switch to depression in people with BD. Hence, it appears likely that changing seasons can exert extreme effects on mood in those susceptible to such effects (Fig. 2). As reviewed by Wang and Chen (2013), the majority of studies (23/29) provide supporting evidence for seasonal mania (manic episodes occurring in spring and summer). They highlight that the heterogeneity of BD may reflect why some sufferers do not show such seasonality, hence seasonal-variation induced switching in BD might be a sub-population of sufferers. In fact, this sub-population may exhibit with a more severe form of the disorder seen in males and females, although rapid cycling is more likely seen in females (Geoffroy et al., 2013). Such seasonality may be associated with BD type II patients, particularly in subjects that evidence with late evening preference and irregular bed-rise times (Baek et al., 2014). It was recommended that future studies aimed at understanding seasonal variation in BD require stringent research criterion (Murray et al., 2013). Considering the advent of modern electric lighting and its widespread use, such studies should also utilize light level readers. Importantly however, seasonality in BD is associated with a family history of BD (Brambilla et al., 2012) and appeared heritable in a twin study (Jang et al., 1997). Hence, it is likely there is a strong genetic component to seasonal changes-induced switches in mood.

In any investigation on the putative mechanism(s) underlying BD it is important to keep in mind that BD is a genetic-based disorder. Heritability studies of BD estimate a 60–80% heritability supporting this genetic basis for sufferers. Numerous GWAS studies have been conducted in BD (Baum et al., 2008; Greenwood et al., 2012, 2006b; Lee et al., 2013; Sklar et al., 2008; Smith et al., 2009), but few observed statistical significant findings required for such studies. Such lack of effect may come from the heterogeneity of BD groups where studying subsets of patients may provide greater information. A GWAS study on patients self-identifying as having seasonal patterns of mania *vs.* non-seasonal sufferers discovered an association for rs41350144 which lies within the intron of NF1A on 1p31 (Lee et al., 2013). Importantly, genes contributing to the control of circadian rhythm are also implicated in BD. Haplotype polymorphisms of the circadian genes Period3 and ARNTL have been associated with BD, as have circadian locomotor output cycles kaput (CLOCK) and GSK3β (McClung, 2013; Nievergelt et al., 2006). At the core molecular level, the mammalian circadian circuit involves the CLOCK, ARNTL (also known as BMAL1) and NPAS2 transcription factors activating the transcription of cryptochrome (CRY1 and CRY2), period (PER1, PER2, and PER3) and other clock-controlled genes (McClung, 2013; Zhang and Kay, 2010). Although not specifically associated with circadian rhythm, the Val66Met genetic polymorphism of the brain-derived neurotrophic factor (BDNF) has specifically been associated with rapid cycling in bipolar disorder (Green et al., 2006; Liu et al., 2008; Muller et al., 2006). Subsequently, elevated plasma levels of BDNF were observed across all states of bipolar disorder (Munkholm et al., 2014). Since BDNF is a major regulator of synaptic transmission and plasticity, investigating its role in the switch between states in BD will prove important.

3.2.1. Origin of seasonal variation-induced changes in mood?

Modern day humans (*Homo sapiens*) originated in the Awash Valley of Ethiopia, a location close to equator where people were subject to a consistent 12:12 light dark cycle [12 h of daylight followed by 12 h of light; (White et al., 2003)]. Out of Africa migration of the human population led to genetic modulation of the circadian clock systems. This process also lead to risk variants associated with neuropsychiatric disorders, providing candidate genes for photoperiod-related environmental interactions (Forni et al., 2014). Such pressures may not have acted alone however. As these modern day humans entered the northern hemisphere, they were likely to encounter our predecessors *Homo neanderthalensis.* We know now that Neanderthals did not simply die out, but interbred with modern humans because modern humans originating from outside of Africa carry 1–4% of Neanderthal genes (Green et al., 2010). Support that Neanderthal genes may have contributed to susceptibility genes for BD comes from studies demonstrating a lower incidence of BD among those of African descent (Goodwin and Jamison, 1990; Neighbors et al., 2003; Perron et al., 2010; Weber et al., 2010). Considering Neanderthals spent 100,000s of years in the northern hemisphere, extreme responses to seasonal variation could have arisen leading to the disorder we now know as BD (Sherman, 2012). Seasonal changes require the body to exert homeostatic control, whereby decreased day lengths perceived through the eye and processed by the SCN of the hypothalamus can induce a reduced metabolic rate, slower movement, greater need for sleep, reduced responsiveness to sex, *etc*. These behaviors are all associated with depression. When the days start to lengthen, the same mechanism should induce increased metabolic rate, more energy, a greater desire to forage and find mates (goal-directed activities), behaviors associated with mania/hypomania. Therefore, it remains possible that during such a time-period evolutionary pressures could introduce random mutations producing aberrant responses to such changes in day-length, representing poor homestatic control. This evolutionary origin of bipolar disorder theory was detailed by Sherman (2012). Links to the mechanism(s) of how altered seasons, or photoperiod lengths, could induce such vast changes in behavior have however – up until recently – remained elusive.

3.2.2. Photoperiod-length-dependent neurotransmitter switching

Seasonal variation can induce changes in mood in those with a susceptibility to such effects. The mechanism of these effects, especially how the same person can exhibit such varied behaviors with differing underlying mechanisms, has been elusive. Conventional wisdom thought that the adult brain was hard-wired with specific neurons releasing set neurotransmitter levels. Increasingly however, the plasticity of the adult brain has been demonstrated, including in response to varied photoperiods as occur in seasonal variation. The first observation of photoperiod-dependent neurotransmitter respecification following changes in physiological levels of environmental illumination came from a developmental study in *Xenopus laevis* (Dulcis and Spitzer, 2008). The authors found that light can dynamically regulate the number of dopaminergic neurons in the developing hypothalamus and by innervating the melanotrope cells, it control skin pigmentation in tadpoles. An increase in the number of neurons expressing the dopaminergic phenotype occurred following two-hour exposure of tadpoles to a white background or to

constant light. The newly expressing neurons were not new added cells *via* proliferation or migration. The additional neurons came from recruitment of neuropeptide Y (NPY)-expressing neurons that were already integrated in the neuronal network controlling skin pigmentation. Recruited NPY neurons responded to a 2-h hyper-activation of the retinohypothalamic projection by co-expressing dopamine as an additional neurotransmitter. Ablation experiments aimed at compromising endogenous dopaminergic cells in the same network, showed that the recruitment of such reserve pool neurons could restore the camouflage behavior almost completely when natively dopaminergic neurons were ablated.

The exuberant plasticity of the young nervous system is often present in a more restrained form in the adult nervous system. Activity-dependent modulation of axonal sprouting, dendritic remodeling and synaptic strengths is robust in the developing nervous system and more modest but still present in the mature nervous system (Kozorovitskiy et al., 2005). Transmitter respecification however, does not appear to require either morphological remodeling or new network formation (involving changes in axon pathfinding, dendritic remodeling and synaptic strength), and is compatible with the limited remodeling ability of the mature CNS.

The follow-up questions that remained to be addressed was whether this novel form of neuroplasticity could be elicited in the nervous system of higher vertebrates, including mammals, and in the mature nervous system. There were few examples in the literature that provided insights on the possibility that neurons could switch to a different neurotransmitter in the mammalian system following activity/photoperiod manipulation. Neurons of the cervical spinal cord in cats display this type of recruitment for the cholinergic phenotype during development (Chakrabarty and Martin, 2010; Chakrabarty et al., 2009). The authors of these studies found that extensive circuit activation of the corticospinal tract affects the total number of ChAT-expressing neurons during a two-week period. In this case, newly cholinergic neurons were recruited from a reserve pool of spinal neurons that received the descending cortical input. Pharmacological manipulations aimed at blocking activity during this critical period abolished refinement of ChAT neurons in the spinal cord that displayed an immature neurotransmitter expression pattern.

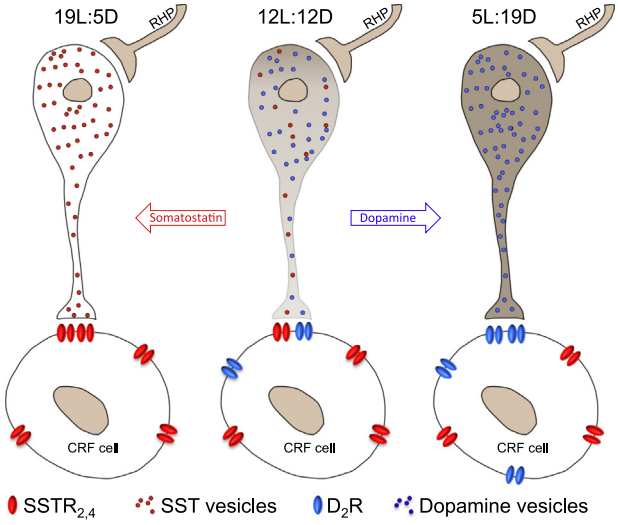


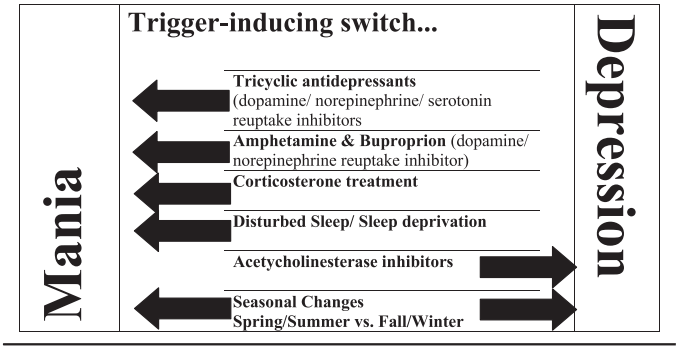
Fig. 3. Schematic model of photoperiod-induced neurotransmitter switching and receptor matching as occurs in nocturnal rats. Activation of the retino-hypothalamic projection (RHP) during a short-activity (19L:5D) photoperiod shifts transmitter expression in PaVN neurons to somatostatin (SST) while a long-activity (5L:19D) photoperiod shifts transmitter expression to dopamine. Dopamine type-2 receptor (D_2R) expression on corticotrophin releasing factor (CRF) cells changes in parallel with changes in dopamine expression while SST type-2,4 receptor ($SSTR_{2,4}$) expression remains constant.

As far as neurotransmitter switching in the mature nervous system, striatal TH-positive neurons increase in number in mouse and macaque models of Parkinson's disease (Aumann et al., 2008; Tande et al., 2006). Following MPTP- and 6-OHDA-treatments, lesions of the dopaminergic substantia nigra pars compacta were observed to partially recover by inducing phenotypic respecification of neurons intrinsic to the mouse striatum. Interestingly, newly TH-immunoreactive neurons in the macaque striatum expressed both DAT and glutamic acid decarboxylase, suggesting that they were recruited from a population of GABAergic interneurons (Tande et al., 2006).

Despite the studies summarized above, the first clear demonstration that neurotransmitter plasticity can be induced in the *mature* nervous system and can affect behavior came from a study in adult rats following exposure to altered photoperiods (Dulcis et al., 2013). In this study, adult rats were kept in either long-day low-activity inducing (19 h of light and 5 h of dark) or short-day high-activity inducing (5 h of light and 19 h of dark) cycles. After one week, neurotransmitters released by hypothalamic neurons switched from dopamine to somatostatin phenotype during long-day cycles (Fig. 3). The opposite occurred after 1-week exposure to short-days (switch from somatostatin to dopamine). Hence, the altered photoperiod diverging from a balanced day-night cycle (12 h light and 12 h dark a day) induced individual neurons in the hypothalamus to change expression of their neurotransmitters. In the same study, authors were able to show that neurotransmitter switching was coupled to dopamine- and somatostatin-receptor matching in the post-synaptic targets, the corticotrophin releasing factor (CRF)-releasing cells. The appearance of more dopaminergic interneurons presynaptically was paralleled by an increased expression of dopamine type-2 receptors (D_2Rs) postsynaptically (Fig. 3). Long-day photoperiods, lead to an increase of CRF titer in the cerebral spinal fluid (CSF) collected in the third ventricle following photoperiod manipulation. It is well known how changes in CRF concentration in the CSF modulate the level of circulating corticosteroids, which play a role in stress and depression. Dopamine is a neurotransmitter that plays a role in cognition (Arnsten et al., 1994; Vijayraghavan et al., 2007) motivation (Matsumoto and Hikosaka, 2009; Young, 2009; Young and Geyer, 2010), reward (Schultz, 2002), and decision-making (Floresco et al., 2006, , 2009; St Onge and Floresco, 2009; van Enkhuizen et al., 2014a). To investigate whether photoperiod-induced changes in dopamine expression had any consequences on animal behavior, the rats were tested in the elevated plus maze (EPM) and forced swim test (FST) as indicators of anxiety/risk-preference and despair-like behaviors respectively. Relative to controls, rats exposed to short-day cycles spent more time exploring the open arms of the EPM and spent less time immobile in the FST. In contrast, long-day exposure produced the opposite effects: rats explored the open arms less and exhibited increased immobility time. Interestingly, CRF expression can induce elevations in hippocampal acetylcholine (Desvignes et al., 2003). Such an increase is consistent with physostigmine-induced increases in immobility in the FST in mice that is hippocampal-mediated (Mineur et al., 2013). Further links between acetylcholine levels and behavioral despair are reports that acetylcholinesterase levels in the frontal cortex of mice negatively correlated with immobility in the FST (Livneh et al., 2010). Interestingly, this effect can also be seen in diurnal rodent species, whereby long-darkness photoperiod lengths induced depression-relevant behaviors in sand rats (Ashkenazy-Frolinger et al., 2010). Hence, there is evidence that 7-day exposure of rodents to short-activity photoperiod lengths can have a cascade effect which could result in elevated acetylcholine levels leading to depression-relevant behaviors.

The identity of the neurotransmitters expressed in a population of mature neurons has been thought to be fixed and immutable. *In vivo* observation of changes in transmitter specification in the adult rat brain linked to changes in behavior will substantially advance our scientific knowledge and suggest the value of

Table 1
Summary of triggers that induce switching to each state of bipolar disorder. Clear from the table is that altering catecholaminergic homestatic control induces mania, as does sleep deprivation, and long-activity photoperiod lengths. While antidepressants and sleep deprivation can treat depression, patients can switch to a manic episode. There are few specific triggers that induce depression, but elevating acetylcholine levels and entering periods of low photoperiod lengths are two known triggers. Interestingly, changing photoperiod lengths to high-activity can imbalance catecholaminergic control, while low-activity lengths can elevate acetylcholine levels. Hence, this photoperiod changing hypersensitivity mechanism may have originally underlain switching between states and the other triggers simply alter that system. Any model organism relevant to switching/cycling in bipolar disorder should exhibit a hypersensitivity to these some if not all of these triggers.



determining whether there are comparable changes in the striatum, cortex, and hippocampus. The switch between TH to somatostatin and CRF production in adult rats dependent upon photoperiod length provides mechanistic support that the same adult human could exhibit extreme opposite behaviors when exposed to similar seasonal-induced changes in photoperiod length. The heritability of BD would promote studies identifying a genetic polymorphism that induces a susceptibility to such photoperiod-induced neurotransmitter switching.

3.3. Summary of putative mechanism(s) underlying switching between states of BD

It is clear from this review of the literature that the mechanism (s) underlying cycling/switching between states in BD will not be easily discovered. Switches to manic episodes appear to be driven by elevated catecholamines (dopamine and norepinephrine, or their precursor TH), or at least poor catecholaminergic homeostasis. Disruption in daily rhythm, or entry into high-activity photoperiod lengths (spring/summer) can also induce switches into a manic episode. It is interesting to note that entry into high-activity photoperiod lengths (spring/summer) elevate TH levels. Hence, there is distinct overlap between the stimuli that can induce a manic state. The triggers that switch sufferers to a depressed state appear less clear, with elevated acetylcholine levels, stress, and entry into low-activity photoperiod lengths (fall/winter) among the few certainties. Again, there is overlap between mechanisms underlying switching to this state, whereby entry into low-activity photoperiods can indirectly increase stress-related neurotransmitter and acetylcholine levels (Table 1). Most importantly, the neurotransmitter switching that occurs in response to changing photoperiod lengths provide insight into how the same adult brain can exhibit polar opposite behaviors representing distinct neural mechanisms at different time points. An important question remains however, as to what genetic polymorphism(s) make sufferers susceptible to extreme variation to these environments.

4. Future directions

It remains unclear as to whether there are specific behaviors associated with the triggers mentioned above that induce switching in BD. The literature almost exclusively measures mood using clinician-interviewed rating scales of mood, which are difficult to quantify and test across species since interpretative leaps must be made for animals (Geyer et al., 2012; Young et al., 2011, 2013, 2009). While measuring mood state is important, equally important would be to quantify behavioral changes using clinical neuroscience techniques that are likely more closely tied to altered brain function at the circuit level, as detailed by NIMH-sponsored initiative such as CNTRICS and RDoC (Barch and Carter, 2008; Carter et al., 2011; Cuthbert and Insel, 2010; Morris and Cuthbert, 2012). Collectively, these findings would provide a framework into which experimental assessment of these neural mechanistic changes and their behavioral effects (in humans and animals) can be investigated. Numerous laboratory-based cross-species tests of cognitive state exist however (Young and Geyer, 2014) and could be used to quantify changes in behavior of patients during switches from one mood state to another. Hence, one of the most important strategies for identifying mechanisms underlying such switching will be to utilize these cross-species relevant behavioral tests during pharmacological treatments, or changing seasons. Utilizing cross-species relevant behaviors, would enable similar tests to be conducted on model organisms thought to reflect the altered neurocircuitry seen in BD patients, consistent with the approach by the RDoC initiative (Cuthbert and Insel, 2010; Morris and Cuthbert, 2012). Considering the cognitive performance of patients with BD is linked to their functional outcome (Green, 2006), measuring such performance across mood states will be vital for treatment development. Current treatments can deleteriously affect cognitive performance. For example, lithium significantly impairs cognitive performance in a variety of domains (Amado et al., 2005; Stip et al., 2000). Thus, by using clinical neuroscience tools, targets could also be identified that relate to cognitive dysfunction, enabling targeted treatments for this long-overlooked domain to be developed. Longitudinal studies on treatment- and light exposure-induced switching of behavior should also be conducted using such tests. Behaviors to focus on will be those that can be conducted repeatedly and that likely differentiate depending on when in a manic or depressed state. A key example of such laboratory-based techniques differentiating behavior in the two states is the hypersensitivity of patients in a manic or depressed to reward (Cassidy et al., 1998) or punishment (Adida et al., 2011; Must et al., 2013) respectively. Tasks such as the Iowa Gambling Task which differentially measures responses to reward and punishment (Bechara et al., 1994) would be useful since it is possible to test the risk-preference of mice (van Enkhuizen et al., 2014a) and rats (Rivalan et al., 2009, 2013) in such a task. Another example includes sensorimotor gating measured using the prepulse inhibition (PPI) of startle. PPI is impaired in patients with BD mania (Perry et al., 2001), an effect replicated in severely hyperdopaminergic mice (Powell et al., 2008), but these deficits are not observed in depressed subjects (Kohl et al., 2013) or mice with elevated acetylcholine (Clark et al., 2005). Hence, future studies using cross-species assessment tools in BD sufferers exposed to switch-inducing triggers can be conducted.

In addition to the assessment of patient and model organisms in cross-species relevant tasks, a key future direction will be to identify what manipulation(s) would provide the optimal model organism. As was described above, rs41350144 which lies within the intron of NF1A on 1p31 may be a susceptibility gene for seasonality in BD (Lee et al., 2013). Other genes linked to psychiatric conditions have been recreated and inserted into mice, such as the disrupted in schizophrenia 1 (DISC1)/boymaw transfusion gene (Ji et al., 2014) that has been related to schizophrenia and BD. Furthermore, a key element of catecholaminergic

homeostasis in the prefrontal cortex is the catecho-methyltransferase (COMT) gene (Allen et al., 1997; Risbrough et al., 2014; Tunbridge et al., 2012). COMT clears dopamine in the prefrontal cortex and the allelic variants of COMT result in faster (val/val) or slower (met/met) dopamine clearance (Allen et al., 1997). These allelic variants have been recreated in mice and have similar functional consequences (Risbrough et al., 2014). Another genetic polymorphism identified as relevant to rapid cycling in BD is the BDNF Val66Met polymorphism (Green et al., 2006; Liu et al., 2008; Muller et al., 2006). Given that this polymorphism has also been recreated in mice (Bath et al., 2012; Chen et al., 2006), testing the effects of pharmacological treatments or seasonal variation known to induce switching in any of these mouse lines on cross-species relevant behaviors could provide insight as to their importance for cycling in BD.

The literature review highlighted that altered catecholaminergic homeostasis likely plays a role in switching between mood states in BD. One key mechanism of such homeostasis in addition to COMT is the re-uptake of dopamine, and to a lesser extent norepinephrine, by the DAT. Several studies link altered DAT functioning in patients with BD. For example, polymorphisms in the DAT gene have been linked with BD (Greenwood et al., 2006a; Pinsonneault et al., 2011), which likely lower functional DAT levels (Horschitz et al., 2005). In support of this possibility, reduced striatal DAT levels are seen using positron emission tomography study in unmedicated BD patients (Anand et al., 2011) and from their postmortem tissue (Rao et al., 2012). Hence, mice with reduced functioning of the DAT may recreate the impaired catecholaminergic homeostasis seen in patients and mediate switching between states. Mice with extremely reduced DAT function (10% compared to wildtype controls) exhibit numerous behavioral abnormalities that are consistent with BD mania patients, including (1) hyper-exploration and straighter movement seen in the Behavioral Pattern Monitor (Perry et al., 2009; Young et al., 2010a, 2010b), (2) that is treated with chronic valproate administration (van Enkhuizen et al., 2012), (3) which degrades with repeated testing, similar to SRT treatment (Young et al., 2010b) and (4) high-reward preference increased risk-preference as measured by the Iowa Gambling Task (van Enkhuizen et al., 2014a). The 10% of DAT levels seen in these mice are much lower than unmedicated BD patients however [approximately 80% (Anand et al., 2011)]. Interestingly, rats placed in high-activity photoperiod lengths (that induce EPM-related risk-preferring behavior) have lower DAT levels compared to those kept in a balanced photoperiod (Dulcis et al., 2013). Hence, it is possible that mice with low, but not extremely low DAT levels, may better recreate the state seen in BD sufferers, whereby stimuli resulting in a switch to a mania-like state would further lower their DAT levels.

Other manipulations that would be useful to investigate whether they contribute to switching are manipulations of genes that underlie circadian rhythm. Naturally, any animal with an altered circadian rhythm may elicit altered behavioral responses to changing photoperiod length in a manner consistent with that of BD. Genetic mutants such as *Clock*Δ19 mice have a deletion of exon 19 in the CLOCK gene and exhibit BD-relevant behaviors such as lower immobility in the FST, sweet sucrose solution and cocaine preference, and have lower reward thresholds identified using intra-cranial self-stimulation (McClung et al., 2005; Roybal et al., 2007), and impaired PPI (van Enkhuizen et al., 2013b). Some of these behaviors are attenuated by lithium treatment (Roybal et al., 2007). These *Clock*Δ19 mice do not however exhibit increased specific exploration or straight line movements (van Enkhuizen et al., 2013b) seen in BD mania patients (Minassian et al., 2011; Perry et al., 2009). Moreover, this mutant arose from a random deletion not a targeted recreation of changes seen in patients with BD. Importantly, the effect of altered photoperiod lengths in these mice have yet to be established, nor have they been conducted in other circadian gene relevant BMAL1 and NPAS2 mutant mice.

Finally, while it is clear that there has been a strong seasonal variation driving switches in mood states in BD, this effect may have been reduced over time with the increased use of artificial lighting. In fact, people's internal circadian clock do not entrain to solar time unless they are exposed to a minimum of 7 days of natural sunlight during wilderness camping (Wright Jr. et al., 2013). The increased availability of low level lighting from smartphones, tablets, and readers likely reduces solar entrainment even further. Importantly, while 7 days were required for human solar entrainment, the same number of days were required for entraining rats to altered photoperiod length-induced neurotransmitter switching (Dulcis et al., 2013). Combined, these premises support the possibility that mood switching in BD could have derived from natural sunlight variation in seasons, and that modern electrics may confound these effects. Irrespective of modern lighting-induced limitation in seasonal switching, this hypothesis would mean that the mechanisms underlying switching in BD remain and can be investigated. This mechanism could also be recreated in animals exposed to altered photoperiod lengths. Furthermore, studies identifying a susceptibility gene that engenders hypersensitivity to seasonality switching could also be conducted (*e.g.*, NF1, BDNF, CLOCK, DAT *etc.*). Importantly, using photoperiod chambers and the ability to conduct cross-species relevant testing of mania- and depression-relevant behaviors in mice, such seasonality-induced switching studies can be conducted. The key remains to identify a manipulation that results in a *hypersensitivity* to such changes, and the triggers outlined above.

Acknowledgments

We thank Drs. Geyer, Minassian, Perry, Spitzer for their support. These studies were supported by NIH, United States Grants R01-MH042228, R01-MH071916, a Kavli Grant KIBM-2012-008, as well as by the Veteran's Administration VISN 22 Mental Illness Research, Education, and Clinical Center.

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