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Review

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

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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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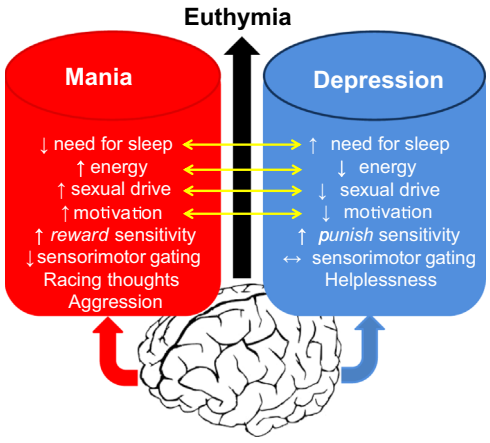

Fig. 1. Symptoms of the extreme states of bipolar disorder, mania and depression. Bipolar disorder is a unique disorder that transcends domains of function because the same patient can exhibit depression or mania at different points in their life. Periods when they exhibit symptoms of neither state are 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