



# The catecholaminergic–cholinergic balance hypothesis of bipolar disorder revisited



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## ARTICLE INFO

### Article history:

Accepted 27 May 2014

Available online 5 August 2014

### Keywords:

Bipolar disorder

Mania

Depression

Acetylcholine

Dopamine

Mice

## ABSTRACT

Bipolar disorder is a unique illness characterized by fluctuations between mood states of depression and mania. Originally, an adrenergic–cholinergic balance hypothesis was postulated to underlie these different affective states. In this review, we update this hypothesis with recent findings from human and animal studies, suggesting that a catecholaminergic–cholinergic hypothesis may be more relevant. Evidence from neuroimaging studies, neuropharmacological interventions, and genetic associations support the notion that increased cholinergic functioning underlies depression, whereas increased activations of the catecholamines (dopamine and norepinephrine) underlie mania. Elevated functional acetylcholine during depression may affect both muscarinic and nicotinic acetylcholine receptors in a compensatory fashion. Increased functional dopamine and norepinephrine during mania on the other hand may affect receptor expression and functioning of dopamine reuptake transporters. Despite increasing evidence supporting this hypothesis, a relationship between these two neurotransmitter systems that could explain cycling between states of depression and mania is missing. Future studies should focus on the influence of environmental stimuli and genetic susceptibilities that may affect the catecholaminergic–cholinergic balance underlying cycling between the affective states. Overall, observations from recent studies add important data to this revised balance theory of bipolar disorder, renewing interest in this field of research.

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## 1. Introduction

Bipolar disorder is a debilitating neuropsychiatric illness that affects approximately 1% of the global population (Merikangas et al., 2011). A fundamental and distinctive characteristic of bipolar disorder is its cyclical nature involving switches between periods of mania and depression, distinguishing it from other psychiatric disorders such as schizophrenia and major depressive disorder. Symptoms of mania include elevated or irritable mood, hyperactivity, racing thoughts, less need for sleep, grandiosity, and sometimes psychotic symptoms. Depression is largely associated with symptoms seemingly opposite to those of mania, such as sad mood, poor self-esteem, insomnia, lethargy or feeling ‘slowed down’, and anhedonia (DSM-V, 2013). Despite the availability

of a broad range of antipsychotics, antidepressants, and mood stabilizers, the treatment of bipolar disorder remains inadequate and an unmet public health need. Together with the multifaceted symptomatology, about a third of bipolar disorder patients attempt suicide (Novick et al., 2010), and the associated mortality rate from suicide attempts is high in this population (Osby et al., 2001). A better understanding of the mechanisms underlying the specific states of mania and depression could improve development of targeted therapies and ultimately benefit patients.

## 2. The original adrenergic–cholinergic balance hypothesis of mania and depression

Several decades ago, an adrenergic–cholinergic balance hypothesis was first postulated, proposing that the underlying mechanisms of mania reflect an imbalance of high adrenergic activity, whereas depression is a state caused by relative high cholinergic compared to adrenergic activity (Janowsky et al., 1972). Evidence for the involvement of central acetylcholine in the

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regulation of depression arose from reports of cholinergic agonists and acetylcholinesterase inhibitors inducing severe depression in humans and antagonizing symptoms of mania (Janowsky et al., 1994). These compounds increase central cholinergic tone because acetylcholinesterase is the primary enzyme responsible for breaking down acetylcholine throughout the nervous system. Various acetylcholinesterase inhibitors (Gershon and Shaw, 1961; Rowntree et al., 1950; Bowers et al., 1964), including physostigmine (Janowsky et al., 1973b; Modestin et al., 1973b, 1973a; Janowsky et al., 1974; Davis et al., 1978; Oppenheim et al., 1979; Risch et al., 1981) have been reported to induce symptoms of depression in human subjects. Other agents that induce depression are the direct cholinergic muscarinic receptor agonist arecoline (Nurnberger et al., 1983), the non-selective muscarinic receptor agonist oxotremorine (Davis et al., 1987), and acetylcholine precursors including deanol, choline, and lecithin (Casey, 1979; Davis et al., 1979) [see Janowsky et al. (1994) for review]. Importantly, symptoms observed after administration of these compounds were similar to those that manifest in naturally occurring depression (Janowsky et al., 1994). These depressive states induced by cholinergic agonists or acetylcholinesterase inhibitors were observed in a wide range of populations, including healthy subjects (Risch et al., 1981; Nurnberger et al., 1983), marijuana-intoxicated subjects (El-Yousef et al., 1973), patients with Alzheimer's (Davis et al., 1979), and patients with a psychiatric illness such as depression, schizophrenia, or bipolar disorder (Janowsky et al., 1974, 1980). Furthermore, patients with an affective component displayed an exaggerated depressive behavioral response after increasing central acetylcholine levels compared to healthy volunteers. Hence, a super- or hypersensitivity of patients with endogenous depression or bipolar disorder for cholinergic manipulations was observed, supportive of a cholinergic imbalance during periods of depression (Janowsky et al., 1994).

In further support of the central acetylcholine-mediation of effects, the centrally acting agent physostigmine antagonizes mania and induces depression, whereas its non-centrally acting congener neostigmine does not, thus suggesting a central mechanism (Janowsky et al., 1973b). In addition, the centrally acting muscarinic antagonist scopolamine blocks the effects of physostigmine, whereas the non-centrally acting methscopolamine does not cause behavioral effects (Janowsky et al., 1986). Further supporting a role for central muscarinic acetylcholine mechanisms in contributing to depression comes from neuroendocrine and sleep electroencephalography (EEG) studies. Physostigmine administration increases serum adrenocorticotrophic hormone, cortisol, epinephrine, and  $\beta$ -endorphin serum levels, all neuroendocrine compounds that are increased in endogenous depression (Janowsky et al., 1986) and concomitantly increase pulse and blood pressure levels. Furthermore, physostigmine further shortens the sleep EEG marker rapid eye movement (REM) latency in depressed patients. REM latency shortening itself is thought to be a marker of depression, an acetylcholine-mediated phenomenon that increases blood pressure and pulse rate (Dube et al., 1985; Sitaram et al., 1987). Significantly, these physostigmine-induced changes, as with the behavioral, cardiovascular, and neuroendocrine changes described above, are antagonized by scopolamine (Janowsky et al., 1986). Hence, centrally acting acetylcholine, acting particularly via muscarinic acetylcholine receptors, mediates physiological changes similar to those present during depressive behaviors.

Importantly, investigations into the mechanisms underlying depression and mania support an adrenergic–cholinergic balance. Intravenous administration of the dopamine/norepinephrine reuptake inhibitor methylphenidate antagonized the depressive behavior induced by physostigmine in humans (Janowsky et al., 1973a). Conversely, the behavioral activation and manic symptoms caused by methylphenidate were antagonized by physostigmine (Janowsky et al., 1973a), supporting an adrenergic–cholinergic

balance hypothesis. Moreover, methylphenidate as well as other psychostimulants such as amphetamine can induce symptoms relevant to mania in healthy persons (Peet and Peters, 1995) or exacerbate symptoms of mania in patients with bipolar disorder (Meyendorff et al., 1985; Hasler et al., 2006). Therefore, mania was thought to involve an underlying pathophysiology of hypocholesteremia and increased adrenergic signaling in contrast to depression, which was thought to have the converse.

Since the original concept of the adrenergic–cholinergic hypothesis was proposed in 1972 and the latest review was written in 1994, years of extensive research have been conducted. Both preclinical and clinical studies have led to significant discoveries, warranting an updated review on this potential neurochemical imbalance theory underlying bipolar disorder. Today's technology is far superior to that available a few decades ago, with neuroimaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) including novel radioligands being possible to quantify receptors in vivo in the human brain. Other techniques include different manipulations such as viral knockdown of genes in animal models. At the time of the adrenergic–cholinergic hypothesis of bipolar disorder, little was known about dopamine, let alone its contribution to mania. More recently however, research supports a strong contribution of dopamine to the mechanism(s) underlying mania. Hence, a catecholaminergic (i.e., dopamine and norepinephrine) mechanism may better describe the potential biological underpinnings of mania. Although the importance of the cholinergic system during depression was recently reviewed (Dagyte et al., 2011), bipolar disorder was not its primary focus and it was not contrasted with mania. Thus, the purpose of this comprehensive review is to provide an overview of recent evidence from both human and animal studies that support a catecholaminergic–cholinergic balance theory of bipolar disorder.

The original adrenergic–cholinergic balance hypothesis of mania and depression in bipolar disorder is updated with recent observations in a revised catecholaminergic–cholinergic hypothesis of bipolar disorder. First, we discuss clinical findings regarding the involvement of the cholinergic and catecholaminergic system and their interactions in bipolar depression and mania respectively. We summarize data from neuroimaging studies, discuss neuropharmacological evidence, and briefly mention some genetic association studies. While discussing depression, it is important to note that it currently remains difficult to differentiate between bipolar and unipolar depression. We have therefore included findings from both affective states, highlighting differences and interactions where they occur. After a clinical update, we will discuss observations from preclinical studies investigating both the cholinergic and catecholaminergic systems in animal models. Finally, recommendations for future studies are made followed by concluding remarks.

## 2.1. Bipolar depression—evidence from humans

The original hypothesis of bipolar disorder was largely based on findings of increased acetylcholine by different manipulations causing depression. Since then, a variety of studies have supported these observations and renewed interest in this old theory. Studies have also led to a monoamine deficiency theory, in particular reduced serotonin deduced from the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression. Here, we will update evidence regarding the involvement of the cholinergic system in depression (Table 1).

### 2.1.1. Observations from neuroimaging studies

In order to present an overview of neuroimaging data concerning cholinergic receptors, it must be mentioned that over the past

**Table 1**  
Summary of human findings on the cholinergic system in depression.

Evidence	Observations	References
Neuroimaging	↓ M <sub>2</sub> in BD depression, but not MDD ≈ M <sub>2</sub> /M <sub>4</sub> in BD (postmortem) ↓ M <sub>2</sub> /M <sub>3</sub> in BD (postmortem) ↓ M <sub>2</sub> in MDD (postmortem) ↓ β <sub>2</sub> -nAChR in MDD ↓ β <sub>2</sub> -nAChR in BD depression, but not euthymic ↑ choline in MDD	Cannon et al., 2006 Zavitsanou et al., 2005 Gibbons et al., 2009 Gibbons et al., 2009 Saricicek et al., 2012 Hannestad et al., 2013 Charles et al., 1994; Steingard et al., 2000
	Antidepressant effects of scopolamine Antidepressant effects of scopolamine in MDD and BD depressed  Antidepressant effects of scopolamine as adjuvant with SSRI in MDD Antidepressant effects of nAChR antagonist mecamylamine as adjuvant with SSRI Mood stabilizing effect of nAChR antagonist mecamylamine in BD Antidepressant effects of nAChR agonists	Janowsky, 2011 Furey et al., 2006, 2010; Drevets and Furey, 2010; Frankel et al., 2011 Khajavi et al., 2012 George et al., 2008 Shytle et al., 2000 Gatto et al., 2004; Dagyte et al., 2011
Genetic	M <sub>2</sub> associated with MDD M <sub>2</sub> associated with BD depression α <sub>7</sub> -nAChR associated with BD α <sub>2</sub> -nAChR not associated with BD	Comings et al., 2002; Wang et al., 2004 Cannon et al., 2011 Hong et al., 2004; Ancin et al., 2010 Lohoff et al., 2005

m=muscarinic, BD=bipolar disorder, MDD=major depressive disorder, nAChR=nicotinic acetylcholine receptor, SSRI=selective serotonin reuptake inhibitor, ↑=increased, ↓=decreased, ≈=no effect.

several decades increasingly more subtypes of cholinergic receptors have been discovered. Cholinergic receptors are divided into the ionotropic nicotinic and metabotropic muscarinic (M) acetylcholine receptors. Several subtypes of the nicotinic receptors have been discovered, differing in their α and β subunit composition (Ferreira et al., 2008). Of the muscarinic receptors, to date five different subtypes have been discovered (M<sub>1</sub> to M<sub>5</sub>). This diversity in composition and subtypes of acetylcholine receptors plus the use of radioligands having varying degrees of specificity for these receptor subtypes makes studying receptor functioning in patients complex. Nevertheless, several reports exist that have enhanced our current understanding of the acetylcholine receptor system in patients with depression.

PET imaging is an excellent methodology to determine whether abnormal receptor expression occurs in living patients. For example, using PET imaging, reduced M<sub>2</sub> receptor binding was observed within the anterior cingulate cortex of individuals with bipolar depression, but not in patients with major depressive disorder, compared to healthy subjects (Cannon et al., 2006). For their PET scans, the authors used a radioligand whose binding can be reduced by direct competition for receptor binding from endogenous acetylcholine. Therefore, this reduced M<sub>2</sub> receptor binding noted above was likely because of increased endogenous acetylcholine levels and not a decreased M<sub>2</sub> receptor population. This interpretation is supported by a postmortem study, in which M<sub>2</sub> and M<sub>4</sub> receptor density was unaltered in bipolar disorder subjects compared to controls (Zavitsanou et al., 2005). However, another postmortem study reported reduced M<sub>2</sub> and M<sub>3</sub> receptor binding in discrete regions of the frontal cortex of bipolar disorder patients and reduced M<sub>2</sub> receptor binding alone in major depressive disorder patients (Gibbons et al., 2009). Together, this possible reduced receptor density could reflect a compensatory mechanism to maintain normal cholinergic activity as a result of long-term hypercholinergia in bipolar disorder depression. In a more recent study investigating the nicotinic receptors using SPECT and MRI scans, it was observed that major depressive disorder patients had a lower availability of β<sub>2</sub>-subunit-containing nicotinic receptors compared to healthy comparison subjects (Saricicek et al., 2012). Importantly, no differences in β<sub>2</sub> nicotinic receptor availability were observed after endogenous bound acetylcholine was washed out in postmortem samples, suggesting that the low levels of β<sub>2</sub> nicotinic receptors in vivo were likely due to high levels of

extracellular acetylcholine. Moreover, acutely ill patients had lower β<sub>2</sub> nicotinic receptor levels than remitted subjects, suggesting that elevated acetylcholine activity is more closely associated with depressive symptoms. These findings were confirmed in patients with bipolar disorder, where lower β<sub>2</sub> nicotinic receptor availability was observed in depressed bipolar disorder subjects compared to both euthymic and control subjects (Hannestad et al., 2013). As with the major depressive disorder study, differences in β<sub>2</sub> nicotinic receptor levels disappeared after acetylcholine was washed out, suggesting again that increased endogenous acetylcholine functioning may underlie depression. This theory is also supported by increased levels of choline, the rate-limiting precursor to acetylcholine, observed in brains of depressed patients measured in vivo (Charles et al., 1994; Steingard et al., 2000). Altogether, these neuroimaging data support a hypercholinergic nature of depression resulting in altered (i.e., decreased) compensatory levels of both muscarinic and nicotinic acetylcholine receptors.

### 2.1.2. Observations from neuropharmacological studies

Additional support for a hypercholinergic imbalance during depression comes from observations of the antidepressant effects of the non-competitive muscarinic antagonist scopolamine in patients (Janowsky, 2011). Intravenously administered scopolamine rapidly attenuated symptoms of depression in both major depressive disorder and bipolar depressed patients (Furey and Drevets, 2006), a finding replicated in patients with major depressive disorder (Drevets and Furey, 2010; Furey et al., 2010) and bipolar disorder depression (Frankel et al., 2011). Another study demonstrated the effectiveness of oral scopolamine as an adjuvant to citalopram in alleviating the symptoms of major depression (Khajavi et al., 2012).

Other support for a cholinergic role in depression comes from drug studies targeting the nicotinic receptors, although results so far have been mixed [see Dagyte et al. (2011)]. That nicotinic receptors play a role in mood regulation, may partially explain the high prevalence of smoking in patients with affective disorders (Glassman et al., 1990) and the high rates of depression in these patients upon nicotine withdrawal. It is unclear however, whether depressed smokers use nicotine to alleviate their symptoms (self-medicate) or if smoking increases the risk of developing depression (Markou et al., 1998; Shytle et al., 2002). Inconsistent results on the treatment of depression have been observed when



nicotinic receptor agonists and antagonists are given (Shytle et al., 2002; Dagyte et al., 2011). For instance, the nicotinic receptor antagonist mecamylamine reduced symptoms of depression as an augmentation strategy with SSRI treatment (George et al., 2008) and stabilized mood in bipolar patients (Shytle et al., 2000), while antidepressant effects with nicotinic receptor agonists have also been described (Gatto et al., 2004; Dagyte et al., 2011). Together, both nicotinic and muscarinic receptors are widely expressed and co-localized in the brain (Ferreira et al., 2008). Studies from drugs targeting both receptors underscore the importance of cholinergic systems in depressed states and offer potential therapeutic targets.

### 2.1.3. Observations from genetic studies

Although the field of genetics exceeds the scope of this review, some findings from single-nucleotide polymorphisms (SNP) association studies deserve mentioning. Regarding the muscarinic receptors, the  $M_2$  receptor gene has been associated with major depressive disorder (Comings et al., 2002; Wang et al., 2004). More recently, genetic variation within the  $M_2$  receptor gene has been associated with the above-mentioned reduced  $M_2$  receptor binding in patients with bipolar disorder depression (Cannon et al., 2011). Other linkage studies observed genetic variation within the  $\alpha_7$  nicotinic receptor gene associated with bipolar disorder (Hong et al., 2004; Ancin et al., 2010), but not the  $\alpha_2$  nicotinic receptors gene (Lohoff et al., 2005).

### 2.1.4. Summary of findings associating acetylcholine with bipolar disorder

In summary, these data support a hypercholinergic state during periods of bipolar depression. As a result of these elevated acetylcholine levels, compensatory decreases likely occur in both muscarinic and nicotinic acetylcholine receptors, in particular the  $M_2$  and  $\beta_2$  receptors. Treatment studies with anticholinergic drugs are few so far, although results with scopolamine seem promising and may provide a target for potential new drugs.

## 2.2. Bipolar mania—evidence from humans

Increased functional catecholamines (norepinephrine and dopamine) was postulated several decades ago as a mechanism underlying the manic phase of bipolar disorder, termed the catecholamine hypothesis (Bunney and Garland, 1982). Over time, the role of catecholamines in the etiology of bipolar disorder mania remains relevant, with supportive evidence ranging from more recent neuropharmacological and neuroimaging studies (Garakani et al., 2007; Cousins et al., 2009). Several reviews so far have described the importance of hyperdopaminergia during mania (Vawter et al., 2000; Manji et al., 2003; Berk et al., 2007). Here, we will review recent findings on the involvement of the catecholaminergic system in bipolar disorder mania (Table 2).

### 2.2.1. Observations from neuroimaging studies

Dopamine receptors are grouped into two families: the  $D_1$ -type ( $D_1$  and  $D_5$ ) and  $D_2$ -type receptors ( $D_2$ ,  $D_3$ , and  $D_4$ ). These subtypes of dopamine receptors have been studied in patients with bipolar disorder. For instance, lower  $D_1$  receptors were observed in the frontal cortex, but not the striatum, of bipolar disorder subjects across all states compared with healthy controls (Suhara et al., 1992). Lower  $D_1$  receptor levels could reflect higher synaptic dopamine levels, supporting a hyperdopaminergic state in these bipolar disorder patients. No difference in  $D_2$  receptor availability was observed between nonpsychotic bipolar disorder patients and healthy individuals however (Anand et al., 2000; Yatham et al., 2002), although increased caudate  $D_2$  receptor density was observed in psychotic bipolar disorder patients compared to

healthy individuals (Pearlson et al., 1995; Wong et al., 1997). Treatment with the mood-stabilizing medication valproate decreased dopaminergic function in manic bipolar disorder patients (Yatham et al., 2002), perhaps underlying its mechanism of efficacy. Besides dopamine receptors, the dopamine transporter—the primary mechanism for reuptake of free dopamine in the presynaptic neuron (Cooper et al., 1991)—has also been studied extensively in bipolar disorder research (Vaughan and Foster, 2013). Higher striatal dopamine transporter binding was observed in both depressed (Amsterdam and Newberg, 2007) and drug-free euthymic (Chang et al., 2010) bipolar disorder patients. In contrast however, reduced striatal levels of dopamine transporter were observed in unmedicated depressed and euthymic bipolar disorder patients (Anand et al., 2011), in the postmortem tissue of bipolar disorder patients (Rao et al., 2012), but also in patients with attention deficit disorder (Fusar-Poli et al., 2012). Future and larger studies should investigate dopamine transporter levels in patients with bipolar disorder mania in relation to behavior and symptomatology.

### 2.2.2. Observations from neuropharmacological studies

Evidence for increased catecholaminergic activity underlying bipolar disorder mania comes from pharmacological interventions commonly used for treatment. Both typical and atypical antipsychotics, commonly used to treat mania, have direct and indirect actions on lowering dopamine signaling. Numerous antidepressants increase levels of synaptic catecholamines, and subsequently can switch a patient from a depressive to manic state (Salvi et al., 2008). Mood stabilizers such as lithium and valproate also exert some actions on dopamine signaling (Cousins et al., 2009), with valproate increasing dopamine transporter gene expression in human cells (Wang et al., 2007). Other support comes from psychostimulants such as amphetamine and cocaine that increase extracellular dopamine and norepinephrine and can induce symptoms similar to mania (Jacobs and Silverstone, 1986; Malison et al., 1995), while amphetamine withdrawal is frequently associated with depression (Jacobs and Silverstone, 1986). The euphoric effects of amphetamine have been reversed by the mood stabilizer lithium and antipsychotics in some reports (Van Kammen and Murphy, 1975; Silverstone et al., 1980), but not others (Brauer and De Wit, 1997; Silverstone et al., 1998). Other agents such as the dopamine precursor L-dopa and dopaminergic agonists pramipexole and bromocriptine can also induce mania (Cousins et al., 2009). Interestingly, pramipexole and bromocriptine improved the mood of bipolar disorder depressed patients (Silverstone, 1984; Zarate et al., 2004), supporting a catecholamine deficiency during depression. Other support for a hypodopaminergic state during depression comes from reduced cerebrospinal fluid (CSF) levels of the metabolite of dopamine homovanillic acid in untreated bipolar disorder depressed patients (Subrahmanyam, 1975; Gerner et al., 1984). When bipolar disorder depressed patients were treated with medication, normal or increased homovanillic acid levels were observed compared to controls. In contrast, increased CSF homovanillic acid levels are observed during manic episodes of bipolar disorder (Sjostrom and Roos, 1972; Gerner et al., 1984).

Tyrosine hydroxylase activity is the rate-limiting step in dopamine synthesis. Treatment with the tyrosine hydroxylase inhibitor alpha-methyl-para-tyrosine therefore depletes catecholamines and was observed to reduce symptoms of mania, while it increased depression (Brodie et al., 1971; Bunney et al., 1971). Euthymic patients with bipolar disorder became hypomanic after recovery from catecholamine depletion by treatment with the synthesis inhibitor (Anand et al., 1999). Catecholamine synthesis and release, in particular dopamine compared to norepinephrine, can also be reduced by administration of a tyrosine-free mixture

**Table 2**  
Summary of human findings on the catecholaminergic system in mania.

Evidence	Observations	References
Neuroimaging	↓ D <sub>1</sub> receptors in BD across states	Suhara et al., 1992
	≈ D <sub>2</sub> receptors in non-psychotic BD	Anand et al., 2000; Yatham et al., 2002
	↑ D <sub>2</sub> receptors in psychotic BD	Pearlson et al., 1995; Wong et al., 1997
	↑ DAT in BD depression	Amsterdam and Newberg, 2007
	↑ DAT in drug-free euthymic BD	Chang et al., 2010
Neuropharmacological	↓ DAT in drug-free euthymic or depressed BD	Anand et al., 2011
	↓ DAT in BD (postmortem)	Rao et al., 2012
	Valproate↓dopamine functioning in BD mania	Yatham et al., 2002
	Valproate↑DAT gene expression	Wang et al., 2007
	Antidepressants can switch depression to mania	Salvi et al., 2008
	Amphetamine and cocaine↑mania-like symptoms	Jacobs and Silverstone, 1986; Malison et al., 1995
	Amphetamine withdrawal→depression	Jacobs and Silverstone, 1986
	Euphoria by amphetamine reversed by lithium and antipsychotics	Van Kammen and Murphy, 1975; Silverstone et al., 1980
	Euphoria by amphetamine not reversed by lithium and antipsychotics	Brauer and De Wit, 1997; Silverstone et al., 1998
	L-dopa, pramipexole, and bromocriptine→mania	Cousins et al., 2009
	Pramipexole and bromocriptine improves mood in BD depression	Silverstone, 1984; Zarate et al., 2004
	↓ CSF HVA levels in drug-free BD depressed	Subrahmanyam, 1975; Gerner et al., 1984
	≈ or↑ CSF HVA levels in medicated BD depressed	Subrahmanyam, 1975; Gerner et al., 1984
	↑ CSF HVA levels in BD mania	Sjostrom and Roos, 1972; Gerner et al., 1984
	AMPT↓mania, but↑depression	Brodie et al., 1971; Bunney et al., 1971
Genetic	After AMPT recovery euthymic BD→manic	Anand et al., 1999
	Tyrosine free diet↓BD mania	McTavish et al., 2001
	Tyrosine free diet↓mania-like effects of amphetamine and methamphetamine	McTavish et al., 1999b
	D <sub>1</sub> receptors associated with BD	Ni et al., 2002; Dmitrzak-Weglarz et al., 2006
	D <sub>1</sub> receptors not associated with BD	Nothen et al., 1992; Cichon et al., 1996
	D <sub>2</sub> –D <sub>5</sub> receptors not associated with BD	Cousins et al., 2009
	COMT associated with rapid cycling in BD	Cousins et al., 2009
	DAT associated with BD	Greenwood et al., 2001, 2006; Pinsonneault et al., 2011; Kelsoe et al., 1996; Horschitz et al., 2005

BD=bipolar disorder, DAT=dopamine transporter, CSF HVA=cerebrospinal fluid homovanillic acid, AMPT=alpha-methyl-para-tyrosine, COMT=catechol-O-methyl transferase, ↑=increased, ↓=decreased, ≈=no effect.

(McTavish et al., 1999a). This diet attenuated manic symptomatology in patients (McTavish et al., 2001) and reduced the psychostimulant effects of both amphetamine and methamphetamine in healthy volunteers (McTavish et al., 1999b). Together, these multiple lines of pharmacological evidence implicate an overactivity of catecholamines, in particular dopamine, in mania, while the opposite may be true for depression.

### 2.2.3. Observations from genetic studies

Over the years, several potential candidate genes associated with the catecholaminergic system conferring susceptibility to the development of bipolar disorder have been identified. A comprehensive overview would go beyond the scope of this review however, and therefore we briefly present some of these findings. Mixed results have been observed for the D<sub>1</sub> receptor with some studies observing linkage of polymorphisms of the D<sub>1</sub> receptor gene to bipolar disorder (Ni et al., 2002; Dmitrzak-Weglarz et al., 2006), while other studies do not support this link (Nothen et al., 1992; Cichon et al., 1996). For the other dopamine receptors (D<sub>2</sub>–D<sub>5</sub>), the majority of studies fail to show an association with bipolar disorder (Cousins et al., 2009). Polymorphisms of genes coding for breakdown pathways of catecholamines have also been investigated. Catechol-O-methyl transferase (COMT) which acts similarly to the dopamine transporter but in the prefrontal cortex, conferred susceptibility for bipolar disorder including occurrence of rapid cycling (Cousins et al., 2009). In addition, studies have begun to investigate the effects of the COMT Val 158Met gene polymorphism on behavioral organization in a small sample of manic bipolar disorder patients (Minassian et al., 2009). Studying

genetic variants of dopamine-related genes such as COMT in relation to human behavior can be informative in understanding dopamine functioning in bipolar disorder (Henry et al., 2010). Another protein involved in the synthesis of dopamine—dopa decarboxylase—was generally not associated with bipolar disorder (Cousins et al., 2009). Finally, polymorphisms of the dopamine transporter gene have been linked to bipolar disorder on numerous occasions (Greenwood et al., 2001, 2006; Pinsonneault et al., 2011) with a possible locus for bipolar disorder observed near the dopamine transporter on chromosome 5 (Kelsoe et al., 1996). Moreover, a missense mutation in the dopamine transporter gene has been associated with reduced cell surface expression of dopamine transporters in patients with bipolar disorder (Horschitz et al., 2005). Overall, progress has been made in delineating polymorphisms of both the norepinephrine transporter and dopamine transporter related to bipolar disorder. The mixed findings to date (Hahn and Blakely, 2007) and linkage of dopamine transporter with attention deficit disorder (Vaughan and Foster, 2013) and schizophrenia, indicates that future research is required to fully examine the role of these transporters in bipolar disorder.

### 2.2.4. Summary of findings associating catecholamine with bipolar disorder

In sum, these data support increased catecholaminergic activity underlying the manic phase of bipolar disorder. Data from pharmacological interventions highlight the implication of both increased dopamine and norepinephrine activations during mania and the reverse during depression. Although neuroimaging studies

fail to reveal consistent abnormalities in specific receptors or other proteins involved in the catecholaminergic system, increased D<sub>2</sub> receptor density in psychotic bipolar disorder patients underscores the involvement of the dopaminergic system in bipolar disorder. Similarly, genetic studies so far are inconsistent but may prove to be an exciting future area of research.

### 2.3. Bipolar depression—evidence from animals

Investigating aspects of depression in animals such as rodents is a complex endeavor. Difficulties in discriminating between unipolar and bipolar depression is even more troublesome in animal research. Because preclinical psychiatric models are often based on behaviors representing symptoms in patients, models of unipolar and bipolar depression are commonly interwoven and separation is rarely attempted. With this caveat in mind, we will highlight data from studies in animals that support a cholinergic imbalance during depression (Table 3).

#### 2.3.1. Nicotinic manipulations

Assessing depression-like behavior in rodents can be assessed by different behavioral paradigms, which are all characterized by different strengths and weaknesses (McGonigle, 2014). The most commonly used assay to study antidepressant effects and depression is the measurement of immobility duration in the tail suspension test (Cryan et al., 2005) and forced swim test (Petit-Demouliere et al.,

2005), which is interpreted as a measure of depression-like “behavioral despair”.

Using these assays, various results have been observed from investigations on cholinergic manipulations in rodents. For instance, treatment with an  $\alpha_7$  nicotinic receptor agonist induced antidepressant-like activities in mice as measured by reduced immobility times (Andreasen et al., 2012). Treatment with a high affinity subtype-selective nicotinic receptor agonist also reversed depression-like behavior in the learned helplessness model of depression in rats (Ferguson et al., 2000). Furthermore, nicotine alleviated anhedonia-like behavior in a rat chronic mild stress model of depression (Andreasen et al., 2011), and also produced antidepressant-like effects in the tail suspension test and forced swim test (Andreasen and Redrobe, 2009b). Nicotine also augmented the antidepressant-like effects of citalopram and the norepinephrine transporter inhibitor reboxetine in mice, whereas the broad nicotinic receptor antagonist mecamylamine had no such effect (Andreasen and Redrobe, 2009a). Similar to some studies in humans, mice exhibited depression-like behavior upon withdrawal from chronic nicotine exposure (Markou and Kenny, 2002; Roni and Rahman, 2014). Other studies have also demonstrated antidepressant-like effects using the tail suspension test and forced swim test using mecamylamine (Rabenstein et al., 2006; Mineur et al., 2007; Andreasen and Redrobe, 2009b) and other nicotinic receptor antagonists (Hall et al., 2010). Moreover, the high affinity nicotinic receptor partial agonist varenicline (Rollema et al., 2009) and full agonist cytosine (Mineur et al.,

**Table 3**

Summary of cholinergic findings from animal studies and depression-like behavior.

Manipulation	Observations	Interpretation	References
<b>Nicotinic</b>			
$\alpha_7$ -nAChR agonist	↓ immobility in mice	Antidepressant-like	Andreasen et al., 2012
Subtype-selective nAChR agonist	Reversed learned helplessness in rats	Antidepressant-like	Ferguson et al., 2000
Full nAChR agonist	↓ immobility in mice	Antidepressant-like	Mineur et al., 2007
cytosine			
nAChR agonists	≈ immobility in mice	No effect	Andreasen et al., 2009
Nicotine	↓ anhedonia-like behavior in chronic mild stress model in rats	Antidepressant-like	Andreasen et al., 2011
Nicotine	↓ immobility in mice	Antidepressant-like	Andreasen and Redrobe, 2009b
Nicotine	↑ effects of SSRI citalopram and NET inhibitor reboxetine in mice	Antidepressant-like	Andreasen and Redrobe, 2009a
Withdrawal from chronic nicotine exposure	↑ immobility in mice	Depression-like	Markou and Kenny, 2002; Roni and Rahman, 2014
nAChR antagonist mecamylamine	No augmenting effects of citalopram and reboxetine in mice	No effect	Andreasen and Redrobe, 2009a
nAChR antagonist mecamylamine	↓ immobility in mice	Antidepressant-like	Rabenstein et al., 2006; Mineur et al., 2007; Andreasen and Redrobe, 2009b
Different nAChR antagonists	↓ immobility in mice	Antidepressant-like	Hall et al., 2010
nAChR partial agonist varenicline	↓ immobility in mice	Antidepressant-like	Rollema et al., 2009
nAChR antagonist	↓ immobility in mice	Antidepressant-like	Andreasen et al., 2009
<b>AChE inhibition</b>			
Physostigmine	↑ immobility in rats	Depression-like	Hasey and Hanin, 1991
Physostigmine	↑ immobility and other behaviors in mice (reversed by muscarinic and nicotinic receptor antagonists and SSRI fluoxetine)	Depression- and anxiety like and reversal	Mineur et al., 2013
<b>Genetic</b>			
FSL rats	↑ behavioral and physiological response to cholinergic agents	Depression-like	Dilsaver et al., 1992
FSL rats	↓ activity, ↓ body weight, ↑ sleep, cognitive difficulties	Depression-like	Overstreet, 1993
FSL rats	Blunted response to effects of cocaine	Depression-like	Fagergren et al., 2005
<b>Treatments</b>			
Lithium and valproate	↑ AChE activity in rat brain	Antidepressant-like	Varela et al., 2012
Lithium	↑ muscarinic receptors in rat hippocampus	Antidepressant-like	Marinho et al., 1998
Citalopram	Reversed memory impairment by ↑ ACh release in rat hippocampus	Antidepressant-like	Egashira et al., 2006

nAChR = nicotinic acetylcholine receptor, SSRI = selective serotonin reuptake inhibitor, NET = norepinephrine transporter, AChE = acetylcholinesterase, FSL = Flinders Sensitive Line, ↑ = increased, ↓ = decreased, ≈ = no effect.

2007) also reduced immobility time in the forced swim test and tail suspension test. Another study suggested that nicotinic receptor antagonists, but not agonists, induced antidepressant-like effects in mice in the forced swim and tail suspension tests (Andreasen et al., 2009). Strain differences in laboratory animals may account for some of the discrepancies between agonist and antagonist effects described above (Andreasen and Redrobe, 2009b), but other underlying differences in effects remain unclear. Using tests that go beyond measuring immobility time such as the tail suspension and forced swim test is advisable for assessing depression-relevant behaviors.

### 2.3.2. Acetylcholinesterase inhibition

Other studies have focused on examining the effect of elevating functional acetylcholine on depression-relevant behaviors. In an early study, the acetylcholinesterase inhibitor physostigmine reduced mouse locomotor activity at higher doses (Dunstan and Jackson, 1977). Consistent with observations in humans, treatment with physostigmine increased immobility time in rats, suggestive of increasing depression-like behaviors (Hasey and Hanin, 1991). This immobility time was negatively correlated with expression of a variant acetylcholinesterase mRNA expression in mice (Livneh et al., 2010), suggesting that greater inhibition of acetylcholinesterase causes increased immobility in the forced swim test. Similar to rats and humans, physostigmine also induced depression- and anxiety-like behaviors in C57BL/6 mice also (Mineur et al., 2013) without affecting locomotion. In these mice, both muscarinic and nicotinic receptor antagonists and the SSRI fluoxetine reversed the effects of physostigmine, although fluoxetine also reduced immobility time in control animals. Assessing whether other acetylcholinesterase inhibitors could also induce depression-relevant behaviors in animals would provide convergent support that elevated acetylcholine functionality may underlie depression.

### 2.3.3. Evidence from genetic studies

Other support for increased extracellular cholinergic tone underlying depression-like behaviors comes from specific lines of rats. A selectively bred line of rats with increased sensitivity to acetylcholinesterase, the Flinders Sensitive Line, exhibit an exaggerated behavioral and physiological response to cholinergic agents such as nicotine (Dilsaver et al., 1992). Furthermore, this line exhibits depression-like behaviors including lower startle thresholds (Markou et al., 1994), fulfilling some criteria of face, construct, and predictive validities [see Overstreet (1993) for review]. More recently, the Flinders Sensitive Line model of depression was demonstrated to exhibit a blunted response to the behavioral effects of cocaine (Fagergren et al., 2005). Hence, this Flinders Sensitive Line with its hypersensitivity to cholinergic manipulations together with another animal model for cholinergic supersensitivity (Orpen and Steiner, 1995) supports a cholinergic imbalance contributing to depression-related behaviors.

### 2.3.4. Evidence from treatments for bipolar disorder

Finally, rodent studies investigating the mechanisms behind approved treatments for bipolar disorder may also inform us on the biological underpinnings of the disorder, particularly when focus is placed on treatments for bipolar depression. For example, the mood stabilizers lithium and valproate both increased acetylcholinesterase activity in the brain of rats (Varela et al., 2012). Lithium can also upregulate hippocampal muscarinic receptors in rats (Marinho et al., 1998). Furthermore, treatment with amphetamine decreased levels of acetylcholinesterase activity in the striatum of rats (Varela et al., 2012). Alternatively, the SSRI citalopram reversed memory impairment induced by scopolamine and tetrahydrocannabinol (THC) by

enhancing acetylcholine release in the hippocampus of rats (Egashira et al., 2006). Taken together however, these data support a catecholaminergic–cholinergic interaction underlying behaviors relevant to depression.

A better understanding of the cholinergic contribution to depression-related behaviors may arise from examining other aspects of these behaviors beyond immobility measured in the forced swim or tail suspension test. It has been noted that such immobility could arise as an adaptive learned response to conserve energy (Arai et al., 2000). Moreover, this behavior is heavily influenced by activity levels. Hence, multiple behavioral tests assaying various aspects of depression-like behaviors are recommended. For example, people with depression exhibit poor decision-making as a result of a poor choices following punishing stimuli, e.g., in the Iowa Gambling Task (Adida et al., 2011). By utilizing the rodent version of this task (Rivalan et al., 2009; Young et al., 2011b; van Enkhuizen et al., 2013b), it could be determined whether cholinergic manipulations described above result in punishment-sensitive depression-related behaviors. Alternatively, measuring reward responsiveness in the response bias probabilistic reward task which is available for humans and rodents is another approach (Der-Avakian et al., 2013). Such complementary evidence would provide what is referred to as convergent validity for a particular manipulation (Young et al., 2010a), increasing the likelihood of its relevance to the neurobiology underlying depression.

### 2.3.5. Summary of findings associating acetylcholine with depression-like behavior

Overall, data from animal studies highlight the importance of the cholinergic system underlying depression-like behavior as well as its treatment. Recent studies have focused on the nicotinic system although the results have lacked consistency and need further elucidation. Together with results from the effects of physostigmine in rodents and older data from the Flinders Sensitive Line of rats, these studies support a cholinergic imbalance during periods of bipolar depression.

## 2.4. Bipolar mania—evidence from animals

When attempting to model bipolar disorder in rodents, studies often focus on recreating mania-relevant behaviors. Mania is characterized by mood symptoms such as elevated mood and ‘racing thoughts’, which to our knowledge no one has attempted to recreate in rodent models. However, hyperactivity, inhibitory deficits, and cognitive dysfunction can be assessed in animals, at least partially mirroring behavior in humans. In this section, we will describe some of the findings in this body of research that underscore the importance of a dysfunctional catecholamine system in the neurobiology underlying bipolar disorder mania (Table 4).

### 2.4.1. Psychostimulant-induced mania like behavior

Evidence that psychostimulants can induce mania-like behavior in healthy humans and exacerbate symptoms in patients (see above) has resulted in the use of stimulants in rodents to model mania. Specifically, amphetamine-induced hyperactivity in rodents is one of the most frequently used models for bipolar disorder mania (Young et al., 2011a). Other stimulants such as the direct dopamine agonist quinpirole (Shaldubina et al., 2002) and the selective dopamine transporter inhibitor GBR12909 (Young et al., 2010c) have also been used for the purpose of modeling hyperactivity as mania-like behavior in rodents. These treatments either directly activate catecholamine receptors or elevate extracellular levels of dopamine and norepinephrine. Importantly,



**Table 4**

Summary of catecholaminergic findings from animal studies and mania-like behavior.

Manipulation	Observations	Interpretation	References
<b>Stimulants</b>			
Amphetamine	Hyperactivity in rodents	Mania-like	Young et al., 2011a
Direct DA agonist	Hyperactivity in rats	Mania-like	Shaldubina et al., 2002
quinpirole			
Selective DAT inhibitor GBR12909	Unique behavioral pattern in BPM consistent with BD patients; impaired PPI;↑motor impulsivity	Mania-like	Young et al., 2010c; Perry et al., 2009; Douma et al., 2011; van Enkhuizen et al., 2013b
<b>Genetic</b>			
DAT knockdown mice	Unique behavioral pattern in BPM consistent with BD patients; attenuated with environmental familiarity, but reinstated with novelty; hypersensitive to stimulants;↓decision-making,↑motivation	Mania-like	Perry et al., 2009; Young et al., 2010b, 2011b; Cagniard et al., 2006
DAT knockout mice	Hyperactive; PPI deficits	Mania-like	Giros et al., 1996; Ralph-Williams et al., 2003
ClockΔ19 mutant mice	Disrupted circadian rhythms,↓sleep, hyperactivity,↑reward sensitivity to cocaine, PPI deficits, hyper-exploration,↑hedonia-like behavior,↑DA firing and release	Mania-like	McClung et al., 2005; Roybal et al., 2007; van Enkhuizen et al., 2013a; Spencer et al., 2012
<b>Treatments</b>			
Lithium	↓ stimulant-induced hyperactivity	Antimania-like	Dencker and Husum, 2010
Lithium	↓ mania-like behavior of ClockΔ19 mutant mice	Antimania-like	McClung et al., 2005; Roybal et al., 2007
Lithium	↓ DA release in rats	Antimania-like	Ferrie et al., 2005, 2006
Valproate	↓ stimulant-induced hyperactivity	Antimania-like	Shaldubina et al., 2002; van Enkhuizen et al., 2013c
Valproate (acute)	↓ some behavioral deficits of DAT mouse models	Antimania-like	Ralph-Williams et al., 2003
Valproate (chronic)	↓ some behavioral deficits of DAT mouse models	Antimania-like	Van Enkhuizen et al., 2013c
Antipsychotic aripiprazole	↓ stimulant-induced hyperactivity	Antimania-like	Mavrikaki et al., 2010
Antipsychotics clozapine and olanzapine	↓ PPI deficits of DAT knockout mice	Antimania-like	Powell et al., 2008
AMPT	↓ some behavioral deficits of DAT mouse models	Antimania-like	van Enkhuizen et al., 2014

DA=dopamine, DAT=dopamine transporter, BD=bipolar disorder, BPM=behavioral pattern monitor, PPI=prepulse inhibition, AMPT=alpha-methyl-para-tyrosine, ↑=increased, ↓=decreased.

such stimulant-induced hyperactivity can be attenuated by treatments approved for bipolar disorder mania such as lithium (Dencker and Husum, 2010), valproate (Shaldubina et al., 2002; van Enkhuizen et al., 2013c), and antipsychotics (Mavrikaki et al., 2010). Hence, elevated catecholamine functioning may indeed play a vital role in the neurobiology underlying bipolar disorder mania.

#### 2.4.2. Evidence from genetic studies

Despite the high predictive validity of findings using bipolar disorder treatments, many of these simple models suffer from several shortcomings: for example (1) hyperactivity is present in other disorders such as Attention Deficit Disorder, (2) treatments used for other disorders are efficacious in some models, and (3) mania-relevant behaviors go beyond hyperactivity and reflect a multifaceted symptomatology [see Young et al. (2011a) for extensive review]. With this knowledge, other models have been developed that extend beyond solely measuring hyperactivity. In combination with genetic manipulations, some of these models provide additional evidence for increased catecholamine levels causing mania-like behavior. For example, hyperdopaminergic mice resulting from reduced dopamine transporter functioning have been created and model aspects of bipolar disorder mania. These dopamine transporter knockdown mice have been characterized in a translational behavioral pattern monitor (BPM) and compared with bipolar disorder patients (Perry et al., 2009). Using this approach, a unique behavioral pattern of hyperactivity, hyper-exploration, and more linear patterns of movement was observed in manic bipolar disorder patients that differed from healthy comparison subjects, people with attention deficit disorder, and

individuals with schizophrenia. Interestingly, this specific pattern was also observed in mice with reduced dopamine transporter functioning through genetic knockdown or pharmacological treatment (GBR12909) in the mouse behavioral pattern monitor, while amphetamine did not replicate this pattern since it decreased exploration (Perry et al., 2009). While GBR12909 selectively inhibits the dopamine transporter, in mice amphetamine has a higher potency at the norepinephrine transporter compared to the dopamine transporter (Han and Gu, 2006). Thus, although norepinephrine and dopamine as separate neurotransmitters contributing to bipolar disorder are difficult to isolate due to their close relationship in the metabolic chain, these results suggest that dopaminergic dysfunction is more important in mediating the hyper-exploratory profile observed in manic bipolar disorder patients than noradrenergic dysfunction (Young et al., 2010c). Other studies observed that the hyper-exploratory mania-like profile of the dopamine transporter mouse models was attenuated with environmental familiarity, but reinstated with environmental novelty (Young et al., 2010b). Consistent with stimulant-induced mania in bipolar disorder, these mice were hypersensitive to psychostimulants (Young et al., 2010b). Moreover, treatment with acute (Ralph-Williams et al., 2003) or chronic valproate (van Enkhuizen et al., 2013c) or the dopamine synthesis inhibitor alpha-methyl-para-tyrosine (van Enkhuizen et al., 2014) attenuated some of these abnormal behaviors in mice, but not all. Another strength of these models for bipolar disorder mania is that they exhibit other abnormal behaviors implicated in bipolar disorder such as poor decision-making (Young et al., 2011b), increased motor impulsivity (van Enkhuizen et al., 2013b), increased motivation (Cagniard et al., 2006), and impaired



prepulse inhibition (PPI) (Douma et al., 2011). Therefore, these animal models based on reduced dopamine transporter functioning support increased catecholamine functions underlying many of the abnormal behavior present in manic bipolar disorder patients. Mice with the complete gene encoding for the dopamine transporter protein deleted, have also been investigated as models for bipolar disorder mania. Dopamine transporter knockout mice were hyperactive (Giros et al., 1996) and exhibited PPI deficits (Ralph et al., 2001), which were reversed by treatment with the atypical antipsychotics clozapine and olanzapine (Powell et al., 2008). The hyperactivity of these mice was reversed by stimulant treatment however (Gainetdinov et al., 2001), leading to suggestions that these mice may better model aspects of attention deficit disorder as opposed to bipolar disorder.

Another genetic animal model for bipolar disorder mania is developed from deletion of exon 19 in the gene encoding for the “circadian locomotor output cycles kaput” (CLOCK) protein, which regulates circadian rhythms and is implicated in people with bipolar disorder (Benedetti et al., 2003; Serretti et al., 2003). These *Clock* $\Delta$ 19 mutant mice have disrupted circadian rhythms and exhibit several mania-like behaviors including reduced sleep, hyperactivity, and increased reward sensitivity to cocaine (McClung et al., 2005; Roybal et al., 2007). Several of these aberrant behaviors were normalized by chronic lithium treatment. Moreover, these mice exhibited PPI deficits, hyper-exploration in the behavioral pattern monitor, and exaggerated hedonia-like behavior (van Enkhuizen et al., 2013a). Interestingly, their mania-like behavior and disrupted circadian rhythms may be mediated by increased dopamine firing in the ventral tegmental area (Coque et al., 2011) or relate to increased dopamine release and turnover in the striatum (Spencer et al., 2012). This possibility is buttressed by microdialysis studies in rats indicating that lithium decreased dopamine release (Ferrie et al., 2005, 2006). Together, these investigations suggest that there are several mechanisms by which hyperdopaminergia can occur and lead to mania-like behaviors in bipolar disorder.

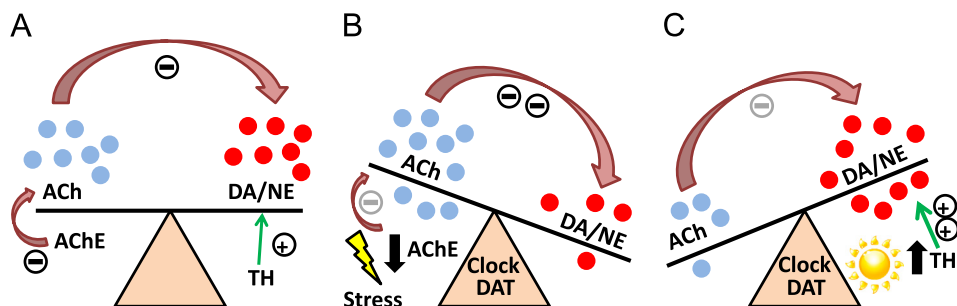
#### 2.4.3. Summary of findings associating catecholamines with mania-like behavior

A variety of stimulants that elevate extracellular dopamine and norepinephrine functions increase activity in rodents and induce certain ‘mania-like’ behavior. Genetic manipulations in mice have further indicated the importance of elevated functional dopamine and norepinephrine in mediating mania-like behaviors that go beyond hyperactivity. The fact that some of these behaviors can be normalized by treatment with medications approved for bipolar disorder support the premise that increased catecholamine may underlie manic behaviors in bipolar disorder.

### 3. Limitations and future studies

This review attempts to provide an overview of different lines of evidence that support a revised catecholaminergic–cholinergic theory of bipolar disorder based on the original adrenergic–cholinergic hypothesis. Data from several studies in both humans and animals have begun to elucidate the mechanisms contributing to depression and mania. One of the key limitations in this review however, is that we have focused on depression and mania as being different disorders, while both these states often occur in the same patient. Understanding how patients cycle from one state to another remains vital and is referred to as the ‘holy grail’ of bipolar disorder research. What happens on a pathophysiological level when patients switch from depression to mania and vice versa could provide the missing link that ties together cholinergic and catecholaminergic abnormalities.

There is an important relationship between acetylcholine and dopamine systems in the brain (Mark et al., 2011). For example, acetylcholine has an inhibitory effect on dopamine-mediated function (Graybiel, 1990). Decreased functional acetylcholine may therefore minimize this inhibition and result in hyperdopaminergia and the manic state. An increase in acetylcholine activity could then inhibit dopamine neurotransmission, resulting in a depressive state. Factors influencing both systems may include both internal and external stimuli (Fig. 1). Stress effects for instance, are unequivocally linked to the cholinergic system (Gold and Chrousos, 2002; Srikumar et al., 2006) and may thus play a key role in the neurobiological switch process from one bipolar state into another. Stress reduces acetylcholinesterase activity in the hippocampus of animals (Das et al., 2000; Sunanda et al., 2000), increasing acetylcholine activity and resulting in a shift towards more depression-like behavior. A hypersensitivity to bright light on the other hand may also cause a switch and is indeed thought to underlie the onset of seasonal mania (Wang and Chen, 2013). Light level-related cycling may be explained from an evolutionary theory of bipolar disorder going back to the era of early Neanderthals. This theory postulates that long periods of short daylight (resulting in hibernating in caves during winter in which conserving energy would be beneficial) resulted in depression-relevant behaviors, while periods of longer light necessitated an onset of mania-relevant behaviors (increased energy to run and hunt all day long) (Sherman, 2012). Studies in animals support this theory, where short photoperiods induced depression- and anxiety-like behaviors in diurnal rodents (Krivisky et al., 2012). More recently, altering photoperiod lengths also switched the behavior of rats into mania- or depression-relevant behaviors that were accompanied by increased or decreased levels of tyrosine hydroxylase respectively (Dulcis et al.,



**Fig. 1.** Potential influences disturbing the catecholaminergic–cholinergic balance hypothesis of bipolar disorder, resulting in a switch to and from depression and mania. In healthy individuals, acetylcholinesterase (AChE) regulates extracellular ACh, which is in balance with functional dopamine (DA) and norepinephrine (NE) (A). External stimuli such as stress may decrease AChE activity, thereby increasing extracellular ACh and the inhibitory effect on DA and NE activity resulting in depression (B). Other stimuli such as increased photoperiod exposure can increase tyrosine hydroxylase (TH), which is the precursor to DA and NE, potentially leading to a switch into manic behavior (C). Certain genes such as the DA transporter (DAT) or Clock gene may alter susceptibility to these external stimuli and could therefore regulate such cycling behavior.

2013). Importantly however, the behavioral responses of these rats were not extreme. Combining such environmental approaches with potential genetic susceptibility relevant to bipolar disorder could be helpful in elucidating the mechanism(s) underlying the switch between depression and mania neurobiology (Malkesman et al., 2009). Another mechanism by which these environmental stimuli could alter the neurobiology of patients could be through the molecular clock machinery. The mechanisms responsible for the homeostasis of circadian rhythms may be susceptible to external stimuli in patients with bipolar disorder and subsequently influence the homeostasis of dopamine/norepinephrine (transporters), evoking a switch into either depression or mania. Future studies should investigate these combination approaches, ideally in cross-species translational studies. Increasingly, similar behaviors can be assessed in animals and humans using similar paradigms that could broaden our knowledge on the interactions between genetic susceptibility and environmental stressors on the changing neurobiology in patients.

#### 4. Summary and conclusions

We have updated and revised the original adrenergic–cholinergic balance hypothesis of bipolar disorder with more recent observations from both human and animal studies. In sum, dysfunctional cholinergic neurotransmission may underlie phases of depression in bipolar disorder, which are restored during euthymic phases. When experiencing periods of mania however, aberrant activations of the catecholamines dopamine and norepinephrine may be the predominant underlying factor. This concept is buttressed by findings from neuroimaging and pharmacological studies in both humans and rodents. Future studies may elucidate mechanisms by which this imbalance in biological systems shifts and switches a patient from one mood state into another. For now, this review highlights the importance of the cholinergic system in depression and its potential to be targeted by novel antidepressants as well as the importance of the catecholaminergic system in mania.

#### Acknowledgments

We thank Dr. Brook Henry, Ms. Mahalah Buell, and Mr. Richard Sharp for their support. This study was supported by National Institute of Mental Health Grant MH071916 as well as by the Veteran's Administration VISN 22 Mental Illness Research, Education, and Clinical Center.

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