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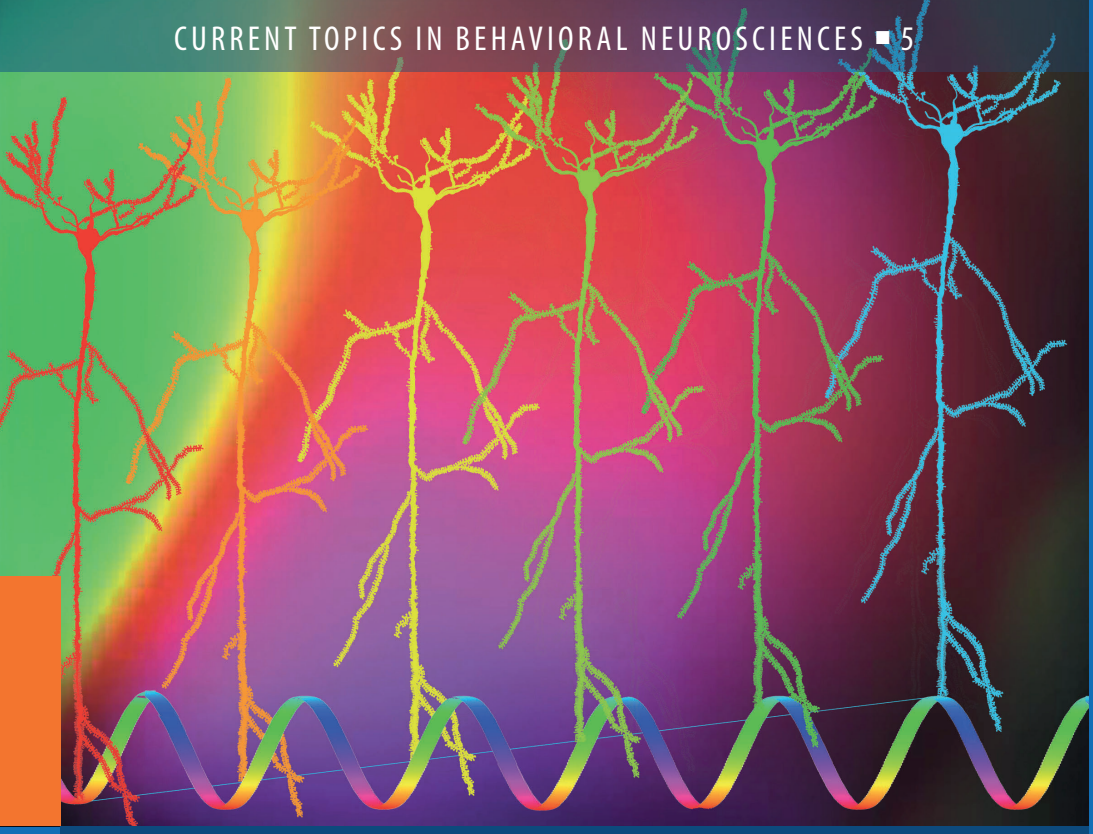

Behavioral Neurobiology of Bipolar Disorder and its Treatment

Husseini K. Manji
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Editors

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Husseini K. Manji • Carlos A. Zarate
Editors

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Preface

Bipolar disorder (BPD) is a common, chronic, recurrent mental illness that affects the lives and functioning of millions of individuals worldwide, and is a major public health problem. Recent estimates suggest that BPD affects 1–2% of the general population (Goodwin and Jamison 2007). Indeed, the World Health Organization's (WHO) Global Burden of Disease noted that unipolar depression is the leading cause of disability worldwide, and that together mood disorders account over 10% of disability worldwide (World Health Organization 2008). A growing number of recent studies indicate that outcome is quite poor for many individuals with BPD. The illness is characterized by high rates of relapse, chronicity, lingering residual symptoms, subsyndromes, cognitive and functional impairment, psychosocial disability, and diminished well-being (Belmaker 2004).

Furthermore, available therapeutic options for the treatment of BPD are often insufficient for effectively managing the acute episodes, relapses, cyclicity, suicide attempts, and recurrences that are the hallmarks of this disorder, or for restoring premorbid functioning (Insel and Scolnick 2006; Machado-Vieira et al. 2008). Relatedly, a sizable proportion of patients with BPD fail to respond to or tolerate currently available treatments, especially for the treatment and maintenance of bipolar depression (Gitlin 2006; Judd et al. 2002). It is particularly sobering to note that, with the exception of lithium, all available Food and Drug Administration (FDA)-approved treatments for BPD are either anticonvulsant or antipsychotic drugs originally developed to treat other conditions (Zarate and Manji 2008). In our field, there is wide consensus that better treatments for BPD are urgently needed. "Better treatments" essentially means treatments that are more effective for more patients, that act faster, and that have fewer side effects. The inordinately high personal, familial, societal, and financial burden of this disorder underscores the urgent need to develop novel drugs to treat it.

BPD is, obviously, an extraordinarily complex disease. Previous neurobiological studies of mood disorders focused primarily on abnormalities of the monoaminergic neurotransmitter systems, on characterizing alterations of individual neurotransmitters in disease states, and on assessing response to mood stabilizer, antipsychotic, and antidepressant medications. The monoaminergic systems are

extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits thought to support the behavioral and visceral manifestations of mood disorders (Drevets 2000). Studies of cerebrospinal fluid (CSF) chemistry, neuroendocrine responses to pharmacological challenge, and neuroreceptor and transporter binding demonstrated a number of abnormalities in monoaminergic neurotransmitter and neuropeptide systems in mood disorders (Goodwin and Jamison 2007). Unfortunately, these observations did not greatly advance our understanding of the underlying biology of recurrent mood disorders, which must be able to explain the cyclic and often profound mood disturbances that can become progressive over time. BPD likely arises from the complex interaction of multiple susceptibility (and protective) genes and environmental factors, and the phenotypic expression of the disease includes not only mood disturbance but also a constellation of cognitive, drive, motor, autonomic, endocrine, and sleep/wake abnormalities.

However, the last decade has been a truly remarkable one for biomedical research. The "molecular medicine revolution" has brought to bear the power of sophisticated cellular and molecular biologic methodologies to tackle many of the society's most devastating illnesses. While identifying the full human genetic sequence was a major step forward, many other advances of significant importance have aided our efforts to elucidate the pathophysiology of severe psychiatric illnesses. Indeed, psychiatry, like much of the rest of medicine, has entered a new and exciting age characterized by vastly improved technologies; these, in turn, have brought about both rapid advances in our knowledge and the promise of future gains in our understanding, particularly with regard to genetics, and molecular and cellular biology. For instance, the development of a multitude of new methodologies for brain imaging, genetic and genomic analyses, molecular engineering of mutant animals, novel routes for drug delivery, and sophisticated cross-species behavioral assessments makes it possible to study psychiatric and neurological diseases and disorders on the physiological level – from genes to cells, circuits, and illness phenotype. Thus, recent years have witnessed a more wide-ranging understanding of the neural circuits and the various mechanisms of synaptic and neural plasticity, the molecular mechanisms of receptor and postreceptor signaling, a finer understanding of the process by which genes code for specific functional proteins, and the identification of potential susceptibility and protective genes in many neuropsychiatric disorders, that, in toto, reduce the complexity in gene to behavior pathways.

Given the major public health problem posed by BPD, it should be obvious that we believe that a book highlighting the most recent research and clinical findings in BPD can bring much needed additional attention to this field. Our goal was to create the most informative and contemporary compendium of recent research into BPD. Toward that end, this volume assembles an impressive international array of major leaders from a broad swath of interrelated disciplines, from clinical phenomenology to basic molecular and cellular neurobiology, genetics, neuroimaging, and circadian physiology. The chapters contained herein provide a unique and broad perspective on BPD and the most recent research drawn from a variety of disciplines investigating this complex disorder.

The phrase “translational research” is one that has been used with increasing frequency in medicine in general, and neuroscience in particular. The National Institutes of Health (NIH) broadly defines translational research as "the process of applying ideas, insights and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease." Translational research, which many of us are now engaged in, is the key to transforming scientific laboratory research into applications that benefit patient health and medical care and, in this context, the discovery of novel therapeutic agents. Translational research fuels our search to understand brain function, as well as the new ideas, new approaches, and new technologies used to ask and answer key questions about pathophysiology and disease mechanisms. Toward that end, the chapters collected in this volume clearly show how much has already been done to expand our knowledge of BPD.

In the opening chapter of the book, *Drs. Mitchell and colleagues* lay the foundation for this volume by exploring the course and outcome of this complex disorder. Their careful examination of clinical phenomenology is followed by several chapters describing the most recent genetic findings. As *Drs. McMahon and Wendland* so succinctly review, in the past few years significant progress has been made in finding common variants that might contribute to susceptibility for BPD. *Dr. Petronis and colleagues* note that epigenetic research has great potential to enhance our understanding of the molecular basis of BPD, and their chapter reviews the epidemiological, clinical, and molecular findings in BPD from the perspective of inherited and acquired epigenetic misregulation. Next, *Drs. Glahn and Burdick* introduce the concept of endophenotypes – indicators of processes mediating between genotype and phenotype – and present data suggesting that neurocognitive and personality traits appear to be appropriate endophenotypes for BPD.

Two chapters exploring the use of animal models discuss the way that such models are being used to refine and expand our knowledge of BPD; *Dr. Einat* describes endophenotype- and lesion-based models in BPD, and *Dr. Chen* discusses genetic-based animal models. Both chapters highlight how the use of animal models has the potential to greatly accelerate the research process and spawn new hypotheses and discoveries in all areas of biomedical research. Notably, these two chapters also discuss the challenges of creating a truly physiologically representative animal model to study BPD. These thoughtful and comprehensive chapters underscore the point that while no perfect animal model exists for any aspect of any CNS disorder, the limitations and strengths of most models have been extensively empirically investigated, and these issues are particularly important now, given the rapid growth of genomic and proteomic technologies.

These chapters are followed by a number of chapters offering a thorough and unique overview of the neurobiology of BPD. The chapter by *Dr. Walderhaug and colleagues* opens this portion of the book with a comprehensive review of the neurotransmitters serotonin, norepinephrine, dopamine, and acetylcholine, and the role these systems play in BPD. *Dr. Benes* then describes the variety of abnormalities affecting the gamma aminobutyric acid (GABA)ergic system that have been identified in postmortem studies of the corticolimbic system. *Drs. Gawryluk and Young* provide a valuable and comprehensive overview of the signal transduction

pathways involved in the molecular biology of BPD and the indications for the mechanisms of disease and treatment. These concepts are expanded in the chapter by *Dr. Du and colleagues* exploring the role of synaptic and neural plasticity in the pathophysiology of BPD. Finally, *Dr. Kato* provides a fascinating overview of the evidence for mitochondrial dysfunction in BPD.

Taken together, these chapters highlight how our evolving knowledge of neuroplasticity is revolutionizing our understanding of disease etiology in BPD. In this regard, BPD is treated first as a disease with molecular underpinnings that is susceptible to environmental and genetic regulation. These molecular underpinnings point to targets for the development of novel pharmacotherapeutics. Cellular signaling cascades regulate the multiple neurotransmitter and neuropeptide systems implicated in CNS disorders and are targets for the most effective treatments. The next level of integration is through brain circuitry, particularly how molecular events and adaptations to genetic or environmental vulnerabilities result in maladaptive communication within and between regions of the brain that regulate behavior.

Two chapters give a thorough overview of the most recent neuroimaging findings in BPD. *Drs. Savitz and Drevets* highlight findings suggesting that BPD is being increasingly recognized as a neuropathological disorder characterized by reductions in grey matter (GM) volume, and neuronal and postmortem glial cell changes. *Drs. Blumberg and Blond* review converging functional neuroimaging evidence implicating state and trait dysfunction in a ventral prefrontal cortex–amygdala neural system in BPD. These chapters highlight how neuroimaging continues to be a tremendously useful tool in BPD research; indeed, translational imaging has been particularly valuable in the neurosciences where, due to the inaccessibility of the human brain, the use of radioisotopes (PET and SPECT) and MRI is central to the assessment of brain penetration, target engagement, brain function, and neuropathology. In addition, the chapter on sleep and biological rhythm abnormalities in the pathophysiology of BPD by *Drs. Levenson and Frank* carefully reviews the known sleep and biological rhythm abnormalities associated with BPD; the chapter describes the nature of these circadian rhythm abnormalities and reviews the evidence supporting their role in bipolar episodes.

The closing chapters of this book are devoted to exploring treatment strategies for BPD, including both traditional and novel therapeutics, as well as non-pharmacological treatments. In his chapter, *Dr. Bowden* describes the practical issues of selecting and adapting medications to treat the specific clinical features of a patient with BPD – with an emphasis on specific guidelines – and emphasizes the tactics needed to accomplish this specific to individual medications. *Dr. Loo and colleagues* review the non-pharmacotherapeutic, somatic treatments that play an essential role in the management of BPD, most notably electroconvulsive therapy (ECT). Finally, our closing chapter on potential novel therapeutics for BPD reviews a number of key targets/compounds that could result in putative novel treatments for BPD. As these chapters highlight, both currently available and novel therapeutics for this disorder offer significant treatment advantages over those available just 5 or 10 years ago.

As mentioned above, the broad concept of translational research is key to our progress, because it gives us the tools to integrate disparate findings and make sense of them. Translational research essentially helps us to create a bridge between basic science and clinical developments and between clinical development and practice. It is our hope that the thorough and comprehensive overview of recent research provided in these pages will provide readers with a way to make sense of the many novel findings presented, to extract integrated themes, and to draw insight from the diverse chapters.

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Course and Outcome of Bipolar Disorder

Philip B. Mitchell, Dusan Hadzi-Pavlovic, and Colleen K. Loo

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Abstract Bipolar disorder (BPD) is capricious illness. For some, it is a condition of few episodes; for others, it is unremitting. For some, elevated moods predominate; for others, depression is the major key. For a minority, the condition is predictably cyclical; for most, it is unpredictably chaotic. This chapter examines those studies that have attempted to draw coherence from this enigmatic disorder. Where possible, we will focus on data derived from prospective longitudinal investigations, while using as necessary the more limited retrospective or cross-sectional reports. For the sake of parsimony, we will limit discussion to those studies that have used the conservative historical definitions of BPD (as used in DSM-IIIR, DSM-IV, and ICD-10), eschewing the recent controversial concepts of "pediatric" BPD and "soft BPD spectrum."

Keywords Bipolar disorder · Cycling · Longitudinal · Outcome

1 Historical Legacies

The current distinction between the two major psychoses [schizophrenia and bipolar disorder (BPD)] that underpins the DSM-IV and ICD-10 nosologies derives from the writings of Emil Kraepelin (1899). Drawing on the work of his nineteenth century German predecessor Kahlbaum (Angst and Gamma 2008; Healy et al. 2008; Hippius and Müller 2008), Kraepelin's central differentiation of manic-depressive psychosis from dementia praecox was that the former was a disorder of "good prognosis." He described a characteristic pattern of full remission between the manic or depressive episodes, as opposed to the deterioration or chronicity which he observed in dementia praecox. However, Kraepelin also described inter-episodic "chronic mild weaknesses" in manic-depressive psychosis, i.e., low-grade manic and depressive symptoms, reflecting his belief (Angst and Gamma 2008) of a continuum of severity from health to illness.

2 The Course of BPD Prior to the Introduction of Modern Psychotropic Agents

A major issue when considering the course of BPD is the impact of medications – not only in terms of improving outcome but also the potential for destabilizing the illness, for example, manic episodes induced by antidepressants or lithium withdrawal (Suppes et al. 1991). This chapter will not review evidence-based therapies for BPD, which are dealt with elsewhere in this book. Nonetheless, it is pertinent,

where possible, to examine the course of this condition in its "native" form, prior to the introduction of modern psychotropic agents in the 1950s.

An intriguing overview of the natural course of BPD in the pre-drug era (in descriptions roughly dating from Esquirol in the nineteenth century to Astrup in the mid-twentieth century) was recently published by Alvarez Ariza et al. (2009). Alvarez Ariza concluded that there were a number of commonalities between these historical reports: a high probability of recurrence; onset usually with a depressive episode; manic episodes of shorter duration and more likely to fully remit than depressive episodes; and, overall, good recovery between episodes.

Perhaps, the most comprehensive data on the natural course of BPD before the introduction of modern therapies were those collected in the Iowa 500 study (Winokur and Tsuang 1996). Using files from the Iowa Psychopathic Hospital, Winokur and colleagues obtained clinical details on BPD patients admitted between 1934 and 1944. As that hospital had routinely collected follow-up information from patients, relatives, or clinicians every 6–12 months, it was possible for Winokur's group to determine the progress of this condition in the era prior to the advent of lithium, neuroleptics, or antidepressants. Informative data were obtained on 87 patients with BPD who had been followed up between 6 months and 20 years (with an average of 2.2 years). Over that period of time, 54% recovered fully at some stage, while 21% were continuously symptomatic over the follow-up period. This pattern was not distinguishable from unipolar depression, but contrasted markedly with schizophrenia, in which 78% showed continuous illness and a further 13% deteriorated. Most BPD patients took 2–3 years to recover from their index episode (of mania or depression); however, for those able to be followed up over 10–20 years, all fully recovered at some stage. About 5% of those initially diagnosed with depression went on to develop mania over the follow-up period, most within 3 years of the index admission.

3 Methodological Issues

Interest in both the natural course of BPD and the response of this disorder to treatment has increased, leading to increasing recognition of the limitations of the current nomenclature regarding the course and outcome of this condition. Recently, a working group of the International Society for Bipolar Disorders published a report on this issue (Tohen et al. 2009). In that paper, consensus opinion was reached regarding the definition of nine key terms (response, remission, recovery, relapse, recurrence, subsyndromal states, predominant polarity, switch, and functional outcome) commonly used to describe course and outcome in BPD. Pertinent to this chapter, Tohen and colleagues distinguished between "relapse" (which they

defined as a new episode occurring within 8 weeks of an index episode) and "recurrence" (a new episode occurring after eight weeks) – definitions similar to those recommended for major depressive disorder (MDD) by Frank et al. (1991). Because most of the BPD literature had hitherto not distinguished between these time intervals, and tended to use these terms interchangeably, we will arbitrarily use the term "recurrence" here to cover both concepts.

4 Childhood and Adolescent Antecedents of BPD

It has long been recognized (based largely on retrospective reports) that BPD often presents for the first time during adolescence. In the first prospective study of this, Geller et al. (2008) demonstrated a continuity of childhood/adolescent onset DSM-IV BPD-I with adult illness.

Elucidation of replicable antecedent clinical or biological abnormalities prior to the onset of syndromal BPD would assist clinicians in early diagnosis of this condition and enable development of early identification and intervention programs. In recent years, there has been a growing recognition of the importance of identifying such antecedent features, with a concurrent increased number of cross-sectional and longitudinal "high risk" studies of young offspring of parents with BPD (recently reviewed by Duffy 2009). Two cross-sectional studies (Lapalme et al. 1997; Birmaher et al. 2009) reported increased rates of syndromal BPD and MDD in these children, as well as increased rates of non-specific symptoms such as anxiety and subthreshold mood symptoms. There was no increase in the rates of attention-deficit hyperactivity disorder (ADHD) in those studies, an issue of pertinence in view of the high rates of reported comorbidity between that disorder and "pediatric" BPD (Biederman 2006). Similarly, the prospective longitudinal studies (Akiskal et al. 1985; Hammen et al. 1990; Egeland et al. 2003; Hillegers et al. 2005; Shaw et al. 2005; Duffy et al. 2009) have not found increased rates of childhood or adolescent ADHD in these "high risk" samples, nor have they demonstrated increased rates of pre-pubertal mania (which would be expected if "pediatric" BPD were a true antecedent of adult BPD-I). These prospective trials found higher rates of anxiety disorders, major mood disorders (mainly depression), and subthreshold depressive and "activation" symptoms. Other prevalent symptoms included sleep disturbance, distractibility, and a greater sensitivity to stress.

In a retrospective and uncontrolled investigation of the occurrence of any more "immediate" prodromal symptoms, Mantere et al. (2008) found that prodromal symptoms were present in 45% of those with BPD-I and 50% of those with BPD-II. The mean duration of such symptoms was 31 days prior to syndromal onset and did not differ between BPD-I and BPD-II disorders. Most symptoms were mood-congruent, though some were non-specific features, particularly anxiety.

5 The Onset of BPD: Age

Most patients with BPD report that the illness first presents in the mid-to-late teenage years or twenties. The mean age of onset reported in three large datasets (STEP-BD, Stanley Foundation Bipolar Network, and the Sydney Black Dog Institute; reviewed by Mitchell et al. 2009) ranged from 17.4 to 22.9 years.

Onset occurs earlier in those with a positive family history of BPD (Taylor and Abrams 1981). Furthermore, a number of reports indicate that age of onset is genetically determined. Bellivier et al. (2003) reported three genetically determined age of onset subtypes: early (mean 17 years), intermediate (25 years), and late (40 years). In a similar study, Hamshere et al. (2009) reported on a mixture analysis that found three distinct age of onset groups for BPD-I: $\leq$22 years, 25–37 years, and $\geq$40 years. Hamshere and colleagues described differential clinical characteristics in these groups. The early-onset group had a stronger family history of affective disorder, more frequent suicide attempts, a greater proportion of rapid-cycling patients, more episodes of mania, and more episodes of depression. This suggestion of a greater severity of illness in the early-onset group has been supported by Perlis et al. (2009) who found that those who had a first episode before the age of 13, had (over their lifetime) fewer days euthymic, more impaired functioning, and earlier recurrence. Coryell et al. (2009) also reported that an earlier age at onset portends greater depressive symptom burden. Lin et al. (2005) reported linkage of a number of loci with age of onset of the first manic (but not depressive) episode.

5.1 Specific Age-Related Presentations

5.1.1 Postpartum BPD

For many women, BPD presents for the first time in the postpartum period. For those with pre-existing BPD, the postpartum period is a period of high risk for relapse (Freeman et al. 2002). Munk-Olsen et al. (2009) reported that 27% of mothers with prior BPD were admitted within 1-year postpartum, and that a previous diagnosis of BPD was the strongest predictor of a postpartum psychiatric admission.

5.1.2 Late-Onset BPD

Late presentation of BPD (onset in the 60s or later) is less likely to be associated with genetic factors, rather related to neurological conditions such as cerebrovascular disease or traumatic brain injury, or more subtle organic processes such as small vessel disease in the brain; for instance, Tamashiro et al. (2008) reported more white matter hyperintensities in those with late-onset presentations. While

late-onset manic presentations have usually been associated with greater morbidity and mortality (Tohen et al. 1994), a recent report (Oostervink et al. 2009) from the prospective, longitudinal European EMBLEM study found a more favorable outcome in the late-onset (>60 years) group compared to an early-onset elderly BPD sample.

6 The Onset of BPD: Polarity

While most retrospective studies have reported a depressive onset to be more common than mania, this has not been consistently demonstrated. In the three large datasets reviewed by Mitchell et al. (2009), 52–53% of patients reported their first episode to be depressive, with 16–26% reporting the initial presentation as hypo/manic.

A number of retrospective studies have explored clinical correlates of the polarity of the onset episode. Perlis et al. (2005) reported on 704 BPD-I patients from the STEP-BD study. Depressive onset was associated with an earlier onset of illness, more lifetime depressive episodes, and more time depressed. Examining the UK Wellcome Trust genetic sample, Forty et al. (2009) reported similar findings. Using linear regression, initial onset with depression (compared to mania) was associated with earlier age of onset, predominant lifetime depressive polarity, more frequent and more severe depressive episodes, and less prominent lifetime psychotic episodes.

Another means of assessing the phenomenon of the illness onset being depressive is to prospectively evaluate a sample of MDD patients, investigating for rates and correlates of "conversion" to BPD. First, in terms of rates of such "conversion," Angst et al. (2005) reported on a prospective evaluation of hospitalized depressed patients. They found a conversion rate of 1% per year to BPD-I and 0.5% per year to BPD-II disorder. Males and those with an early onset of depressive illness were at greater risk of converting to BPD-I, whereas BPD-II conversion was associated with being female, later onset of depression, and a positive family history of mania. Examining a community sample of 14 to 24-year olds followed up over 10 years, Beesdo et al. (2009) reported that 3.6% of those with initial unipolar depression subsequently developed hypo/mania, with risk particularly high in those with adolescent onset (<17 years).

There have been other studies of predictors for those who convert from MDD to BPD. Coryell et al. (1995), in a 11-year prospective follow-up study, reported that those who converted to BPD-I were more likely to have been psychotic or hospitalized at the index depressive episode than those who continued to have a diagnosis of MDD. Those who converted to BPD-II were more likely to manifest mood lability in the depressive state (Akiskal et al. 1995).

7 Subtypes and Patterns of BPD Based on Course of Illness

7.1 Bipolar I and II Disorders

Dunner and Fieve (1974) distinguished between BPD-I and BPD-II on the basis of the severity of the elevated phase of the condition, defining BPD-I by the occurrence of at least one lifetime manic episode, and conversely BPD-II by the presence of hypomanic and depressive episodes. Although originally developed from observations of patients hospitalized for depression, this distinction has been extrapolated to all BPD patients. BPD-I and BPD-II appear to remain diagnostically distinct and consistent over time (Coryell et al. 1989).

7.2 Rapid-Cycling Illness

Rapid-cycling BPD is defined by the occurrence of four of more distinct episodes of hypomania, mania, depression, or mixed episodes over a 12-month period. The term "rapid-cycling" was first used in reference to BPD in 1979 (Wehr and Goodwin 1979) in the circumstance of accelerated cycles in patients treated with tricyclic antidepressants. Rates of rapid-cycling in cross-sectionally evaluated samples vary from 23% to 45% (Mitchell et al. 2009). It would appear that for most patients, this represents an ephemeral phase of their illness. Coryell et al. (2003) reported that 80% of such patients were no longer rapid-cycling after a mean follow-up period of 13.7 years. Following the STEP-BD sample for 12 months, Schneck et al. (2008) found that only 5% were still rapid-cycling, and furthermore, 34% had no more mood episodes in that year.

7.3 Nature of the Cycle

While not incorporated in the DSM-IV or ICD-10 systems, the nature of the "cycle" for BPD patients has been well described and has been enshrined in the European clinical tradition (Angst and Sellaro 2000). Many patients have circumscribed cycles in which they either transition from depression to mania prior to recovery (the so-called depression-mania-interval, or DMI pattern) or from mania to depression prior to recovery (the *mania-depression-interval* or MDI pattern). The MDI pattern appears to indicate a greater likelihood of response to lithium than does DMI (Kleindienst et al. 2005). Furthermore, MacQueen et al. (2002) reported that patients who become depressed following a period of euthymia are more likely to respond to antidepressants than do those who are depressed following a hypo/manic episode. The Zurich study by Angst and colleagues (Angst and Sellaro 2000)

demonstrated that males experience more cyclic episodes (mania and depression) than females.

7.4 Predominant Polarity

While Colom and Vieta (Colom et al. 2006) recently proposed that BPD should be subgrouped on the basis of "predominant polarity" – with a threshold of two-thirds of episodes being used to define the predominant pole – there is a long tradition of this broad concept in the BPD literature. Angst and Gamma (2008) described a continuum of illness (using Kraepelin's broad concept of manic-depressive psychosis) varying from those with recurrent mania (M) to those with recurrent depressive episodes (D), with the intermediate presentations being severe mania and milder depression (Md), severe manic and depressive episodes (DM), and severe depressive and milder elevated phases (Dm).

"Unipolar mania" is one extreme of Colom and Vieta's modern concept of predominant polarity. This is Angst's "M" group. In the nineteenth century, Kleist (Angst and Gamma 2008) subgrouped serious mood disorders into those patients with unipolar mania, those with unipolar depression, and those with both manic and depressive episodes. Relatively uncommon in BPD samples (the prevalence rates in the literature for unipolar mania vary from 5% to 28% of those with BPD), there have been few studies of this population. Shulman and Tohen (1994) examined the stability of this clinical presentation, finding a persistent subsample. When they followed 27 patients with unipolar mania more than 20 years, seven still had unipolar mania. Perugi et al. (2007) reported that most clinical features of unipolar mania were similar to those with "classic" BPD (i.e., those manifesting with both manic and depressive episodes). There were only a small number of differences, with the unipolar mania sample evidencing more mood-congruent psychotic symptoms, a more frequent chronic course, and a greater likelihood of a more hyperthymic temperament (notably, no unipolar manic patients had a depressive temperament).

However, at least in terms of symptoms, it is now apparent that depression is the predominant affect of BPD for most patients. Two reports from the NIMH Collaborative Depression Study (Judd et al. 2002; Judd et al. 2003a) demonstrated that patients experience depression (as either symptoms or a syndrome) much more frequently than hypomania or mania. First, in a study of patients with BPD-I, Judd et al. (2002) reported on a follow-up of 146 patients over an average period of 12.8 years. Assessing weekly symptom status, the authors found that patients experienced depressive symptoms for 32% of the weeks over that period. This compared with only 9% of the time accounted for by hypomanic or manic symptoms and 6% for cycling or mixed presentations. When the depressive symptoms were examined in detail, it was apparent that most were not related to major depression, with 14% of the weeks being due to minor depression or dysthymia and 9% due to subsyndromal depression. Only 9% of the time was spent experiencing major

depression. It was also apparent that a prolonged depressive or mixed/cycling episode at intake into the study was one of the major indicators of chronicity at follow-up.

In the second paper, Judd et al. (2003a) reported on weekly symptomatic status in BPD-II patients from the same cohort. Eighty-six patients were followed up for a mean of 13.4 years. In this population, depression was even more prevalent than within the BPD-I sample, accounting for 50% of weeks, compared with 1% of weeks in hypomania and 12% cycling or mixed. When the specific form of depression was examined, 24% of weeks were experienced in minor depression or dysthymia and 14% in subsyndromal depression. Again, major depression was relatively less common, accounting for only 13% of time. Comparing the BPD-I and BPD-II groups, Judd et al. (2003b) reported that BPD-II patients were statistically more likely to experience both major and minor depressive episodes. They were also more likely to have both a chronic course and shorter intervals between episodes.

The Zurich study (Angst and Sellaro 2000) reported that females experience more depressive episodes than males, but there were no differences in the rates of manic or mixed episodes between the genders. Coryell et al. (2009) recently reported on the 20-year follow-up of the NIMH collaborative Depression Study, which demonstrated that patients experience an increase in the predominance of depressive symptoms in their third, fourth, and fifth decades. Furthermore, they reported that the proportion of time spent depressed or hypo/manic correlates over follow-up periods, particularly for depression.

8 Duration and Outcome of Individual Episodes

In the Zurich longitudinal sample (Angst and Sellaro 2000), the average episode duration for pure depression, mania, or mixed episodes was 3 months, whereas cyclic episodes (mania and depression) lasted almost 50% longer. Two reports from the NIMH Collaborative Depression Study are relevant to this issue. After 8 weeks, only 44% of those admitted with bipolar depression had recovered, compared with 61% of those with mania and 33% of subjects in a mixed or cycling episode (Keller et al. 1986). After 1 year, 78% had recovered from an initial bipolar depressive episode, compared with 93% of those who were manic and 68% of those in a mixed or cycling presentation (Keller 1988).

In general, however, most studies of the outcome of individual episodes have focused on mania. Keck et al. (1998) investigated the 12-month course of illness in 134 patients following hospitalization for treatment of a manic or mixed episode. Outcome was examined in terms of syndromic (resolution of the DSM-III-R syndrome), symptomatic, and functional recovery, and was considerably less favorable than is generally considered by clinicians. Syndromic recovery occurred in only 48% of subjects but, even more dramatically, full symptom resolution was found in only 26%, and functional recovery in only 24% over that year. Those

outcomes for mania were strikingly worse than the prior reports of Keller; there is no clear explanation for the differences between the two reports.

In recent years, there have been a number of studies reporting on the outcome of *first-onset* mania, though it should be noted that there have been no reports on the outcome of first episode bipolar depression. Tohen et al. (2003) published the first report on the outcome of first manic or mixed episodes, following subjects over a 2-year period. He reported 98% syndromal recovery and 72% symptomatic recovery within 2 years. However, only 43% had functionally recovered within 2 years – a finding similar to that of Keck and colleagues. In terms of recurrence rates, within 2–4 years of the first manic hospitalization, 57% had switched to the opposite pole or had a new illness episode(s). Within 2 years of syndromal recovery, 20% had a new episode of mania, 20% had a new episode of depression, and 19% switched without recovery. The predictors of recurrence of mania were mood-congruent psychosis, lower pre-morbid occupational status and an initial manic presentation. Predictors of the occurrence of depression were higher pre-morbid occupational status, an initial mixed episode, and comorbidity.

Salvatore et al. (2009) reported on the 2-year stability of diagnosis in the 500 patients diagnosed with BPD-I in the above study. They found 97% diagnostic stability. Patients were more likely to change from other diagnoses to BPD-I (rather than vice versa), specifically from MDD, severe with psychotic features; psychotic disorder NOS; brief psychotic disorder; and schizophreniform disorder.

In the other major study examining the outcome of first episode mania, Yatham et al. (2009) reported on the 1-year follow-up of 53 subjects. In the first year, 53% had a mood episode. The mean time to recurrence was 8 months, with such recurrence being more likely in those with an early age of onset.

9 Recurrence Rates and Clinical Outcomes

While some of the older writings suggested that BPD was frequently a predictably cyclic disorder, this is rarely so. In an elegant historical critique, Lewis (1968) described this as an "intermittent" rather than a "regularly periodic" condition. In later years, this was confirmed in sophisticated statistical investigations, with Gottschalk et al. (1995) reporting that the evidence from patient daily self-rated moods suggested a low-dimensional chaotic process. Huber et al. (1999) proposed using stochastic resonance as a model for recurrence.

9.1 Retrospective or Cross-Sectional Studies

Most patients who experience an episode of mania go on to have future episodes of mania and/or depression (Angst and Sellaro 2000), although recurrence rates differ substantially between studies. In the Stanley Foundation Bipolar Network and the

Black Dog Institute Bipolar Disorders Clinic (Mitchell et al. 2009), 85% and 56% of patients, respectively, had experienced at least four hypo/manic episodes, while 79% and 65% had experienced at least four depressive episodes.

Kraepelin reported that over the years, there was a progressive shortening of inter-episodic intervals. However, Eliot Slater later reanalyzed Kraepelin's data (translated by Oepen et al. 2004), concluding that this apparent phenomenon was a distortion due to persons with an average tendency to cycle more rapidly being sampled increasingly often with rising episode count. Oepen and colleagues termed this "Slater's fallacy." More recent studies have confirmed Slater's conclusion. Angst and Sellaro (2000) found from their longitudinal studies that although there is an initial shortening of cycle length (in their data over the first three cycles), there is no predictable change after that, with a subsequent median cycling of 18 months. Examining the US Collaborative Study of the Psychobiology of Depression cohort, Coryell et al. (1994) reported no shortening of cycle length in a 10-year prospective follow-up. Similarly, Winokur et al. (1994) also reported that the illness does not become more recur more frequently over time.

9.2 Prospective Studies

Using the Zurich longitudinal study dataset, Angst et al. (2003) reported that patients with BPD-I had a median of 0.40 episodes per year, while those with BPD-II had a median of 0.30 episodes per year. These were both more frequently recurrent than unipolar depression for which there was a median of 0.20 episodes annually. A number of prospective studies have also been reported from the USA. Tohen et al. (1990) followed 75 inpatients at the McLean Hospital for over 4 years; most had well-established BPD. They found that only 28% did not experience a recurrence of mania or depression over that period of time. Goldberg et al. (1995) also prospectively followed the course of illness in discharged hospitalized manic patients. Over 4.5 years, only 41% had a good outcome and more than 50% were re-hospitalized at some time. In a more recent study of the STEP-BD cohort, Baldassano (2006) reported that 5% of patients relapsed each month (80% of the relapses being depressive in nature), and the rate of hospitalizations was 14.2 per 100 patient years.

10 Predictors/Correlates of Recurrence

One of the most consistently replicated predictors of increased proneness to future recurrences is the number of past episodes (Winokur et al. 1994; Kessing et al. 2004; Judd et al 2008). Other clinical predictors of greater likelihood of recurrence

include past hospitalizations (Winokur et al. 1994), a family history of BPD (Winokur et al. 1994), and residual depressive or hypomanic symptoms (Coryell et al. 1998; Judd et al. 2008). In a 15-year prospective study, Coryell et al. (1998) also reported that poor optimal functioning in the 5 years prior to baseline assessment predicted a greater likelihood of episodes 15 years later.

In terms of predictors of relapse into specific poles of the illness, Perlis et al. (2006), using the STEP-BD sample, found that shorter time to depressive recurrence was associated with residual depressive or manic symptoms, and the proportion of days depressed or anxious in the prior year. On the other hand, a shorter time to manic recurrence was predicted by residual manic symptoms, and days with elevated mood in the prior year.

There is also growing evidence that various forms of comorbidity are associated with greater risk to recurrence. Otto et al. (2006) followed 1,000 patients in the STEP-BD study, finding that comorbid anxiety was associated with earlier recurrence, fewer days well, slower recovery from depression, and lesser quality of life and role functioning. Comorbid alcohol abuse (particularly that secondary to the onset of BPD) has been associated with a greater risk of recurrence (Strakowski et al. 2005). Cannabis use has similarly been shown to be linked to more time in affective episodes and a rapid-cycling pattern (Strakowski et al. 2007). Van Rossum et al. (2009) reported from the EMBLEM study that cannabis users were less compliant with medications and had higher overall illness severity, higher mania levels, and more psychosis.

There has also been increasing awareness of the high level of physical illness comorbidity in those with BPD (Kupfer 2005). In one of the few studies to examine the impact of this on outcome (albeit in a cross-sectional design), Calkin et al. (2009) studied the relationship of body mass index (BMI) and outcome, using structural equation analysis. In their sample, 39% of the 276 tertiary care patients were obese. A higher BMI was associated with a chronic illness course, longer duration of illness, and worse disability scores. It is difficult, however, to determine the direction of causality in such studies, as more severe illness may lead to more medications, and hence a greater likelihood of weight gain.

In terms of potential organic determinants of relapse, Dupont et al. (1990) reported that deep white matter hyperintensities (as demonstrated on brain magnetic resonance imaging scanning) were associated with more hospitalizations and impaired fluency and recall. Berk (2009) has hypothesized that such changes in brain structure may represent neuroprogression due to oxidative stress.

There has also been interest in identifying the psychosocial precipitants of episodes of bipolar depression or mania. In one of the first studies to address this issue, Miklowitz et al. (1988) demonstrated that relapse was more likely with higher family expressed emotion and affective style. Adverse life events also appear to be important in triggering episodes, particularly first episodes, but also subsequent ones (Ellicott et al. 1990). In a study that focused on the relationship of life events and specific episode types, Malkoff-Schwartz et al. (1998) reported that manic episodes were precipitated by life events associated with social rhythm disruption,

while severe stressful life events (irrespective of their impact on social rhythms) were related to both manic and depressive relapses.

11 Other Outcomes

11.1 Disability

There has been increasing interest in the profound functional disability caused by BPD (Mitchell et al. 2004) and the predictors of such poor outcome. Judd et al. (2005) reported that impairment increases with each increment in depressive symptomatology for BPD-I and BPD-II, and with each increment in mania symptomatology for BPD-I (but not BPD-II). Rosa et al. (2009) found that predictors of poor inter-episode function were previous mixed episodes, current subclinical depression, previous hospitalizations, and older age.

11.2 Death Rates

The Zurich longitudinal study by Angst et al. (2002) provides the best evidence on the long-term mortality rate for BPD. The investigators followed up 406 hospitalized patients with mood disorders (220 with BPD and 186 with depression) over a 34 to 38-year period. That study found an overall increase in death rates for patients with BPD, with a standardized mortality ratio (SMR) due to all causes (suicide and natural causes) of 1.58. This was due to both increased suicide rates (SMR 12.28) and increased rates of cardiovascular death (SMR 1.84). Suicide rates were lower in those who had been treated (SMR 5.2) compared with those untreated (13.1). For all vascular deaths, including that due to cerebrovascular disease, the SMR was 1.69. When BPD subtypes were specifically examined, there was a higher mortality in the BPD-I patients (SMR 1.86) compared to those with BPD-II (SMR 1.18); the difference was mainly due to greater rates of cerebrovascular death [BPD-I (2.04) versus BPD-II (0.61)]. In one of the few other studies examining overall death rates in BPD, Baldassano (2006) estimated a death rate of 0.11/100 patient years in the STEP-BD sample.

Further evidence supporting a high mortality related to physical illness in those with BPD comes from the UK GP database (Osborn et al. 2007). That large population-based study reported a greater death rate from coronary heart disease in BPD patients aged 50–75 years compared with controls, with a hazard ratio (HR) of 1.52. There was also a greater death rate from stroke in that same age group compared to controls (HR 1.63). There were no differences in death rates due to physical illness in the younger and older age groups (18–49 or $\geq$75 years,

respectively). Another recent report found no increase in rates of cancer in those with BPD (Hippisley-Cox et al. 2007).

12 Conclusion

How do these studies of course and outcome inform future research into furthering our understanding of the neurobiology of BPD? They highlight the centrality of recurrence and cycling as the core features of this highly disabling condition – phenomena that persist despite the development of multiple mood stabilizers since lithium in the late 1940s. Notably, rarely is the condition regularly periodic – a critical issue, as some researchers have based mechanistic theories upon that simplistic supposition. Recurrence at a median rate of at least one episode every 2–3 years is the norm. Until we elucidate the pathological biological underpinnings of such recurrence, our capacity to develop novel effective therapies that truly impact the course of this illness will be severely constrained.

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Genetics of Bipolar Disorder

Jens R. Wendland and Francis J. McMahon

Contents

Abstract In this chapter, we will attempt to outline the current state of genetic knowledge for bipolar disorder and briefly summarize the main findings from genetic epidemiology studies. We then review the most recent original literature, based largely on genome-wide association study methods. We conclude with some ideas about future directions.

1 Introduction

There is a broad consensus that the etiology of bipolar disorder (BPD) has a genetic basis. This consensus rests substantially on genetic epidemiology studies that have demonstrated the high familiality and heritability of BPD. The identification of

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specific genes involved in BPD has therefore been a high priority. Such genes, or their associated cellular mechanisms, should provide insight into the molecular etiology of BPD, but might also serve as novel targets for prevention, diagnosis, or treatment.

Below, we outline the current state of genetic knowledge for BPD and briefly summarize the main findings from genetic epidemiology studies. We also review the most recent studies, which are based predominantly on genome-wide association study (GWAS) methods. Although some GWAS are still ongoing and it may be too early to reach definitive conclusions, it is already becoming clear that the GWAS method does identify markers that can be consistently replicated across studies. However, as with other common diseases, the markers identified so far seem to confer very modest risk for BPD, and it now seems clear that there are no common variants of major effect size for BPD. Also, as with other common diseases, the genes implicated so far were largely unexpected and would not have been predicted on the basis of current pharmacological or neurobiological theories. As the GWAS era winds down, new strategies for BPD genetics research are being explored. These new strategies involve, among others, redefinition and dissection of the BPD phenotype, novel molecular methods such as next-generation sequencing, and new bioinformatics approaches aimed at integrating genetic findings with neurobiology.

2 Genetic Epidemiology of BPD

Most lifetime prevalence estimates for BPD range between 1 and 2% in the general population. It has long been recognized that BPD runs in families, leading to a number of family and twin studies. Among common complex genetic disorders, BPD is one of the most highly heritable, with about 80% of the phenotypic variation attributable to genetic effects.

The familial aggregation of BPD has been demonstrated in controlled systematic studies. Close relatives of probands with BPD have about a five- to tenfold higher risk of BPD, and a 10- to 15-fold higher risk of major depression, compared to close relatives of healthy individuals [reviewed in (Smoller and Finn 2003)].

2.1 Twin Studies

Twin studies have been used to investigate the amount of familial aggregation associated with BPD that is explicable by genes. Dizygotic (DZ) twins share about half of their genes, while monozygotic (MZ) twins inherit identical genes, even though both kinds of twins share similar environments. Thus, comparing

MZ and DZ twins can parse environmental and genetic contributions to a phenotype. For BPD, it has been consistently observed that MZ twins have a much higher concordance for BPD than dizygotic twins. This difference in concordance leads to heritability estimates from large twin studies in the range of 59–87% (Bertelsen et al. 1977; Cardno et al. 1999; Edvardsen et al. 2008; Kendler 1993, 2001).

2.2 Family Studies

Family studies have also helped define the range of clinical phenotypes present in the relatives of people with BPD. In the most informative family studies, so-called controlled family studies, case, and healthy control participants are typically ascertained regardless of family history, and their relatives are then systematically evaluated for phenotypes of interest. Several large BPD family studies were published in the 1980s (Weissman et al. 1984). These studies have shown that relatives of probands with BPD are also at increased risk for other mood and anxiety disorders, as well as alcohol and substance-related disorders. Some studies also found a modestly increased risk of schizophrenia. This idea was supported by a recent large study that joined relatives based on registry data and clinical diagnoses (Berrettini 2000; Lichtenstein et al. 2009).

Family studies can also be used to help determine the way in which an illness is inherited. The formal fitting of inheritance models to family data is known as segregation analysis. Segregation analysis has been largely unsuccessful for BPD, since most studies have been unable to distinguish between polygenic, multifactorial, and major locus models of inheritance. This probably reflects the limited ability of segregation analysis to cope with heterogeneity and the assortative mating, parent-of-origin effects, and other nonstandard inheritance patterns that have often been observed in BPD (McInnis et al. 1993; McMahon et al. 1995; Stine et al. 1995).

3 Molecular Genetics

3.1 Genetic Linkage and Candidate Gene Studies

Numerous linkage and candidate gene studies have been conducted in BPD. In general, they have not yielded widely accepted findings. Therefore, we will not review these studies here and instead refer the interested reader to several excellent published reviews (Barnett and Smoller 2009; Burmeister et al. 2008; Craddock and Sklar 2009).

3.2 Genome-Wide Association Studies

GWAS use common genetic markers that are spread across the entire genome to test for associations between individual marker alleles and disease. Thanks to high-throughput technology, hundreds of thousands to millions of markers can be assayed in a single experiment. In this section, we will first describe the basic concepts of GWAS and some of the challenges associated with the analysis of such large datasets. We will then review GWAS in BPD and discuss the results and implications for BPD genetics research.

The central methodological feature of GWAS is the highly parallel, simultaneous determination of many genotypes for single nucleotide polymorphism (SNP) markers located throughout the genome. Initial arrays were only capable of interrogating a few hundred SNPs in a single experiment (Wang et al. 1998), but within less than a decade, this number was scaled up by three orders of magnitude. Such high-density arrays are designed on the basis of HapMap data (International HapMap Consortium 2003), so that each marker actually samples not just a single base pair but also nearby regions that may be hundreds or thousands of base pairs in size. Modern SNP arrays provide nearly complete coverage of common genetic variation, at least in populations of non-African ancestry (Barrett and Cardon 2006). After raw data cleaning and quality control procedures (which are very important), GWAS data are typically analyzed using one marker at a time. This introduces a considerable multiple hypothesis testing problem. To minimize type I error, most researchers have accepted a p value threshold of ~10^{-8} (Dudbridge and Gusnanto 2008) for samples of European ancestry. Such a threshold means that GWAS are underpowered to detect small effects unless sample sizes are very large (greater than 1,000 cases and 1,000 controls).

As of early 2010, no single BPD sample has yielded a p value below this threshold in a GWAS (Wellcome Trust Case Control Consortium 2007; Baum et al. 2008; Ferreira et al. 2008; Hattori et al. 2009; Scott et al. 2009; Sklar et al. 2008; Smith et al. 2009). Some signals have been identified in studies that combined more than one BPD sample in joint or meta-analyses (Fig. 1). The first of these (Baum et al. 2008) implicated the gene diacylglycerol kinase eta (DGKH), which is known to be involved in pathways sensitive to lithium, a mood stabilizer frequently used to treat BPD. Subsequent studies (Ferreira et al. 2008; O'Donovan et al. 2008) have implicated novel genes (*ANK3*, *CACNA1C*, and *ZNF804A*) that suggest novel biological pathways. Reminiscent of the family studies that found increased rates of major depression among the relatives of individuals with BPD, one study found a locus that may be involved in both disorders (McMahon et al. 2010).

Taken together, these studies can be regarded as a "successful start to a long journey" (Craddock and Sklar 2009), but it is important to realize that the effect sizes are very small. This means that although the identified genetic markers are associated with BPD at genome-wide significance thresholds, their individual contribution to the genetic risk of BPD is very modest. For example, an individual who carries one of the identified markers might have a 1.1–1.3-fold increased risk

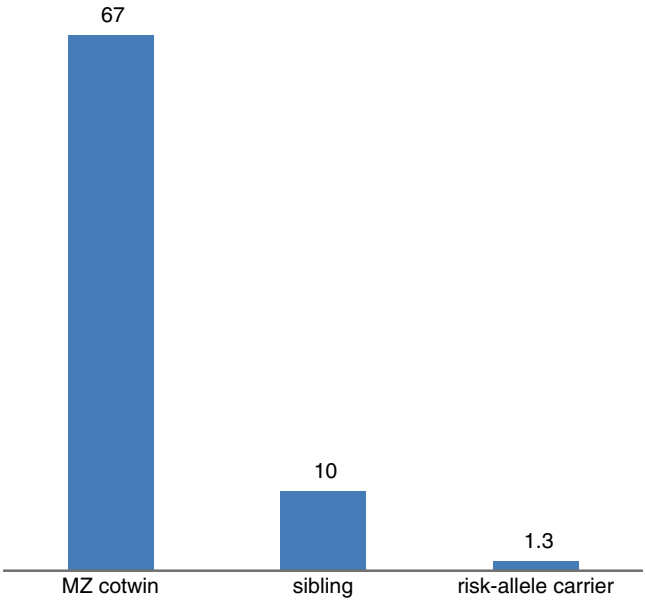

Fig. 1 The "missing heritability" of bipolar disorder (BPD). Twin studies show that the monozygotic (MZ) co-twin of a person with BPD has 60 to 80-fold increased risk of BPD, while a sibling has about a tenfold increased risk. In contrast, a carrier of a typical "risk-allele" identified by a genome-wide association study has only a 1.3-fold increased risk. It would take over 50 such risk alleles to fully account for the risk observed in MZ twins

of the illness, compared to a 60–80-fold increased risk for an identical twin or a tenfold increased risk for a sibling of someone with BPD (Fig. 2). Clearly, additional genes are yet to be found. Still, the current findings might shed some light on the biology of BPD [see (Maher 2008) for a general review on small effect sizes and GWAS].

In summary, several GWAS have been completed so far in BPD. A few markers hold up to stringent statistical thresholds, but their effects on BPD risk are quite small. The lack of common variants that confer substantial risk for BPD leaves considerable room for novel strategies in future research, some of which we will discuss below.

4 New Strategies in BPD Genetics Research

4.1 Redefining the Phenotype

The genetic studies we have reviewed so far rely on standard clinical definitions of BPD. While such definitions can be quite reliable, it is unknown how closely they correspond to a shared underlying biology. Indeed, BPD is actually a quite

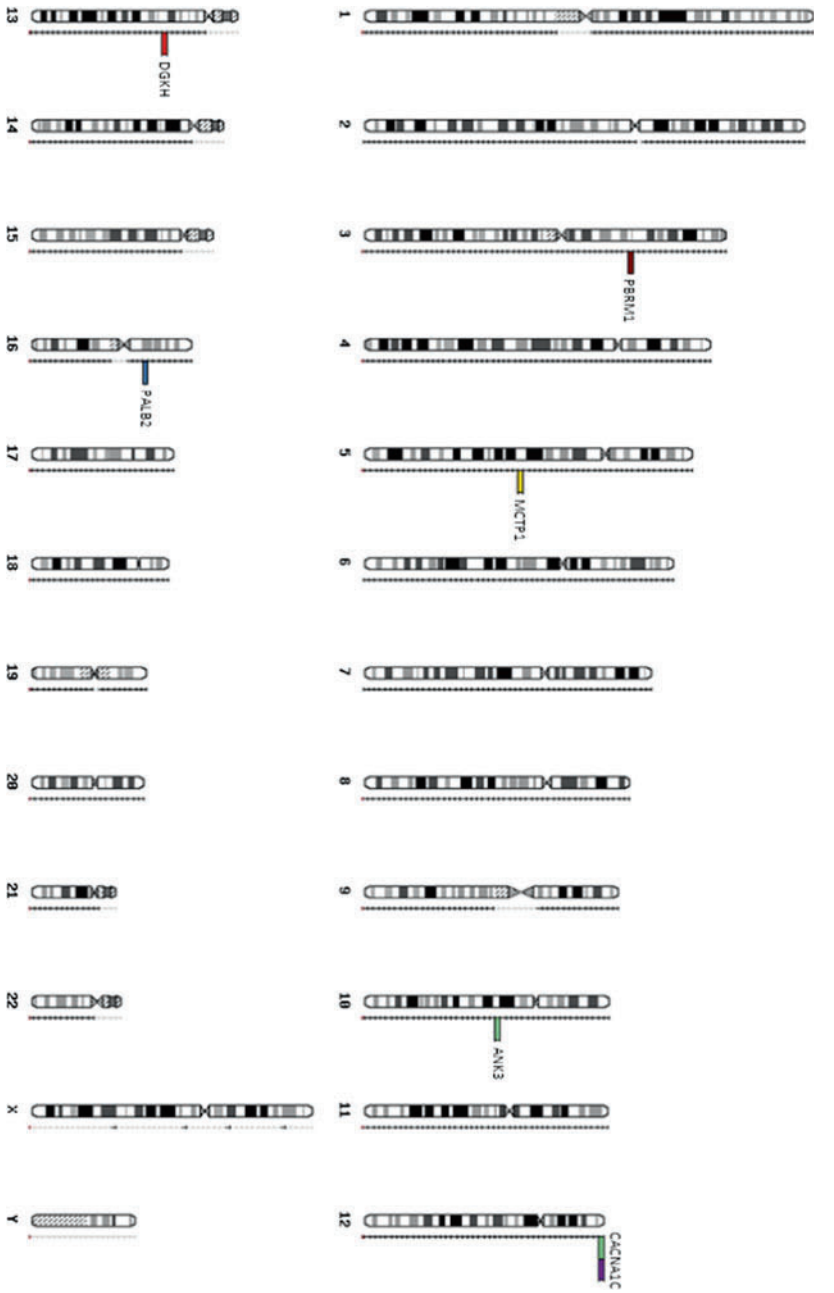

Fig. 2 Key genome-wide association findings in bipolar disorder (BPD) samples as of June 2010. Each finding is indicated by a box drawn near the chromosomal location of the associated marker(s) and annotated with the name of the nearest gene(s). Each study is assigned a unique color, but many of the samples reported to date contain overlapping individuals. Figure drawn using HGVbaseG2P at www.hgvbaseg2p.org

heterogeneous entity at the clinical level, and it seems likely that at least several conditions, with distinct etiologies, comprise what we call BPD. Some studies, based on GWAS data, have even suggested overlap in genetic risk factors between BPD and schizophrenia, despite markedly different clinical courses and treatments (Purcell et al. 2009). Two commonly used scientific approaches to address these phenotype limitations are the search for subphenotypes and intermediate or endophenotypes. Both of these approaches have been applied to BPD, but comprehensive genetic studies are still underway.

Subphenotype studies usually aim at dissecting current case definitions into several *phenomenologically* more "pure" phenotypes, based on clinical or other data. This can be as straightforward as dividing cases into groups based on a particular clinical feature, such as age of onset. More complex studies use methods such as cluster or factor analyses to try to discern the best set of cases or clinical features that can then be tested for association with genetic variants. These strategies have been used in BPD primarily on a candidate gene basis, with some success (Craddock et al. 2010; Schulze et al. 2005), but the overall results have been mixed. It is possible that applying subphenotype methods to samples that were collected under standard case definitions leads to biased ascertainment with a consequent loss of statistical power. Perhaps the studies to date, which have focused on common genetic variants, have missed effects that will only be evident when it becomes possible to study less common variants. It is also possible that the key assumption underlying subphenotype analyses – that phenotypic homogeneity reflects biological and genetic homogeneity – may not be correct for something as complex as BPD. Thus, it remains an open question whether subphenotype approaches will prove valuable in genetic studies of BPD.

Intermediate and endophenotype approaches are intended to use biologically valid and easily measurable phenomena related to the phenotype of interest as biomarkers for some underlying genetic vulnerability. In BPD studies, such biomarkers can be derived from data obtained in brain imaging, biochemical measures of blood or cerebrospinal fluid, or EEG wave patterns, just to name a few. The key assumption in these kinds of studies is that biomarkers are a more stable indicator of underlying biological dysfunction. Like subphenotypes, this approach has had some success in genetic studies (Dick et al. 2006; Hariri et al. 2005), but it is not clear how useful it will be in the longer term. Endophenotype approaches to nonpsychiatric disorders have generally not proven to be more powerful than clinical diagnoses for GWAS, but might perform better in studies of less common variation. A major problem with this strategy is that the initial identification of biomarkers generally depends on a statistical correlation with psychiatric phenotypes, with attendant problems distinguishing between state and trait, cause and consequence. The usefulness of biomarkers for BPD genetics research, particularly in GWAS, remains to be fully tested.

4.2 Novel Molecular Tools

The SNP arrays used so far for GWAS capture only a small subset of human genetic variation, namely, that which is represented by common SNPs. Some platforms are also designed to include monomorphic SNPs that can be used to identify known chromosomal regions that are commonly deleted or duplicated (so-called copy-number variants, or CNVs), but much copy-number variation cannot be measured in this way (Kidd et al. 2010). Some of the newest platforms also include less common SNPs identified by research, such as the Thousand Genomes Project, which aims to fully sequence hundreds of unrelated people. However, a full understanding of the inherited risk for BPD and other complex genetic diseases will probably require information on the full range of genetic variation present in our genomes. Epigenetic variation, which includes several kinds of inherited variation not reflected in the DNA sequence, such as histone modifications, may prove to be quite important (Petronis 2010). Genetic variation that arises spontaneously from one generation to the next, so-called de novo variation, is often deleterious and can generally not be captured by standard SNP arrays. Such de novo variation can work at the cytogenetic level, or can lead to smaller CNVs, insertion/deletion mutations, or mutations affecting single nucleotides.

Several large studies are currently underway that use next-generation sequencing (NGS) methodology to identify rare genetic variants. NGS uses new molecular and computing technology to generate large amounts of DNA sequences at high accuracy and at a fraction of the cost of previous sequencing methods. Although this is still a relatively young technology, NGS has already begun to provide a new understanding of human genetic variation. For example, we now know that rare variants, each of which may occur in one or a few individuals out of thousands studied, appear to be more common than previously recognized. Initial studies identified over three million such variants per individual (Lupski et al. 2010; Roach et al. 2010), at least 10,000 of which are predicted to be functional based on our current understanding of gene regulation. Surprisingly, everyone seems to carry several rare variants that would previously have been considered sufficient to cause disease, such as variants that change a conserved amino acid or create a premature stop codon, both of which typically lead to major changes in the functions of the encoded protein. Clearly, we have a lot to learn about the range of genetic variation that is compatible with health before we can fully appreciate how genes cause disease.

In the field of common disease genetics, NGS is driving a shift away from the common variant/common disease hypothesis toward a model that postulates multiple, unrelated mutations in genes (or regulatory regions) that may be variably deleterious but result in a common phenotype. The many rare variants that will be found will pose an even greater multiple hypothesis testing problem than that posed by GWAS, and new analytical strategies will need to be developed. One such approach focuses on the joint analysis of all variants detected in a gene or gene

family (the "mutational load") (Li and Leal 2008), but additional analytic tools will clearly be needed.

4.3 Novel Analytical Tools

Another major challenge for genetic studies of BPD and other complex genetic disorders is the limited availability of tools to identify nonadditive genetic interactions. Given the lack of common loci in the genome of major effect size, it seems reasonable to postulate that several or many genes interact in a manner whereby each gene has little or no effect *itself* (no marginal effect), but can explain more of the phenotype when tested in the context of other interacting genes. Such epistastic effects, however, still await computationally efficient detection strategies and powerful statistical procedures for clear interpretability [for review, see (Cordell 2009)]. This is a heavily researched field and a number of such analyses of BPD can be expected in the near future.

5 Summary

The strong familiality and heritability of BPD remain some of the best clues to its etiology. After a long period of slow progress, individual genes that contribute to the risk of BPD are finally beginning to be identified. As the pace of discovery quickens, we can expect that the identified genes will allow us to piece together a much more coherent understanding of the biological underpinnings of BPD. We hope that such an understanding will drive new discoveries in diagnosis and treatment that will ultimately benefit patients and their families.

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Understanding Bipolar Disorder: The Epigenetic Perspective

Tarang Khare, Mrinal Pal, and Arturas Petronis

Contents

Abstract Bipolar disease (BPD) is a complex major psychiatric disorder that affects between 1% and 2% of the population and exhibits ~85% heritability. This has made BPD an appealing target for genetic studies yet, despite numerous

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attempts, the genetic basis of this disease remains elusive. Recently, it has come to light that epigenetic factors may also influence the development of BPD. These factors act via stable but reversible modifications of DNA and chromatin structure. In this chapter, we revisit the epidemiological, clinical, and molecular findings in BPD and reanalyze them from the perspective of inherited and acquired epigenetic misregulation. Epigenetic research has great potential to enhance our understanding of the molecular basis of BPD.

Keywords Epigentics · Complex diseases · Methylation · Histone modification · Epigenetic model · Epigenotype · Methylome study · Twin discordance · Gender differences · Imprinting · Microarray

1 Introduction

It is generally accepted that complex diseases, such as BPD, are caused by two groups of risk factors: alterations in DNA sequences and hazardous environment. Following numerous successful stories of gene cloning in simple Mendelian diseases, such as sickle cell anemia and cystic fibrosis, a significant effort has been focused on identifying the DNA sequence variations (mutations and polymorphisms) that predispose to complex diseases. Complex diseases – unlike simple Mendelian traits – display an irregular mode of inheritance, discordance of monozygotic (MZ) twins, sexual dimorphism, parent-of-origin effects, reactivity to environment, and fluctuating disease course, among other non-Mendelian features. Genetic association studies identified numerous putative DNA risk factors of small effect, which seem to show little consensus with each other and are unable to pinpoint a mechanism of disease pathogenesis (Baum et al. 2008; Ferreira et al. 2008; Sklar et al. 2008). In addition, when considered individually, the predictive utility of such DNA polymorphisms is low (Craddock and Sklar 2009). In reference to the non-Mendelian intricacies mentioned above, epigenetics – with its well-orchestrated, multifaceted role in regulation of multiple genomic processes – presents us with a new frontier for research into psychiatric and other complex diseases.

2 Concepts in Epigenetics

Epigenetics refers to non-DNA mutational modifications of the genome that regulate gene expression and other genetic/genomic functions, and therefore are essential to normal growth and development. Epigenetic modifications can be attained by modifying either the DNA nucleotides (methylation and hydroxymethylation of

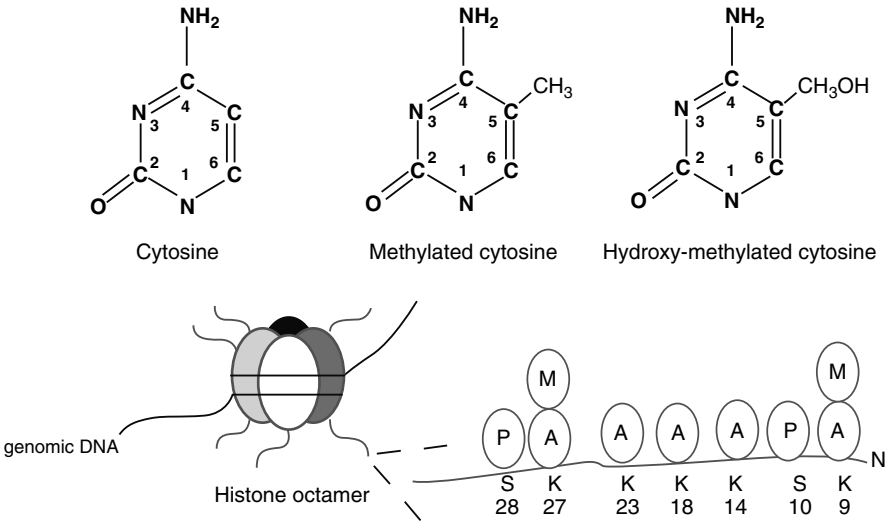

Fig. 1 *Epigenetic modifications of DNA and histone proteins*. (*Top*) Cytosines can be unmethylated (*left*), methylated (*middle*), and hydroxymethylated (*right*). (*Bottom*) At the histone octamer, the protruding N-tails of histones are the sites for modifications. Shown here is an example of various modifications, such as phosporylation (P), methylation (M), and acetylation (A), on H3 protruding N-tail at serine (S) and lysine (K) residues

cytosine residues) or the histone proteins around which chromosomal DNA is wrapped to form nucleosomes and chromatin.

In mammals, genomic DNA modification occurs principally at the fifth position of the cytosine pyrimidine ring at CpG dinucleotides (Fig. 1, top). Mammalian gene promoters are often associated with CpG-rich regions (CpG islands), and their methylation state is highly dynamic during different stages of development (Antequera and Bird 1993). The DNA methylation process is intrinsically linked to the regulation of gene expression, and some genes exhibit an inverse correlation between the degree of methylation at the promoter and the level of expression (Garinis et al. 2002). Presence of DNA methylation prevents the recruitment of transcription factors to the promoter and attracts methyl-binding proteins that initiate chromatin compaction and gene silencing. DNA methyltransferase (DNMT) enzymes are responsible for adding DNA methylation marks on the cytosine residues. The DNMT1 enzyme, also known as a maintenance methyltransferase, ensures the faithful transmission of DNA methylation patterns during mitosis (Bird 2002; Hermann et al. 2004; Vertino et al. 2002). By using cytosine methylation on the template strand, maintenance methyltransferases rebuild methylation profiles on the new strand after passage of the DNA replication fork. Experimental evidence indicates that the fidelity of maintenance methylation is in the range of 95–99% (Genereux et al. 2005; Pfeifer et al. 1990). DNMT3a and DNMT3b are the *de novo* methyltransferases and are involved in methylating repetitive DNA elements, establishing germline-specific DNA methylation imprints, and initiating

transcriptional repression (Bird 2002; Chen et al. 2003; Hermann et al. 2004; Okano et al. 1999; Watanabe et al. 2002). Many studies have attempted to elucidate the mechanism of methyl group addition to the cytosine residue (Hashimoto et al. 2008; Klimasauskas et al. 1994). In contrast, the mechanism(s) or the enzyme(s) performing the demethylation process is still unknown. Recently, another modification on human DNA, hydroxymethyl cytosine (hmetC) was identified and is now under extensive investigation (Kriaucionis and Heintz 2009; Tahiliani et al. 2009).

Another group of epigenetic modifications occur at the octamer units of histone proteins (see Fig. 1, bottom). The protruding tails of histone proteins are the site for multiple posttranslational modifications, such as acetylation, methylation, and phosphorylation (Jenuwein and Allis 2001). Histone acetylation is invariably associated with high gene expression (Choi and Howe 2009; Wade et al. 1997). In contrast, different combinations of histone methylation and phosphorylation can correlate with either gene activation or repression, depending on the residue on which the mark is present (Bartova et al. 2008). Several enzymes, such as histone acetyltransferases (HATs), deacetylases (HDACs), methyltransferases (HMTs), and demethylases (HDMs), that mediate various covalent modifications on histone tails have been identified and their mechanisms of action are well understood. The opposing activity of these enzymes provides a dynamic equilibrium between chromatin structure and associated gene transcription. This diversity of histone modifications provides multiple degrees of flexibility, as the sum of histone modifications at a particular promoter region defines a specific epigenetic state of a gene and guides it for activation or silencing. Histone modifications are also intricately linked to the pattern of DNA methylation at a chromosomal locus. Methyl-binding domain proteins (MBDs), such as methyl-CpG-binding protein 2 (MeCP2), can be recruited to methylated DNA and attract large protein complexes containing HDACs and HMTs, further repressing gene activity (Lachner and Jenuwein 2002; Lachner et al. 2004).

Recently, a third component of epigenetic regulation involving small interfering RNAs (siRNAs)/micro RNAs (miRNAs) has been detected (Hamilton et al. 2002; Morris 2005). Small RNAs are 21–28 nucleotides in length, and are derived from the cleavage of double-stranded RNA. Such RNAs can play a regulatory role at transcriptional and posttranscriptional levels. RNA-mediated gene silencing plays a pivotal role in maintaining chromosomal structure, genome defense, and gene regulation, and has recently been shown to play a significant role in disease progression (Almeida and Allshire 2005; Eckstein 2005; Guil and Esteller 2009; Mishima et al. 2009; Rosell et al. 2009).

3 Bipolar Disorder: The Epigenetic Perspective

The epigenetic model of BPD and other complex diseases relies on three fundamental concepts formed from experimental observations:

1. *The spatiotemporal epigenetic regulation of gene function is highly dynamic*. The epigenetic makeup of a cell is influenced by the organism's developmental program, internal and/or external milieu, and stochastic factors (Riggs et al. 1998; Weaver et al. 2004). Thus, cell types within a tissue and different tissue types have distinct "epigenotypes" to suit their needs of differential gene expression and provide phenotypic plasticity for a fixed genotype (Cheung et al. 2000a, 2005; Eckhardt et al. 2006).
2. *Some epigenetic marks can display partial meiotic stability*. Although it has been generally accepted that, during meiosis, the epigenetic marks are erased in the germ cells and new profiles restated, emerging evidence shows that select loci may escape this complete germline erasure of epigenetic marks, resulting in transgenerational phenotypic effects (Jaenisch and Bird 2003; Klar et al. 1998; Rakyan and Whitelaw 2003; Reik et al. 2001).
3. *Epigenetic factors are critically important to the normal function of the genome*. Aberrations in a cell's epigenetic status might be seriously detrimental to the genome, cell, tissue, or individual (Chan and Rashid 2006; Suter et al. 2004; Tufarelli et al. 2003).

In our view, the epigenetic model of complex disease has great biological and predictive utility. It presents us with the opportunity to investigate and elucidate the peculiar nature of complex diseases with a new theoretical framework and innovative experimental approaches. Below, we discuss the observed non-Mendelian irregularities of BPD from an epigenetic perspective.

4 Discordance of Monozygotic Twins

Phenotypic differences (discordance) in monozygotic (MZ) twins have been frequently observed in complex non-Mendelian diseases. In BPD, on the one hand, concordance is observed at a rate of approximately 62% and 79% in male and female MZ twins, respectively (Bertelsen et al. 1977; Kieseppa et al. 2004; McGuffin et al. 2003). Dizygotic (DZ) twins, on the other hand, display only 12–15% concordance for BPD (Cardno et al. 1999; Kieseppa et al. 2004; McGuffin et al. 2003). Phenotypic differences in MZ twins are often interpreted as evidence for environmental interactions, which is believed to produce disease in one of the two genetically predisposed co-twins. Adoption studies, however, show that raising children born to affected parents in a normal environment do not lower the risk of BPD (Kringlen 1991; Taylor et al. 2002; Tsuang and Faraone 1994). From the epigenetic point of view, discordance of MZ twins can be explained as a cascade of epigenetic changes that begin with a pre-epimutation, an epigenetic problem that arises during germline maturation. The pre-epimutation(s) does not result in a diseased condition, but rather predisposes an individual to developing the disease. The pre-epimutation can be influenced by numerous pre- and post-natal influences, such as tissue differentiation, external environment, hormones, stochastic events, etc.

Thus, due to its dynamic nature, full epimutation can occur only in one twin. Such epigenetic differences in twins can result in full or partial discordance (variations arise in age of onset, disease severity, drug response). Molecular epigenetic differences have been identified in inbred animals (Rakyan et al. 2002), in MZ twins discordant for Beckwith Wiedemann syndrome (Weksberg et al. 2002, 2010), as well as in MZ twins affected with psychiatric disease (Petronis et al. 2003; Rosa et al. 2008). A recent microarray-based DNA methylation analysis revealed that DNA methylation difference(s) in MZ co-twins is a genomewide phenomenon and provided the first annotation of epigenetic metastability of approximately 6,000 unique genetic regions in MZ twins (Kaminsky et al. 2009).

Skewed X-chromosome inactivation in females is another epigenetic process that could partially explain female MZ twin discordance (Loat et al. 2004; Rosa et al. 2008). Several levels of epigenetic regulation, such as DNA methylation, noncoding *Xist* RNA expression, and histone modifications, are involved to achieve faithful X chromosome inactivation. Skewing of X chromosome inactivation is found in many disorders, such as X-linked immunodeficiencies, Lesch–Nyhan disease, and incontinentia pigmenti, among others (Schueler et al. 2000). It has been observed that approximately 50% of female carriers for X-linked mental retardation exhibit skewed X inactivation with an activation ratio of 80:20% or higher between the two X chromosomes (Plenge et al. 2002). In addition, investigating 63 female MZ twin pairs, Rosa et al. (2008) showed greater DNA methylation variation between maternal and paternal X chromosome alleles in discordant versus concordant twin pairs, suggesting a potential contribution from X-linked loci for discordance for BPD within twin pairs (Rosa et al. 2008).

5 Sexual Dimorphism

Sex effects, or sexual dimorphism, refer to differential susceptibility to a disease in both males and females (Ostrer 1999; Seeman 1997). Such differences have traditionally been linked with genetic risk factors on sex chromosomes. In addition, gender-specific effects have been attributed to sex hormones and their crucial role in various regulatory processes and disease states (Arnold 2003; Sit 2004). Sex differences exist in BPD, as highlighted by the higher incidence of rapid cycling, mixed states, and cyclothymia in women and a higher prevalence of early-onset BPD in men (Braunig et al. 2009; Kennedy et al. 2005). These differences, as well as sex effects revealed in genetic linkage and association studies of BPD, could be rationalized by the known epigenetic effects of sex hormones (Kaminsky et al. 2006; Seeman 1997). Interestingly, several genetic association studies revealed that autosomal genes also may exhibit sex effects (Kaminsky et al. 2006). For example, an association study of the orphan G protein-coupled receptor 78 gene (*GPR78*), located on chromosome 4, found two risk haplotypes to be present predominantly in females affected with BPD ($p = 0.038$ and $p = 0.032$) (Underwood et al. 2006). Epigenetics may provide an explanation of sex effects on autosomal genes. Sex

hormones are known to mediate changes in gene expression through epigenetic modifications of target genes. These modifications primarily affect the chromatin structure, making associated genes transcriptionally active or repressed.

Of particular interest are the androgen receptors and estrogen receptors, which belong to the steroid receptor (SR) subset of the nuclear hormone receptor family (Fu et al. 2004; Kinyamu and Archer 2004). SRs respond to steroid hormones by recruiting protein complexes associated with multiple histone modification enzymes, such as HAT, HDAC, and HMT, which allow or restrict access of RNA polymerase II and transcription factors to DNA (Fu et al. 2003, 2004). Several reports have shown that histone modifications, as well as alterations in DNA methylation of specific genes, can be mediated via sex hormones (Saluz et al. 1986; Yokomori et al. 1995). Moreover, the effect of sex hormones has been shown to be gene- and tissue-specific due to differential tissue-specific distribution of sex hormone receptors between the sexes and their target genes (Azzi et al. 2006; Liu et al. 2005). For example, Kulig et al. (1998) demonstrated the tissue-specific effect of sex hormones by estradiol treatment in rats, which resulted in increased prolactin gene methylation and subsequently decreased mRNA only in pituitary and liver tissues (Kulig et al. 1998). From these studies, it is plausible to assume that specific alleles or haplotypes implicated in linkage and association studies might become risk factors only after epigenetic alteration mediated by the endocrine system.

6 Parent-of-Origin Effects

Parent-of-origin effects in human morbid biology refer to the parental gender-specific influence toward the risk of disease development in offspring. There are many reports showing frequent occurrence of maternal transmission of BPD in familial cases (Kato et al. 1996; Kornberg et al. 2000; Lambert and Gill 2002; Lan et al. 2007; Stine et al. 1995). This observation has led investigators to hypothesize involvement of the X chromosome, however, several linkage studies failed to detect major genetic factors on the X chromosome and therefore failed to explain parent-of-origin effects in mood disorders, including BPD (Gershon and Bunney 1977; Hamshere et al. 2009; Mahon et al. 2009; Palo et al. 2010). Other modes of inheritance that might explain parent-of-origin effects are mitochondrial inheritance and genomic imprinting.

Genomic imprinting refers to monoallelic expression of several hundred genes, mainly attributed to the differential epigenetic signatures at maternal or paternal alleles. Classically, imprinted genes exhibit an "on/off" type of gene expression; for example, *H19* is expressed when inherited from the mother, while *IGF2* is exclusively expressed when inherited from the father. Imprinted genes are present in clusters and may exhibit epigenetic regulation in a tissue-specific manner. Regulation of imprinted gene clusters involves one or few regulatory elements that have epigenetic differences at the parental and maternal alleles, referred to as imprinting

centers (ICs) or differentially methylated regions (DMRs). The imprints/epigenetic modifications at ICs are faithfully maintained throughout an organism's development and are only erased and restated during germ cell development (Hajkova et al. 2002; Reik et al. 2001; Sasaki and Matsui 2008).

It is interesting to note that paternal and maternal genes may dominate over each other in different brain regions. In mice, brain regions showing paternal influence are abundant in the hypothalamus and septum areas, which mediate instinctual behavior, such as feeding, mating, and social aggression (Keverne et al. 1996a, b). Maternal influence is observed in areas related to development of higher order cognition, which is interesting given that cognition is impaired in BPD and schizophrenia patients (Barrett et al. 2009; Schouws et al. 2009). Furthermore, imprinting syndromes often exhibit psychiatric comorbidities. An imprinting region, located at chromosome 15q11-13, is involved in the etiology of Prader–Willi and Angelman syndrome (PWS and AS). AS, or "happy puppet" syndrome, is marked by epigenetic downregulation of maternal genes. Affected individuals exhibit hyperactivity and attention-seeking behavior in infancy, with high incidence of autism. In contrast, PWS is attributed to downregulation of paternal genes in the same chromosomal region, which features extremely placid, undemanding behavior in infancy. PWS affected individuals often display a high incidence of psychosis with depression (Knoll et al. 1990). These contrasting behavioral phenotypes and parental contributions in psychiatric disorders inspired Badcock and Crespi (Badcock and Crespi 2006, 2008) to extend the "battle of sex" theory (Moore and Haig 1991) in psychiatry.

7 Other Epigenetic Effects That May Be of Relevance to BPD

Growing evidence suggests that environmental factors, such as diet, chemical factors, and physical factors, as well as psychosocial factors, might modulate the epigenetic profile of the genome, either at specific loci or globally (Cooney et al. 2002; Waterland 2003; Weaver et al. 2004). Dietary influence via epigenetic modulation has been recently hypothesized in schizophrenia, another major psychiatric disease that shares numerous phenotypic similarities with BPD. Offspring whose mothers were exposed to famine showed higher prevalence for schizophrenia, and this was observed in two independent studies: the Dutch Hunger Winter in 1944–1945 and the Chinese famine 1959–1961 (Altschuler 2005; Kyle and Pichard 2006; St Clair et al. 2005; Xu et al. 2009). It was found that these offspring also displayed aberrant epigenetic modifications at the promoter of the imprinted *IGF2* gene (Elias et al. 2004; Kyle and Pichard 2006). In animal models, the addition of methyl-donor supplements, such as folic acid and vitamin B12, during pregnancy was found to enhance overall DNA methylation of the embryonic genome. This effect was well documented at the IAP elements present at *Agouti* gene loci and, as

a result, a change in coat color was observed (Ingrosso et al. 2003; Wolff et al. 1998). Besides diet, epigenetic regulation of genomic function can be influenced by use of recreational drugs. For example, methamphetamine influences DNA methylation by altering expression of DNMT1. Prolonged use of methamphetamine is known to cause exaggerations of aggressive, defensive, and sexual behaviors, sometimes observed in BPD and schizophrenia patients (Numachi et al. 2004).

BPD patients often exhibit sleep–wake dysrhythmic features, such as insomnia, diurnal variation in mood, early morning awakening, cyclicity, and seasonality of recurrences (Boivin 2000; Bunney and Bunney 2000; Grandin et al. 2006; Lenox et al. 2002). Studies of mouse models show involvement of sleep–wake rhythm; for instance (1) mutation in the *Clock* (Circadian Locomotor Output Cycles Kaput Protein) gene in mice leads to a human mania-like behavioral profile (Roybal et al. 2007), and (2) transgenic mice overexpressing *Gsk3b* (Glycogen kinase 3 beta) also show hyperactivity and manic-like behaviors (Prickaerts et al. 2006). A series of genes involved in circadian rhythm also stand out as potential BPD candidates, especially for pediatric BPD, in association studies (Mansour et al. 2006; McGrath et al. 2009; Nievergelt et al. 2006; Ogden et al. 2004). Sleep–wake rhythm is maintained at the suprachiasmatic nucleus (SCN) in hypothalamus and regulated by a transcriptional feedback loop, which can cycle in the absence of environmental input for 24 h (Ko and Takahashi 2006; Reppert and Weaver 2001). A heterodimer of CLOCK and Brain and Muscle ARNT-like Protein-1 (BMAL1) functions as transcriptional activators of target CLOCK genes (*PER 1* and *2*, *CRY1* and *2*). GSK-3β phosphorylates the CLOCK target genes and directs them to the cell nucleus, where they inhibit functional activity of CLOCK/BMAL1 complex, thus completing the transcriptional feedback loop. Melatonin, a key hormone involved in circadian rhythm maintenance, is secreted from the pineal gland, which in turn is regulated by SCN. The secretion of melatonin is affected by the light–dark cycle, where darkness stimulates and light suppresses its production. The light pulse triggers H3Ser10 phosphorylation in SCN neurons and primes H3 for K14 acetylation. These epigenetic modifications are coupled to the active transcription of the CLOCK-targeted genes (Cheung et al. 2000a, b). Interestingly, CLOCK protein possesses intrinsic HAT activity, acetylating histones H3 and H4, with high preference for H3K14 (Doi et al. 2006). Similarly, different histone modifications are also cycled during circadian rhythm for transcriptional repression of clock target genes, for example di- and tri-methylation of H3K27 at *PER 1* and *PER 2* promoter regions (Etchegaray et al. 2006).

It is interesting to note that the mood stabilizers used for treating BPD – lithium and valproic acid – may contribute to reestablishing sleep–wake rhythm by modifying epigenetic signatures. Lithium, which inhibits GSK-3 activity (Jonathan Ryves et al. 2005; O'Brien and Klein 2009), and valproic acid, a potent HDAC inhibitor (Gottlicher et al. 2001; Marchion et al. 2005), are often used in combination and possess neuroprotective effects. Lithium is also known to extend the lifespan of *C. elegans*, which is attributable to the reduced expression of the worm ortholog, *LSD-1* (Lysine-specific demethylase 1), a histone demethylase, thus influencing the epigenetic state of the worm (McColl et al. 2008; Voisine et al. 2007).

8 Experimental Approaches to Epigenetic and Epigenomic Studies of BPD

Several novel approaches for elucidating epigenetic mechanisms and modes of inheritance have been introduced over the past decade. Epigenetic tools are used to investigate two components of the genome: modifications on DNA or on histone proteins. Modifications on histone proteins are primarily investigated by first enriching the DNA fraction bound to a specific histone modification; this is achieved through the use of an antibody specific to the histone modification. Once the enriched fraction has been isolated, it is subjected to locus-specific PCR or can be interrogated on a microarray.

DNA modifications consist of methylated and hydroxymethylated residues of cytosine. Hydroxymethylated cytosine modification is a novel finding, hence, technologies to detect it on a genome scale and to distinguish it from methylated cytosine do not exist at this time; however, there are several techniques for studying methylated cytosine. Bisulfite modification and sequencing is a gold standard for analyzing DNA methylation, but it is generally limited to short DNA stretches. Recently, bisulfite-modified templates were also interrogated on the microarrays (Bibikova et al. 2006).

Native genomic DNA methylation could also be investigated through enrichment procedures that use either methylation-sensitive restriction enzymes or antibodies against methylated cytosines. These enriched templates can then be interrogated on microarrays (e.g., CpG island arrays, tiling arrays). Enrichment procedures with methylation-sensitive enzymes are only informative for CpGs within the restriction site, while antibody-based procedures require large amounts of genomic DNA. These hurdles can be overcome by adopting approaches, such as new generation ("deep") sequencing of bisulfite-converted genomic DNA, that enable high-throughput analysis of the entire DNA methylome at single-base resolution. The drawback of "deep" sequencing is that the generated fragment sequences primarily contain three bases (A, G, and T), and mapping them back to the genome can be a challenge (Varley et al. 2009).

9 Pilot DNA Methylome Study in BPD

To date, only a limited number of studies have investigated the role of epigenetic factors in BPD and schizophrenia (SCZ), which overlaps with BPD, phenotypically. These studies reported aberrant DNA methylation in the promoters of several candidate genes, however, results from independent studies have been inconsistent, and when expressed in quantitative terms, disease-related methylation changes appear to be comparatively subtle (Connor and Akbarian 2008; Dempster et al.

2006; Tochigi et al. 2008). In the prefrontal cortex of individuals with BPD and SCZ, elevated levels of *Dnmt1* gene expression and the methyl donor SAM (S-adenosyl methionine) were observed, implicating a global increase of DNA methylation (Guidotti et al. 2007). However, total methylated cytosine in the peripheral leukocytes in BPD cases and matched controls showed no difference (Bromberg et al. 2009). This inconsistent result accounts for the different tissues analyzed; the former study exploited affected tissue (prefrontal cortex), while the latter studied unaffected tissue (blood leukocytes).

Kuratomi and colleagues (2008) initiated a genomewide epigenetic study in psychiatry by investigating DNA methylation differences in blood lymphoblastoid cells between MZ twins discordant for BPD (Kuratomi et al. 2008). In this study, the affected twin showed increased methylation in the promoter of the spermine synthase gene (*SMS*) and decreased methylation at peptidylprolyl isomerase E-like gene (*PPIEL*). Among them, only *PPIEL* showed an inverse correlation between gene expression and the observed DNA methylation, however, the gene function is not known(Kuratomi et al. 2008).

Recently, Mill et al. (2008) conducted a pioneering study using the microarray technique on brain (frontal cortex) tissue samples ($n = 105$) from deceased patients with psychosis obtained from Stanley Medical Research Foundation (Mill et al. 2008). The authors investigated the enriched unmethylated genome on 12K CpG island microarrays and observed DNA methylation differences in many genes with neurological and non-neurological functions. Several genes involved in glutamatergic and GABAergic neurotransmission pathways showed the presence of epimutations, and these pathways are known for their functional link to BPD etiology (Benes and Berretta 2001; Coyle 2004). Aberrant DNA methylation was detected at loci involved in brain development in BPD and SCZ females; it was also observed at loci involved in stress response in male BPD subjects, as well as those implicated in oxidative stress response in the mitochondrial genes of affected individuals. This methylation aberration in genes involved in brain development or to the stress effect/response supports the popular diathesis-stress hypothesis of psychosis. Interestingly, when the authors examined the microarray data using partial-correlation network analysis, a lower degree of DNA methylation modularity was observed in germline male BPD cases (0.33) compared with unaffected controls (0.47), suggesting that a systemic epigenetic dysfunction may be present.

10 Methodological and Experimental Complexities in Studying Epigenetic Factors in Psychiatric Disease

Several considerations must be made before beginning an investigation of the epigenetic modifications associated with complex diseases. The epigenetic profile differs between different cell and tissue types, hence, identification of the primary

site for disease pathogenesis is vital. In BPD and other psychiatric disorders, the affected tissue is the brain and therefore, *post-mortem* stability of epigenetic factors should be taken into account. It is well known that DNA methylation is far more stable than histone modifications, making it the choice of epigenetic investigation in *post-mortem* brain tissue. However, DNA methylation in nonstem tissues is limited to CpG sites and the epigenetic profile on CpG-deficient regions can only be achieved by analyzing histone modifications.

An association between epigenetic change and disease does not provide a definite conclusion about the directionality of the cause–effect relationship. Epigenetic misregulation can be the cause of the disease or it may be induced by the disease process, compensatory events in the cells and tissues, disease-related changes in lifestyle, treatment, and numerous other detectable and undetectable factors and events. One possible way to gain insight into this problem is to test the tissues that are not involved in the disease process, for example in blood cells or buccal epithelial cells. Vestiges of epimutations in nonbrain tissues will suggest that the epigenetic insult has occurred during early embryogenesis before major tissue differentiation, or was even inherited, rather than appearing as the result of progressing disease. For instance, several studies showed the presence of epimutation at the *IGF2* locus in lymphocytes of colon cancer patients (Cui et al. 2003). Similarly, an epimutation at *KCNQ1OT1* is also observed in lymphocytes as well as skin fibroblasts of patients with Beckwith–Wiedemann syndrome (Weksberg et al. 2002).

11 Summary

As outlined in this chapter, the epigenetic model is consistent with various non-Mendelian features of BPD that are difficult to explain by more traditional theories. Epigenetic regulation is tightly coupled to a large array of genetic and genomic functions and, therefore, studies mapping the epigenetic profiles in normal and disturbed brains may be vital to understanding the molecular etiopathogenesis of BPD and other complex psychiatric diseases. To date, very few comprehensive epigenomic analyses of psychiatric diseases have been performed, but major technological advances and growing interest in epigenetic research will undoubtedly increase our understanding of disease-relevant epigenetic and epigenomic changes. The epigenetic theory does not deny the putative role of DNA sequence variation in complex diseases, but rather suggests that research into epigenetic and genetic factors must be conducted in parallel to better understand the molecular etiology of complex psychiatric disease.

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Clinical Endophenotypes for Bipolar Disorder

David C. Glahn and Katherine E. Burdick

Contents

Abstract Although twin, family, and adoption studies demonstrate that bipolar disorder (BPD) is substantially heritable, the molecular genetic basis for this illness remains elusive. Given evidence that genes predisposing to BPD may be transmitted without expression of the clinical phenotype, interest has arisen in developing endophenotypes – indicators of processes mediating between genotype and phenotype. Patients with BPD have subtle neuropsychological abnormalities, even during periods of symptom remission. Some of these neurocognitive deficits are present in unaffected family members of probands with BPD, suggesting that these measures

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may be quantitative endophenotypes for the disorder. Similarly, BPD is associated with specific personality traits (e.g., reduced inhibition, increased risk-taking) that have been observed in both affected individuals and their family members. In this chapter, we review the evidence for candidate neurocognitive and personality endophenotypes for BPD. We conclude that neurocognitive and personality traits appear to be appropriate endophenotypes for BPD, suggesting that these measures share some genetic factors with the illness.

Keywords Bipolar disorder · Cognitive · Endophenotype · Family studies · Temperament

1 Clinical Endophenotypes for Bipolar Disorder

While twin, family, and adoption studies demonstrate that bipolar disorder (BPD) is substantially heritable (Lichtenstein et al. 2009; McGuffin et al. 2003; Smoller and Finn 2003), its molecular genetic basis remains elusive. Although recent meta-analytic genome-wide association studies have implicated single nucleotide polymorphisms (SNPs) for BPD (Ferreira et al. 2008), the function of these SNPs and their host genes is currently unknown. Furthermore, because these SNPs explain relatively little of the genetic predisposition to BPD, most investigators believe that additional genetic influences on BPD will be identified. Furthermore, the search for genetic loci involved in BPD has likely been stymied by illness complexity, heterogeneity of disease expression, and comorbidity with other disorders that may distort clinical presentation (e.g., substance abuse and anxiety disorders) (Almasy and Blangero 2001). Given evidence that genes predisposing to BPD can be transmitted without expression of the clinical phenotype (McGuffin et al. 2003), interest has arisen in developing indicators of processes mediating between genotype and phenotype. Such endophenotypes are genetically correlated with disease liability, can be measured in all individuals (both affected and unaffected), and provide much greater power to localize and identify disease-related quantitative trait loci than affective status alone (Gottesman and Gould 2003).

Patients with BPD have subtle neuropsychological abnormalities even during periods of symptom remission (Kurtz and Gerraty 2009; Robinson et al. 2006). A portion of these neurocognitive deficits is present in unaffected family members of BPD probands, suggesting that these measures may be quantitative endophenotypes for the disorder (Arts et al. 2008; Glahn et al. 2004). Similarly, BPD is associated with specific personality traits (e.g., reduced inhibition and increased risk-taking) that have been observed in both affected individuals and their unaffected family members (Savitz et al. 2008b). In this chapter, we will review the evidence for candidate neurocognitive and personality endophenotypes for BPD.

2 Defining Endophenotypes

In the late 1960s, Gottesman and Shields coined the term "endophenotype" to describe traits that could be used as proxies for diagnosis in psychiatric genetics research (Gottesman et al. 1987; Gottesman and Shields 1972). The notion of using related or allied phenotypes to explore the genetic underpinnings of illness was widely accepted in other areas of medicine before Gottesman and Shields' seminal work; however, they were the first to suggest this strategy for gene discovery in psychiatry (Gottesman and Gould 2003). Furthermore, the term endophenotype was originally intended to denote a trait that was not an obvious manifestation of an illness (e.g., symptoms) or a closely related risk factor. Instead, an endophenotype was defined as hidden or not discernible by clinical interview (Gottesman et al. 1987; Gottesman and Shields 1972). Over the last 40 years, the definition of an endophenotype has become less precise and even a point of controversy (Insel and Cuthbert 2009). Indeed, the terms endophenotype, intermediate phenotype, risk factor, and (genetic) biomarker are all used to describe measures that are sensitive to liability for an illness but are not formally part of the illness itself. While these terms are used somewhat interchangeably in the literature, each has a different connotation (Bearden and Freimer 2006). The term endophenotype is specific to psychiatric genetics and tends to denote processes associated with psychiatric illnesses that are not readily observable. To reduce confusion in this chapter, we use the term endophenotype exclusively to refer cognitive and personality traits that are sensitive to genetic predisposition to BPD.

Using endophenotypic measures to discover genes for BPD may be advantageous because endophenotypes are thought to be generally less complex than their associated phenotype and thus may be more readily linked to a specific genetic locus (Blangero 2004; Gottesman and Gould 2003). In addition, the study of endophenotypes for complex human psychiatric disorders could potentially be extended to animal models (Gould and Gottesman 2006), advancing our understanding of the neurobiology of psychiatric disorders, and furthering the development of novel medications (Nestler et al. 2002). The National Institute of Mental Health (NIMH) recently convened a workgroup to develop a strategic plan for genetic mood disorders research (Merikangas et al. 2002). Among the many recommendations, the workgroup pointed to the need for the widespread use of an endophenotype-based approach in order to facilitate the identification of susceptibility genes.

3 Evidence for Neurocognitive Endophenotypes for Bipolar Disorder

In order for a cognitive measure, or any marker for that matter, to be considered an endophenotype, it must be shown to (1) be highly heritable, (2) be associated with the illness, (3) be independent of clinical state, and (4) impairment must

co-segregate with the illness within a family, with nonaffected family members showing impairment relative to the general population (Gershon and Goldin 1986; Glahn et al. 2004; Gottesman and Gould 2003; Leboyer et al. 1998; Lenox et al. 2002).

Twin, family, and adoption studies report heritability estimates of adult intelligence between 0.45 and 0.80 (Bouchard and McGue 1981; Bouchard et al. 1990; Devlin et al. 1997; McClearn et al. 1997). Heritability estimates for the cognitive domains of processing speed [$h^2 = 0.26–0.76$ (Luciano et al. 2001; Posthuma et al. 2001; Swan and Carmelli 2002)], attention/vigilance [$h^2 = 0.16–0.89$ (Fan et al. 2001)], executive control [$h^2 = 0.33–0.68$ (Swan and Carmelli 2002)], working memory [$h^2 = 0.2–0.60$ (Ando et al. 2001; Jacob et al. 2001; Neubauer et al. 2000)], and declarative memory [$h^2 = 0.56–0.65$ (Swan et al. 1999)] have been established.

Endophenotypic measures must be associated with the illness being studied (Gottesman and Gould 2003). Although it is unclear how common cognitive impairments are among individuals with BPD, a significant portion of patients with BPD complain of cognitive difficulties (Burdick et al. 2005). Furthermore, formal neuropsychological deficits have been documented in asymptomatic patients who do not complain of cognitive difficulties (Martinez-Aran et al. 2004; Thompson et al. 2005), indicating that neuropsychological impairments may be more widespread than clinical experience would suggest. A recent review concluded that the most consistent "trait" deficits in BPD – impairments observed regardless of mood episodes – appear to be verbal learning and memory, sustained attention, and executive functioning (Quraishi and Frangou 2002). However, as will be shown below, additional cognitive measures may be candidate endophenotypes for BPD (Bora et al. 2009; Torres et al. 2007).

Endophenotypic markers should be somewhat independent of illness state (Gottesman and Gould 2003). While there is clear evidence that patients with BPD exhibit widespread neurocognitive dysfunction during acute episodes of mania (Clark et al. 2001) and depression (Borkowska and Rybakowski 2001), the discovery that these deficits endure during symptom remission raises the possibility that cognitive impairment may represent a trait rather than a state variable (Quraishi and Frangou 2002). Euthymic patients with BPD exhibit limitations in several cognitive domains, particularly in measures of executive function, declarative memory, and sustained attention (Clark et al. 2002; El-Badri et al. 2001; Harmer et al. 2002; Hawkins et al. 1997; Krabbendam et al. 2000; Rubinsztein et al. 2000; van Gorp et al. 1998, 1999; Wilder-Willis et al. 2001; Zubieta et al. 2001). Although euthymic patients with BPD often present with minor affective symptoms that may adversely affect performance on cognitive tests (Clark et al. 2002; Ferrier et al. 1999; Frangou et al. 2005), even patients who have been euthymic for months before assessment have marked neuropsychological impairments (Thompson et al. 2005). Indeed, several recent meta-analyses have documented neuropsychological impairment across a wide variety of cognitive domains in euthymic BPD (Arts et al. 2008; Kurtz and Gerraty 2009; Robinson et al. 2006; Torres et al. 2007). As can be seen in Fig. 1 [adapted from Table 4 of a recent review (Kurtz and Gerraty 2009)], nonsymptomatic patients with BPD performed 0.4–0.9 standard deviations

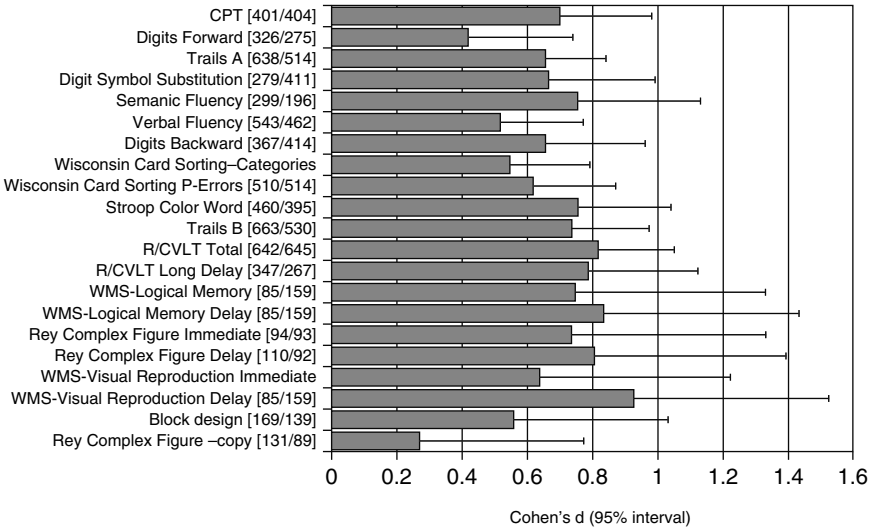

Fig. 1 Neurocognition in euthymia

below healthy subjects on measures of attention (e.g., CPT Cohen's $d = 0.69$), processing speed (e.g., Digit–Symbol Substitution $d = 0.66$), working memory (e.g., Digit Span Backwards $d = 0.65$), declarative memory (e.g., Ray or CVLT learning $d = 0.81$), nonverbal declarative memory (e.g., Visual Reproduction subtest form the Wechsler Memory Scale $d = 0.91$), and executive functioning (e.g., Trail's B $d = 0.72$). Together, these data suggest that a number of different neurocognitive measures from different cognitive domains are associated with BPD independent of clinical symptoms.

While use of psychotropic medications could impact neurocognitive functioning, systematic investigation of the cognitive impact of these agents in patients with BPD has been limited. A qualitative review concluded that although lithium had a negative effect on memory and speed of information processing, patients were often unaware of these deficits (Honig et al. 1999). Engelsmann et al. (1988) found that mean memory test scores remained stable over a 6-year interval in BPD patients treated with lithium. Furthermore, no significant differences were found between patients with short- versus long-term lithium treatment on any measure, suggesting that long-term lithium use is unlikely to cause progressive cognitive decline (Engelsmann et al. 1988). Some antidepressant medications have been shown to have adverse cognitive effects, particularly those with anticholinergic properties (Amado-Boccara et al. 1995). While few studies have examined neurocognitive performance in unmedicated patients with BPD, we found comparably impaired verbal memory in patients receiving psychotropic medication ($n = 32$) and those who were drug-free ($N = 17$) (Bearden et al. 2006), suggesting that cognitive

deficits in patients with BPD are not entirely attributable to medication use. A recent meta-analysis of 12 studies involving 276 lithium-treated and 263 lithium-free patients examined the effects of lithium on cognitive performance in BPD; the investigators found small but significant impairments in immediate verbal learning and memory (effect size = 0.24) and creativity (effect size = 0.33) (Wingo et al. 2009). In contrast, no significant impairments were found for delayed verbal memory, visual memory, attention, executive function, processing speed, and psychomotor performance. Together, these data suggest that lithium treatment appears to have only few and minor negative effects on cognition.

The study of patients with BPD alone cannot determine whether neurocognitive deficits in the euthymic state are the result of an underlying trait or the result of confounding factors, such as the acute or chronic effects of medications, permanent structural changes wrought by prior episodes of acute illness, psychosocial sequelae of previous affective episodes, or subsyndromal symptoms such as sleep cycle alterations (Glahn et al. 2004). To show that cognitive abnormalities are sensitive to the genetic liability for BPD – and thus candidate endophenotypes for the illness – these impairments must be observed in unaffected family members. There is growing evidence that first-degree relatives of BPD probands have mild executive impairments, particularly during tasks that require speeded judgments or sentence completion. Evidence for declarative memory deficits in unaffected siblings of BPD probands is less clear, with some groups reporting mild impairments and others reporting no impairments. A recent meta-analysis reported small but statistically significant differences (e.g., $d < 0.5$) for unaffected first-degree relatives compared to healthy subjects on measures of executive function and verbal memory (Arts et al. 2008). Another recent meta-analysis of 17 published studies included 443 first-degree relatives of BPD patients and reported cognitive impairments in the range of small to medium effect in the domains of attention (0.08–0.51), verbal learning (0.27–0.33), and executive functioning (0.22–0.36) (Bora et al. 2009). However, previous neuropsychological examinations of unaffected relatives of BPD probands were limited by sample size and inconsistencies in the neuropsychological measures applied.

In the largest sample to date, we recently found evidence for several candidate neurocognitive endophenotypes for BPD (Glahn et al. 2010). The goal of the study was to systematically adjudicate neurocognitive endophenotypes for BPD. To that end, we studied 709 Latino individuals from the central valley of Costa Rica, Mexico City, Mexico, or San Antonio, Texas. Of these individuals, 660 were members of extended pedigrees with at least two siblings diagnosed with BPD. Of the 660 subjects from extended pedigrees, 230 had a best estimate consensus DSM-IV diagnosis of BPD (161 Type I; 51 Type II; 6 not otherwise specified) or schizoaffective disorder bipolar subtype ($n = 12$) and were considered part of a "broad" BPD phenotype. Six individuals were diagnosed with schizophrenia or schizoaffective depressive subtype and were excluded from all analyses. Among family members without major psychosis, 243 were unaffected (nonbipolar spectrum) first-degree relatives, 86 were unaffected second-degree relatives, and

42 were unaffected third-degree relatives of affected individuals. One hundred and eight subjects were not biologically related to affected individuals and were used to form an "unrelated" control sample: 59 were subjects who had married into selected families and 49 were community controls. Individuals with the broad BPD phenotype had significantly higher rates of anxiety disorders ($\chi^2 = 32.34$, $p > 0.0001$) and past alcohol abuse/dependence ($\chi^2 = 63.52$, $p > 0.0001$) than their non-BPD family members and unrelated participants. Of these individuals, 56% were prescribed psychotropic medications at the time of assessment: 66 were prescribed antidepressants, 16 were prescribed lithium, 41 were prescribed mood stabilizers, 30 were prescribed anticonvulsants, 57 were prescribed sedatives, 37 were prescribed atypical antipsychotics, 23 were prescribed typical antipsychotics, and 11 were receiving stimulants. All subjects received diagnostic interviews and comprehensive neurocognitive evaluations.

Only 2 of the 21 neurocognitive variables assessed, such as CVLT Semantic Clustering and CVLT Delay Recall, were not significantly heritable and were excluded from subsequent analyses. Performance on these measures was significantly correlated with education and differed by location. When these covariates were omitted from analyses, these indices were significantly heritable. After controlling for multiple comparisons, individuals with the broad BPD phenotype were statistically impaired on 6 of the 20 heritable cognitive measures, such as Digit Symbol Coding, Letter–Number Span, Object Delayed Response, CVLT Learning, Facial Memory Immediate, and Facial Memory Delay, compared to unrelated, unaffected subjects. To examine diagnostic specificity, analyses were repeated after constraining the affected group to BPD-I patients alone. BPD-I patients were impaired on all of the measures identified in the broad phenotype group, and also on semantic fluency. Given that individuals with BPD have increased rates of anxiety and alcohol use disorders, it is unclear whether neurocognitive impairments are due to these co-occurring illnesses or BPD per se. Hence, analyses were repeated with lifetime history of anxiety disorders and alcoholism included as covariates. Similarly, use of psychotropic medications, which may influence neurocognitive performance, was entered as a covariate into the model. However, the addition of these covariates did not significantly change the pattern.

To determine whether neurocognitive performance and liability for BPD had common genetic or environmental influences, genetic and environmental correlations were performed. If the genetic correlation is significantly different from zero, then the traits are influenced by the same genetic factors (e.g., one or more genes influence both traits: pleiotropy). In contrast, if the environmental correlation is significantly different from zero, then the traits are considered to be influenced by the same environmental factors (e.g., education level). Three neurocognitive measures were found to be genetically correlated with BPD: Digit Symbol Coding, Object Delay Response, and Facial Memory Immediate. However, none of the environmental correlations reached significance. This large-scale extended pedigree study of cognitive functioning in BPD identified measures of processing speed, working memory, and declarative (facial) memory as candidate endophenotypes for BPD.

Together, these data strongly suggest that neurocognitive measures are influenced by the same genetic factors that predispose to BPD. However, it remains to be seen if these traits are genetically less complex than BPD itself. Nonetheless, the data presented here suggest that neurocognitive endophenotypes could help localize genes for BPD.

4 Evidence for Temperamental Endophenotypes for Bipolar Disorder

Affective dysregulation is a core feature of BPD, which has alternatively been described as a fundamental abnormality in temperament believed to underlie recurrent mood disorders (Akiskal 1995, 1996; Akiskal et al. 1977; Akiskal and Weise 1992). This theory suggests that a vulnerability to BPD per se is not heritable, but rather that a certain pattern of temperamental variation leads to an increased risk of developing BPD. Although mood fluctuation in the context of BPD results from biological dysregulation, temperament may represent a more direct and proximate effect of biological variation than does bipolarity (Akiskal 1995, 1996), making this a potential endophenotype for BPD. Indeed, temperament has been shown to be a strong predictor of later onset of a major affective disorder. Horwath et al. (1992) demonstrated that subjects with a dominant dysthymic temperament were 5.5 times more likely to develop major depression within a year of evaluation than subjects without depressive features (Horwath et al. 1992). In another study, 35% of subjects presenting with a cyclothymic temperament reported hypomanic, manic, or major depressive episodes within 3 years of assessment (Akiskal et al. 1985).

Family, twin, and adoption studies support at least a moderate genetic influence on temperament, with interclass correlations (ICCs) for monozygotic (MZ) twins typically doubling that of dizygotic (DZ) twins (Goldsmith et al. 1997). Despite frequent reports of near zero or negative correlations among DZ twins and siblings, the high ICC in MZ twins supports a genetic effect on temperament. The ICC for siblings and DZ twins is highly dependent on the measures used to rate temperament, with a well-known bias in parental over-reporting, or magnification of the differences between DZ twins and siblings. When behavioral ratings and self-rating instruments are used, as opposed to parental ratings, ICCs for temperamental behaviors are positive and significantly different from zero (Cherny et al. 1994; Plomin et al. 1993; Saudino and Eaton 1991; Saudino et al. 2004). In addition, results from the Minnesota Study of Twins Reared Apart, which compared ICCs from 100 pairs of MZ twins reared apart during their formative years with the ICCs typically reported in MZ twins reared together, reported no differences on measures of personality (ICCs ranged from 0.48 to 0.50) (Bouchard et al. 1990).

By definition, significant mood disturbance is present among individuals with Axis I affective disorders, often presenting with an episodic, recurrent course

(DSM-IV; American Psychiatric Association, 1987). Temperamental dysregulation, insomuch as it reflects subclinical liability to full mood episodes, is believed to reflect an underlying personality trait in individuals with major depressive disorder and BPD. A number of studies support this notion, with various measures of temperament distinguishing BPD patients from healthy individuals. One widely used measure of temperament, the Temperamental Evaluation of Memphis, Pisa, Paris, and San Diego-Auto questionnaire version (TEMPS-A), has been shown to be a valid and reliable measure for use in patient, family, and high-risk studies (Akiskal et al. 2005a, b). Although additional temperament and personality measures may be useful in patients with BPD, we will limit our review to the TEMPS-A, as it provides substantial evidence of its utility as an endophenotypic marker.

The TEMPS-A is a 110-item self-rated true/false questionnaire scale that is used to characterize affective temperamental style. Its use in previous family studies of BPD, along with demonstrated validity and reliability, makes it a particularly useful tool for studies of candidate endophenotypes. The TEMPS-A is based on interview versions of the dysthymic, cyclothymic, hyperthymic, and irritable temperaments (Akiskal and Weise 1992) and was originally validated in a large cohort of Italian students ($n = 1{,}010$) (Akiskal et al. 1998; Placidi et al. 1998). A four-factor structure, similar to that of the original interview version, was described in the validation sample. The subsequent addition of an anxious temperament scale resulted in a five-factor structure including subscales of dysthymic, cyclothymic, hyperthymic, irritable, and anxious temperaments, which has been upheld in a number of populations including healthy individuals, patients with major depression, patients with BPD, and unaffected relatives of patients with BPD (Mendlowicz et al. 2005). The TEMPS-A characterizes the dominant temperament of a subject, which results in a rate of each temperament within a population (i.e., 10% of patients with BPD have a cyclothymic temperament versus 1% of healthy individuals), or it can be used to derive total scores on each subscale that represent continuous measures of the degree to which a subject demonstrates traits consistent with each temperament.

The TEMPS-A has been used as a measure tapping into a gradient of affective dysregulation that has been proposed to represent the bipolar spectrum, which includes BPD-I, BPD-II, BPD-NOS, and possibly even milder forms of the illness. Several studies have focused on the TEMPS-A in BPD patients across mood states, including euthymia, and in comparison with both healthy individuals and patients with major depressive disorder (Di Florio et al. 2010); these are summarized in Table 1. In addition, temperamental dysregulation has been associated with several important illness features in patients with BPD including earlier age at onset (Oedegaard et al. 2009), rapid cycling (Azorin et al. 2008), increased risk for relapse (Cassano et al. 1989), and decreased response to antidepressant medications (Koukopoulos et al. 1983).

Studies of temperamental variation in euthymic patients with BPD have supported the notion that this phenotype may be independent of clinical state, thereby representing potential trait-like features of the illness. Kesebir et al. (2005) assessed 100 euthymic patients with BPD with the TEMPS-A, reporting that even during

Table 1 TEMPS-A comparisons with bipolar disorder samples

Study	Cyclothymic	Dysthymic	Irritable	Hyperthymic	Anxious
Mazzarini et al. (2009)	BPI > MDD	MDD > BPI	–	BPI > MDD	–
Gassab et al. (2008)	–	MDD > BPI, BPII	–	BPI, BPII > MDD	–
Savitz et al. (2008b)	BPI > HC, MDD	–	BPI, BPII, MDD > HC; BPI > MDD	–	–
Evans et al. (2005)	BP > UR > HC; MDD > UR > HC	BP > UR > HC; MDD > UR > HC	BP > UR > HC; MDD > UR > HC	BP, MDD > HC	BP > UR > HC; MDD > UR > HC
Kesebir et al. (2005)	BPI > UR, HC	UR > HC; HC > BPI	BPI > HC; UR > HC	–	BPI > UR > HC
Nowakowska et al. (2005)	BP > MDD > HC	BP, MDD > HC	BP, MDD > HC	–	–

BPD bipolar disorder, *BPD-I* bipolar disorder I, *BPD-II* bipolar disorder II, *HC* healthy control, *MDD* major depressive disorder, *UR* unaffected relatives

periods of remission, BPD subjects had higher rates of cyclothymic (10%) and hyperthymic (10%) temperament than healthy controls (0 and 0.5%, respectively) (Kesebir et al. 2005). In another study by the same group, recovered patients with BPD demonstrated higher ratings on the cyclothymic scale than both the healthy relatives of individuals with BPD and healthy controls (Mendlowicz et al. 2005). Nowakowska et al. (2005) found that euthymic patients with BPD ($n = 49$) had higher scores on the TEMPS-A cyclothymic, dysthymic, and irritability scales, as compared with 47 healthy controls (Nowakowska et al. 2005). In a large-scale family study, the same three scales, along with the anxious temperament scale, differentiated a group of 159 euthymic BPD subjects from 63 healthy controls (Evans et al. 2005).

BPD family studies suggest that certain temperamental styles are more prominent in families with genetic loading for BPD than families with no history of BPD. In the offspring and siblings of BPD patients, as many as one-third of subjects initially presented with dysthymic, cyclothymic, and hyperthymic features (Akiskal et al. 1985). In addition, Evans et al. (2005) demonstrated the co-segregation of the hyperthymic scale from the TEMPS-A in patients with BPD and their unaffected siblings, with unaffected family members scoring intermediate to patients with BPD and healthy control subjects. In a second study by the same group, the healthy relatives of patients with BPD had lower cyclothymic scores than recovered BPD patients, but higher scores than healthy controls, again supporting the notion of co-segregation (Mendlowicz et al. 2005). In another study that included BPD patients, their affected family members, unaffected family members, and healthy controls, Kesebir et al. (2005) demonstrated that scores on the hyperthymic scale from the TEMPS-A were able to differentiate healthy subjects from all other subject groups.

Finally, although not a specific defining criterion of endophenotypes, several molecular genetic studies have reported associations among candidate genes and temperament (Savitz et al. 2008a; Silberschmidt and Sponheim 2008), providing a proof of concept for its use as an endophenotype in BPD. One such study by Savitz et al. (2008a, b) administered several personality measures, including the TEMPS-A, to a cohort of 31 BPD families. After heritability was confirmed within the sample, ten personality traits were carried forward to genetic analyses. Among several significant associations, the TEMPS-A irritability scale was associated with variation within the catechol-*o*-methyltransferase gene (COMT), and the hyperthymia scale was associated with markers within the brain-derived neurotrophic factor gene (BDNF), both of which have shown evidence of association with BPD in prior work (Burdick et al. 2007b; Liu et al. 2008).

The use of temperamental style as an endophenotype in BPD is largely based on the fact that patients with BPD, by definition, have a more extreme range of affective experience and expression (Savitz et al. 2008b). The evidence to date suggests that measures such as the TEMPS-A may be useful in measuring the underlying biological processes associated with mood dysregulation in patients with BPD, thereby representing a valid candidate endophenotype. Future work is required to expand upon our understanding of the specific temperaments implicated and the genes that may contribute to variation in this trait.

5 Conclusions

Neurocognitive and personality traits appear to be appropriate endophenotypes for BPD, suggesting that these measures share some genetic factors with the illness. This assertion raises two questions. First, if the cognitive deficits or altered personality traits are of genetic origin in BPD, can they be modified through behavioral interventions or pharmacotherapy? Currently, a number of investigators are working to develop strategies to minimize the impact of cognitive deficits in BPD (Burdick et al. 2007a; Goodwin et al. 2008; Jaeger and Vieta 2007). Given that poor cognitive processing is associated with worse clinical outcomes in BPD (Jaeger et al. 2007; Martínez-Arán et al. 2002, 2004; Mur et al. 2009), a number of behavioral interventions and pharmacotherapy have been proposed to help improve psychosocial functioning in individuals affected with the illness. However, if the cognitive deficits found in BPD are genetic, one could argue that these therapeutic approaches may not be helpful. Unfortunately, this position significantly oversimplifies the influence of genetic factors on neuropsychological processing, particularly when considering cognitive functioning during daily activities. Indeed, the potential benefit of remediation or rehabilitation therapies is likely independent of the nature of cognitive deficits in BPD.

Second, if specific neurocognitive or personality measures can be shown to be endophenotypes for BPD, what can we hope to learn from these traits? Typically, the utility of an endophenotype is linked to the potential of the endophenotype to help localize genes predisposing the illness, or the potential of these measures to help characterize the influence of previously identified genes (Blangero 2004; Gottesman and Gould 2003). In addition to these more traditional roles of allied phenotypes, it is possible that endophenotypes will help to categorize individuals with mental illnesses, reducing the heterogeneity of diagnostic categories. If so, it is possible that endophenotypes will improve psychiatric diagnoses, aid in treatment decisions, and help identify individuals at risk for mental illness.

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Strategies for the Development of Animal Models for Bipolar Disorder: New Opportunities and New Challenges

Haim Einat

Contents

Abstract The paucity of appropriate animal models for bipolar disorder is repeatedly mentioned as one of the critical factors hindering research into the pathophysiology of the disorder and the development of truly novel treatments. Recent advances in our understanding of the biological basis of bipolar disorder can be used to identify and develop better models. One possibility that is discussed in a separate chapter of this book is the use of molecular biology techniques to develop animals with targeted mutations related to genes implicated in the disorder. However, the development of such animals may not be enough for usable and helpful models. Additional strategies should, therefore, be combined with targeted mutation methodology to develop good model animals and good tests that will significantly impact our ability to further explore the underlying biology of bipolar disorder and to develop better drugs and treatments.

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The present chapter presents a short introduction related to commonly used models and discusses some of the possible strategies for advancement. These strategies include developing better tests, exploring separate tests for the different domains of the disease, creating test batteries, and developing models for endophenotypes. In addition, the chapter raises the possibility of identifying better model animals using comparative biology approaches. The chapter presents two different ways for identifying advantageous model animals using either specific strains of laboratory animals or using the natural diversity of nontraditional model animals.

In summary, it is concluded that while each strategy offers significant contributions, it is important to combine the different approaches in order to be able to achieve novel, appropriate, and predictive models for bipolar disorder.

Keywords Domains of bipolar disorder · Strain differences · Endophenotypes · Strain differences · Nontraditional model animals · Diurnal rodents · Affective disorders

1 Introduction

The lack of appropriate animal models had been repeatedly cited as one of the significant factors hindering our ability to further understand the underlying biology of bipolar disorder (BPD) and to develop truly novel treatment modalities (Einat 2007a; Tecott and Nestler 2004). Animal models are critical for both basic biological research and for the translation of novel molecular data to the clinic (McKinney 2001). This chapter discusses the present status of animal models for BPD and a number of new strategies that will hopefully culminate in additional and better models.

2 Animal Models – Basics

In general, animal models have to be identified or induced, have to be testable, and have to be valid (Cryan and Slattery 2007; Geyer 2008; Willner 1991). The issue of validity of animal models in psychiatric research has long been debated and, therefore, this issue will be discussed first.

Modeling psychiatric disorders in nonhuman species is associated with significant theoretical and practical limitations. Historically, the psychological theory of behaviorism implicated, amongst many other things, that the development of animal models should be simple and straightforward; however, with the decline of pure behaviorism it was also increasingly recognized that animal models for psychiatric disorders are a complex issue (Willner 1986). A significant conceptual development

in the field was made by the important work of McKinney and Bunney (1969), who defined a number of basic and essential criteria that should be applied when developing or using animal models for psychiatric disorders. These criteria include: (1) the model should be "reasonably analogous" to the human disorder in its main features or symptomatology; (2) the model should cause behavioral changes that can be monitored objectively; (3) the model should produce behavioral changes that are reversed by the same treatment modalities that are effective in humans; and (4) the model should be reproducible by other investigators (McKinney and Bunney 1969). These criteria correlate, at least in part, with the general definitions that are accepted in psychological theories of modeling and include three main axes of validity: *face validity*, *predictive validity*, and *construct validity*.

The term *face validity* pertains to the similarity in the phenomenon between the model and the modeled condition. *Predictive validity* suggests that one variable can be used to predict a different variable, and *construct validity* defines the development of hypothetical constructs and operational definitions that are concerned with the simultaneous process of measure and theory validation and with the evaluation of hypothetical inferred notions (Smith 2005; Strauss and Smith 2008). Two of these axes translate into the criteria defined by McKinney and Bunney (1969). "Reasonable analogy to human disorder or symptoms" is a reflection of face validity, and "reversal by the same treatment modalities that are effective in humans" is a partial reflection of predictive validity. The other two criteria add a practical aspect to the theory, as they demand that the models will include behavioral changes that can be monitored objectively and are reproducible.

This set of criteria (McKinney and Bunney 1969) somewhat neglects the third axis, construct validity. Considering the definition of construct validity in the psychological research field (Smith 2005; Strauss and Smith 2008) it is no wonder that this issue was somewhat left aside by McKinney and Bunney as well as by other researchers. A serious attempt to challenge the issue of construct validity demands a comprehensive theory of the phenomenon being modeled and, considering that our understanding of the etiology and underlying pathophysiology of major psychiatric disorders is limited, it becomes a problematic issue to match a model to a construct that is not really known. Additional terms and definitions were added during the years in an attempt to clarify and operationalize the theoretical and conceptual criteria set earlier. A clear set of rules that is now used by many researchers were defined by Willner and others (Willner 1984, 1986, 1995a); these researchers were trying to combine the ideas of McKinney and Bunney with the concepts of psychological modeling theory and with the practical demands of the fields of biological psychiatry and psychopharmacology. In his substantial writings, Willner (1984, 1986, 1995a) attempted to examine the axes of validity with a practical approach to the development of models for psychiatric disorders and especially for affective disorders. Briefly, Willner set more operant criteria to evaluate the validity of models with somewhat limited interpretations of the validity terms. For face validity, the expectation is that there will be a similarity of symptoms between the model and the disease. For predictive validity, there is an expectation that the model will differentiate between effective and noneffective treatments. For construct validity,

there is an expectation of some level of homology or a similar theoretical rationale that will be a common denominator between the disease and the model, and that this rationale will be at the core of the disorder and not an epiphenomenon (Willner 1986). As indicated by Willner, even with the limited interpretations of the original demands for validity, "these are stringent criteria and it is doubtful whether any animal model (for affective disorders) could meet them fully, in our current state of relative ignorance of psychopathology" (Willner 1986). Although these words were written more than 20 years ago, they are still at least partially relevant today.

With the additional knowledge gathered across the years regarding the etiology and pathophysiology of psychiatric disorders as well as the possible sources for the therapeutic effects of effective medications, it is now at least partially possible to design and use models with some level of construct validity. Or at least, models that have some etiological or mechanistic validity where underlying biological mechanisms involved in the model and in the disorder are related (Malkesman et al. 2009).

Although significant efforts have been invested in developing animal models, there are still scientists who suggest that psychiatric disorders cannot be modeled in animals. One substantial claim is that much of the diagnosis of psychiatric disorders is based on verbal communication, and because language is unique to humans, it is impossible to extrapolate from nonhumans to humans about psychopathology (Hayes and Delgado 2007). Although this claim and others set important limitations on the possible interpretation of animal data, it is impossible to ignore the significant achievements that were demonstrated across the years from research in animal models, both for the understanding of possible mechanisms and for the screening of potential treatments (McKinney 2001).

As mentioned above, models have to be identified or induced. Identification of models pertains to the possibility that by comparing the natural physiology and behavior of different species or different strains, it is possible to identify some that might be relevant to a specific disorder. For example (in the context of a nonpsychiatric disorder), wild fat sand rats are not exposed to sugars in their natural diet; when fed sugars they develop diabetes. Based on this biology, sand rats are used as a model for diabetes in humans and can serve to explore specific mechanisms as well as the possibility of different treatments (Collier et al. 2002; Maislos et al. 2005). Within the context of neurosciences and psychiatry, monogamous prairie voles serve to explore the underlying anatomical, biochemical, and molecular underpinnings of social bonding (for reviews see Aragona and Wang (2004) and Carter et al. (1992, 2008)), and for modeling depression and anxiety related to isolation (Grippo et al. 2008). However, most animal models in psychiatry are induced rather than identified. "Induced" means that a "normal" animal is manipulated so that it will demonstrate pathology. Such manipulations can include specific brain lesions (e.g., bulbectomy (van Riezen et al. 1977)) or 6-HDPT lesion (Petty and Sherman 1981), pharmacological treatments such as reserpine (Einat et al. 1999) or amphetamine (Fessler et al. 1982), specific agonists and antagonists for a unique subgroup of receptors (Einat et al. 2001), or compounds acting on other targets such as intracellular pathways, ion channels, and so on (Einat et al. 2003b). Other possible manipulations are environmental, such as in the forced swim test

or isolation paradigms (Malkesman et al. 2006; Porsolt et al. 1978), breeding for specific traits (Einat et al. 2002; Overstreet et al. 1992) or, more recently, targeted genetic mutations (Malkesman et al. 2009). Some models based on such manipulations will be discussed in detail later in this chapter.

Last but not the least, an animal model has to provide a way to test the behavior, a test that will clearly distinguish between the "healthy" and "sick" animal and that will include clear and replicable measures (Einat et al. 2007; McKinney and Bunney 1969; Willner 1986). This matter is especially important to remember when one attempts to develop a model based on a mechanistic theory such as the newer models induced by targeted mutations. As beautifully termed by Crawley a decade ago (Crawley 2000), the question is often "what is wrong with my mouse?" What tests do we have available to evaluate BPD-relevant behavioral changes? It is important in this context to remember that the model and the test are not the same. The model refers to an animal that in some way represents the disease (or represents a treatment effect); the test is our way of measuring such relevant changes (Szechtman and Eilam 2005). For example, amphetamine-induced hyperactivity is frequently used to model a domain of mania. The model in this case is an animal treated with amphetamine whereas the test measures activity levels (Einat et al. 2007). There is at times a tendency to confuse the model and the test because some of the common models used in the field include both components in one assay. For example, the forced swim test is both a model and a test. The model part is the immersion of rodents in water that results in behavioral and biochemical changes that are relevant to depression, and the behavioral test is the actual measuring of immobility time in the water (Porsolt et al. 1978). The confusion comes from the fact that the induction and the measuring happen at the same place and the same time, but these are clearly separate entities.

3 A Short Summary of What We Have and Use Today

At this time, there are no accepted models that can comprehensively simulate BPD. Most models that were offered across the years and are used by both academic and industry laboratories reflect at best part of the disorder (for a review see Large et al. (2008)). The commonplace way of modeling BPD separates the different poles and uses separate models for depression and mania. Attempts to identify and develop oscillating models are limited and none of the proposed comprehensive models is being used in any major way (Einat et al. 2003a). The lack of an oscillating model was repeatedly mentioned as a major problem in BPD research to the extent that some believe that all other options (nonoscillating models) are completely invalid (Machado-Vieira et al. 2004). However, most researchers would suggest that although nonoscillating models cannot fully represent the entire disorder, such models still have significant value (Cryan and Slattery 2007; Geyer 2008; Gould and Einat 2007).

When looking separately at models for the depression and the mania poles, the availability of models for depression is significantly higher because such models were developed in the context of studying major depression. Some comprehensive reviews on such models are available (e.g., Cryan and Mombereau 2004; Cryan and Slattery 2007) and will not be discussed in the present chapter.

A number of models and tests for mania were suggested across the years with only a few becoming mainstays in the study of BPD and the search for novel treatments. The most frequently used model is based on treating animals with psychostimulant drugs, mostly amphetamine. Comprehensive reviews of psychostimulant-induced models can be found in the literature (e.g., Einat et al. 2007; O'Donnell and Gould 2007). Briefly, this model is based on the fact that administration of low dose amphetamine can induce hyperactivity, suggesting face validity for the increased activity seen in manic patients. Moreover, amphetamine-induced hyperactivity can be reversed by treatment with the prototypic mood stabilizer lithium, adding a predictive validity component to the model (Gould et al. 2007). In addition, psychostimulants can induce mania in susceptible individuals, and lithium can prevent the behavioral effects of stimulants in people, suggesting a common mechanism and some construct validity (for reviews see Einat et al. (2007) and O'Donnell and Gould (2007)).

Variations on this basic model have been suggested, including the exploration of sensitization to psychostimulants as a model for the exacerbation of manic episodes across time (Post et al. 1984), the use of amphetamine–chlordiazepoxide combinations (Arban et al. 2005), and the use of other psychostimulants such as cocaine (Post and Weiss 1989), methylphenidate (Eckermann et al. 2001), or more specific dopamine receptor agonists such as quinpirole (Shaldubina et al. 2002). These variations might have some advantages but conceptually are not much different from the basic model, and they were not demonstrated to have a significantly higher predictive value (for a review see Large et al. (2008)).

An additional pharmacological method for modeling mania is the inhibition of Na–K-ATPase ion pump using ouabain. The administration of subconvulsive doses of ouabain results in mania-like hyperactivity in rodents, and this behavior is inhibited with chronic lithium pretreatment (components of face and predictive validity). Moreover, this model has a mechanistic rationale, since the neurochemical effects of ouabain may be similar to the decreased Na–K-ATPase activity and associated imbalance in electrolyte levels reported in some patients with BPD, adding tentative construct validity to the model (for a review see Herman et al. (2007)).

Some other interesting models have been proposed and tested but, for a variety of reasons, did not become common research tools. One such model that should receive special attention is the sleep-deprivation model (Gessa et al. 1995a). Altered sleep patterns are strongly related to BPD, and sleep disturbance can induce mania in susceptible patients (Perlman et al. 2006; Wehr et al. 1982, 1987). There may also be an underlying disruption of circadian mechanisms in BPD (McClung 2007). Mechanisms underlying circadian rhythm and the sleep–wake cycle are likely to be conserved between humans and nonhuman species, increasing the

probability that models based on these measures will have reasonable predictive and perhaps even construct validity. In line with these ideas and observations, researchers tried to develop a mania model based on sleep deprivation in rodents (Benedetti et al. 2008; Gessa et al. 1995a, b; Willner 1995b). Data obtained with this model demonstrate that sleep deprivation results in behavioral hyperactivity and increased aggression, and that these manic-like behaviors are reversed by lithium treatment (Gessa et al. 1995a). Whereas these results, combined with the increasing implication of circadian rhythms mechanisms in BPD suggest that sleep deprivation could be a good model; there are unfortunately practical problems with the way it was initially suggested.

Specifically, the induction of the model demands lengthy sleep deprivation (72 h); the relevant behavioral and biochemical changes can be tested at the end of the induction period, but can be observed only for a short time (about 30 min) after which the animals fall asleep, which does not allow for comprehensive evaluation of relevant changes (Gessa et al. 1995a). Yet, as will be discussed later, the idea of approaching model development and identification through systems related to circadian mechanisms is clearly at the forefront of such work.

The lack of options for good and predictive models in the field is being increasingly recognized and indeed a number of methods were introduced during the last years in an attempt to identify and develop better models. The rest of this chapter will introduce some of these newer (or renewed) approaches. It is important to note that one central new approach to develop models is based on targeted mutations and genetic manipulation of animals. A separate chapter in this book (By Guang Chen) is wholly dedicated to this approach and accordingly it will be only briefly mentioned in the current chapter.

This chapter emphasizes a number of approaches including: (1) development of appropriate tests for BPD by modeling separate domains of the disorder or modeling endophenotypes and (2) identifying the best model animals through the selection of the best strains or the best species in the context of the specific research question.

4 Development of Appropriate Tests

As mentioned above, regardless of the way a model is induced, there is a need to design tests to evaluate it. Ideally, we want tests that can examine whether the model (the animal) shows a bipolar-like phenotype or, alternately, shows a phenotype similar to the effects of mood stabilizing drugs. How do we know that our model is manic-like, depressed-like, lithium treated-like, and so on? Unfortunately, tests are limited and the limitations are clearly emphasized in new models based on targeted mutations. In such models, a mechanistic hypothesis is tested by manipulating a specific gene in an animal that is suggested to be relevant to the disease or its treatment. However, when the mutant animal is created, it needs to be tested to see if the phenotypic changes indeed support or refute the mechanistic hypothesis. Such an examination should be based on tests that represent the disease or its

treatment but because tests are limited, the ability to truly examine the molecular hypotheses at the behavioral level is minimal, and many times tests with marginal relevance are used possibly because these are the available tools.

For example, based on significant data at the molecular and biochemical level, O'Brien et al. studies the effects of GSK-3 haploinsufficiency (O'Brien et al. 2004) and hypothesized that reduced GSK-3 levels would result in a behavioral phenotype that resembles the effects of lithium treatment. To examine this hypothesis, they tested the animals for exploration (in the open field and in a holeboard apparatus), in the elevated zero maze, in the forced swim test, in the acoustic startle response test, and in prepulse inhibition of startle. This is a comprehensive set of tests but can we learn from it whether the animals phenocopy lithium effects?

Only a few behavioral effects of lithium in rodents are strongly validated and replicable. In fact, from the tests used in the study by O'Brien et al., only lithium's effects in the forced swim test have been reliably demonstrated (Bersudsky et al. 2007). Regarding the other tests, some studies show lithium-induced reduction in spontaneous activity in rodents (Cappeliez and Moore 1990; Hamburger-Bar et al. 1987) but others do not (Borison et al. 1978; Einat et al. 2003b; Furukawa et al. 1975; Gould et al. 2007; O'Brien et al. 2004); lithium's effects in anxiety-related tests is not strongly demonstrated (O'Donnell and Gould 2007) and lithium was not shown to alter behavior in the acoustic startle or prepulse inhibition tests (O'Brien et al. 2004; Ong et al. 2005; Umeda et al. 2006) except maybe when prepulse inhibition is initially disrupted (Ong et al. 2005; Umeda et al. 2006). Therefore, regardless of the results of the specific study, based on these tests it is hard to make any strong conclusions regarding whether the mutant animals indeed phenocopy lithium effects. In a way, this study and others like it demonstrate the paucity of available tests.

4.1 Developing Tests for Behavioral Domains of BPD

One way to enhance the ability to evaluate BPD-like phenotypes in animals is to identify and develop additional tests that can reflect different behavioral domains of the disorder and then develop appropriate test batteries (Einat 2007a). Behavioral domains can be tentatively defined as separable or partially independent behavioral features, and BPD is believed to include a number of such domains (Hasler et al. 2006; Soreca et al. 2009). A similar attempt to model domains is similarly ongoing for schizophrenia and major depression research (for reviews see Cryan and Slattery (2007) and Geyer (2008)). A battery of tests that will include ways to measure changes in a number of such domains could be a partial solution to the current deficiency in appropriate tests. This proposal had been discussed in detail over the last few years (Einat 2006, 2007a, b; Einat et al. 2007) and will therefore be presented here only briefly.

The behavior of BPD patients includes a large variety of symptoms that culminate in the disease phenotype (or possibly phenotypes) in different ways. Regardless of the general discussion of whether BPD is a unique disorder or a combination

of symptoms, it is possible to develop a battery of tests to evaluate the different components of the general phenotype. For example, BPD-related behaviors include hyperactivity, enhanced sensitivity to psychostimulants, increased reward seeking and risk taking behaviors, increased intrusion and aggression, increased sexual activity, and more (Sadock and Kaplan 2002). Similar behavioral changes can be evaluated in animals. Activity can be tested in a variety of systems, response to psychostimulants can be evaluated by administration of such drugs or by operant measures looking at the amount of work animals will invest to receive drugs, risk taking behavior can be tested by tests that were developed in the context of anxiety (risk taking may be a mirror image of anxiety-like behavior), and so on.

Some attempts to develop such a battery of tests are ongoing, with specific tests for separate behavioral domains. For example, a recent study demonstrates that in mice with high preference for sweet solution, the test can be used as a model for increased reward seeking behavior; the high preference is ameliorated by mood stabilizers, but not affected by antidepressants (Flaisher-Grinberg et al. 2009). With the increasing awareness to the different relevant domains of BPD, some recent work with tentative models includes more relevant tests. For example, in a recent study by Shaltiel et al., a battery of tests was used to test the phenotype of GluR6 mutant mice (Shaltiel et al. 2008). Based on molecular and biochemical data, the authors hypothesized that these mice would show a manic-like phenotype; they tested them for spontaneous activity (expecting possibly increased activity levels), response to amphetamine (expecting enhanced response compared with control mice), resident-intruder test for aggression (expecting increased aggression), elevated plus-maze (expecting decreased anxiety-like behavior or in other words, increased risk-taking), and the forced swim test (expecting a lower susceptibility to despair, possibly representing increased vigor and goal directed activity; see also Flaisher-Grinberg and Einat (2009)). Clearly, this battery of tests includes a number of the behavioral domains of BPD and can be very helpful in determining the BPD-relevant phenotype of mice.

Whereas clear advances have been made in this area, more tests for additional domains should be identified or developed and added to the batteries. However, it is important to note that if used alone, none of these tests can really become a single representative test for the disease. Each of these tests can reflect behaviors that might be related to a variety of other diseases or even to variations on normal behavior. For example, increased spontaneous activity can be the consequence of mania-like behavior but also of attention deficit hyperactivity disorder (ADHD)-like behavior or a number of neurological disorders. The strength of a test battery comes from the combination of a number of tests, each reflecting a separate behavioral domain.

4.2 Models and Tests for Endophenotypes of Disease

In a seminal theoretical paper, Gottesman and Shields described “endophenotypes” as “internal phenotypes discoverable by a biochemical test or microscopic

examination" (Gottesman and Shields 1973). They suggested that "if the phenotypes associated with a disorder are very specific and represent more basic phenomena than a complex behavioral facet of the disease, the number of genes required to produce variations in these traits may be fewer than those involved in producing a psychiatric diagnostic entity" (Gottesman and Shields 1973).

The endophenotype approach offers a few advantages to the study of BPD (Chan and Gottesman 2008; Hasler et al. 2006). In the context of the development of animal models, the critical advantage might be that the more elementary construct of an endophenotype may directly be related to specific neuronal mechanisms and specific genes compared with the more complex illness. As such, it could be significantly easier to develop models for endophenotypes compared with models for the disorder (Gould and Gottesman 2006).

A number of endophenotypes proposed for BPD can be modeled in animals. For example, converging lines of evidence supports circadian dysregulation as an endophenotype of BPD. Sleep disturbances are the most common prodrome of mania. Sleep deprivation can induce hypomania or mania in susceptible individuals, mood stabilizers normalize circadian rhythms, evidence suggests that sleep cycles are still unstable in euthymic patients, studies of the general population suggest a genetic basis for circadian characteristics and the circadian clock, and a specific polymorphism in the human CLOCK gene has been associated with illness recurrence in BPD (see (Hasler et al. 2006; McClung 2007) for reviews). In the context of this endophenotype (and in the context of general circadian theories of BPD), a number of recent attempts to develop models by manipulating circadian-related genes show interesting results (Le-Niculescu et al. 2008; McClung 2007; Roybal et al. 2007).

Additional current suggestions for endophenotypes that might be practical goals for modeling include dysregulation of the reward system (Abler et al. 2007) and maladaptive arousal (MacKinnon 2008). Regarding reward systems, a large number of models and tests are available to evaluate reward responsiveness in rodents, developed initially either in the context of affective disorders research or in the context of addiction research. For example, one established test for depression-related anhedonia is the sweet solution preference test. Whereas anhedonia is related to depression (either unipolar depression or bipolar depression), elevated reward seeking behavior can be related to mania and animal models can be identified or developed that show high levels of such behavior. Such models can be used to explore the biological basis of reward seeking and highlight this possible endophenotype of the disease (Flaisher-Grinberg et al. 2009). An additional possibility is exploring maladaptive arousal at a basic level. A recent study demonstrates that BPD patients fail to find a respiratory adjustment when tested for breathing in a 5% CO_2 environment (MacKinnon 2008). This test might reflect a maladaptive arousal endophenotype and can be easily translated to a test for animals.

It is important to note that modeling endophenotypes is a different approach from modeling overt domains of the disorder (discussed in the previous subsection), although at times there might be an overlap. Specifically, to test a domain, one concentrates on an overt, behaviorally expressed component of the disorder whereas

modeling an endophenotype emphasizes the development of a model with genetic relevance rather than a symptom. To use the last example, maladaptive adaptation to 5% CO_2 is not an overt symptom of BPD, but it could be an endophenotype. Moreover, exposure to 5% CO_2 may induce a model and the breathing adjustment may be the test. However, some possible endophenotypes such as the dysregulation of circadian rhythms and reward seeking are also expressed in part as symptoms, and it is therefore possible that some of the models and tests that can be developed for the domains of BPD may also be applicable in the context of exploring endophenotypes.

Nevertheless, the possibility of developing additional new models related to endophenotypes depend on the identification of additional such endophenotypes for the disease and can be based only on more data from human research.

5 Identifying the Best Species and the Best Strains

In a recent editorial published in *Biological Psychiatry*, Thomas Insel suggested that instead of concentrating on the development of animal models for psychiatric diseases, it might be beneficial to the field to emphasize the best model animals (Insel 2007). The idea of model animals can be interpreted in more than one way but in my understanding it distinguishes between two options. Animal models are based on an attempt to phenocopy human pathology by means of external (pharmacological, environmental, and so on) intervention, and model animals are based on innate biological diversity or on genetic manipulations. Regarding the possibility of genetic manipulations, this is an important rising field that is thoroughly discussed by Dr. Chen and his colleagues in a different chapter of this book. This chapter, therefore, discusses a number of possibilities for model animals based on biological diversity and a comparative approach.

5.1 Model Animals Based on Strain Differences

It is well acknowledged by behavioral scientists that different strains of laboratory animals differ significantly in their behavior and biology. These differences can hinder research, because it is hard to compare data across strains. These differences are also important in the development of mutant mice, as the background strain may critically affect outcome (Bailey et al. 2006). However, strain differences can also be used to identify the best model animal in a specific research context. For example, compared with other rat strains, Wistar Kyoto rats demonstrate a number of depression-like behaviors including hypoactivity, fast acquisition of learned helplessness and passive avoidance tasks, high immobility rates in the forced swim test, diminished reward seeking behavior, and greater susceptibility to restraint-induced stress ulcers (Malkesman and Weller 2009; Pare 1994; Pare and

Redei 1993). This unique behavioral pattern is used through comparison with other strains to explore underlying biochemical and molecular mechanisms (for a recent review see Malkesman and Weller (2009)) as well as to screen for the possible antidepressant effects of treatments (e.g., Krahl et al. 2004; Malkesman et al. 2007; Tejani-Butt et al. 2003).

At this time there is no specific established strain that can be used to model either BPD or mania. However, a number of studies implicate at least two strains as relevant to modeling mania. The inbred FVB/NJ strain was demonstrated to have many manic-like behavioral features compared with other strains. These mice show increased activity levels (Lucki et al. 2001; Milner and Crabbe 2008), reduced anxiety-like behaviors suggesting increased risk-taking (Milner and Crabbe 2008), high consumption of sweetened ethanol solution suggesting high reward seeking behavior (Yoneyama et al. 2008), and minimal immobility in the forced swim test suggesting increased vigor and resistance to despair (Lucki et al. 2001). However, one study found that in the amphetamine-induced hyperactivity test, FVB mice do not respond to treatment with the prototypic mood stabilizer lithium (Gould et al. 2007), thus casting some doubt on the utility of this strain as a model animal for manic-like behavior.

Some data also suggest that outbred Black Swiss mice show a number of manic-like behaviors in comparison with other strains. These mice do not show spontaneous hyperactivity but present low anxiety-like behaviors, high preference for sweet solution representing reward seeking, high aggression, low immobility in the forced swim test suggesting increased vigor and resistance to despair, and a high response to low doses of amphetamine suggesting sensitivity to psychostimulant drugs (Flaisher-Grinberg et al. 2008, 2009; Hiscock et al. 2007). Moreover, Black Swiss mice are also sensitive to mood stabilizing treatment as their response to amphetamine was ameliorated by lithium (Gould et al. 2007), their immobility time in the forced swim test was elevated by the mood stabilizer valproate (Flaisher-Grinberg and Einat 2009), and their high preference for sweet solution was reduced by both lithium and valproate (Flaisher-Grinberg et al. 2009). While additional studies of this strain are warranted, the present data suggest that at least at the level of a phenotype, these mice present a set of manic-like behaviors that are sensitive to mood stabilizers; they may, therefore, be an advantageous strain in the context of modeling mania.

5.2 Nontraditional Models

The commonly used model animals in psychiatric research are rats and mice. The reasons for the historical preference of these species are multiple and outside the scope of this chapter. Some of the trivial reasons are of course that rats and mice are relatively advanced mammals with a developed brain and a large range of behaviors. Many of their physiological and biochemical mechanisms are relatively homologous to humans but they are still small enough to permit relatively easy

maintenance and testing in a laboratory environment. Moreover, because of the long history of research in rats and mice there is ample knowledge regarding their genetics, physiology, and behavior, and therefore it is relatively simple to compare new data to previous information and select the best strains for specific experiments. Additionally, the genome of the mouse is now known, reagents for biochemical and molecular analysis are available from commercial suppliers, and specific targeted mutations are possible. The heavy use of rats and mice in research also makes these species a very practical choice as they are available from commercial suppliers for reasonable prices and most animal facilities are well equipped to hold and maintain them.

There is no doubt that significant knowledge has been obtained regarding the underlying mechanisms of BPD using rat and mouse models; however, it is possible that these species may not be the best for all related questions (Smale et al. 2005). A comparative approach using nontraditional model animals is also used in psychiatric research and at times is critical to discovery. One well-known example is the significant work related to the nature of bonding and social behavior done with prairie voles. Studies using this monogamous species contributed significantly to our understanding of the neuroanatomy, biochemistry, and genetics of social behavior and bond formation with important implications for human behavior and human pathology (Aragona and Wang 2004; Carter et al. 1992, 1995, 2008; Grippo et al. 2009). Similarly, work with the diurnal *Octodon degus* show important differences between the biology of circadian rhythms of nocturnal and diurnal rodents with implications for human phase shift and jet lag phenomena (Lee 2004; Vosko et al. 2009).

As mentioned above, significant data implicate circadian rhythms and genes as well as sleep mechanisms in affective disorders in general and BPD in particular (McClung 2007). Considering this strong relationship between circadian mechanisms and affect, it is possible that diurnal rodents can have some advantages as model animals for affective disorders including BPD. Diurnal and nocturnal animals differ with respect to a coordinated and far-ranging suite of behavioral and physiological parameters (Smale et al. 2003, 2005; Challet et al. 2007). Diurnal animals (including humans) are exposed to bright light all day long but nocturnal animals are rarely exposed to daylight. Diurnal mammals are active at times of day when levels of melatonin are low and when the suprachiasmatic nucleus (SCN; the internal clock) is most active, and this is the opposite in nocturnal mammals. The expression of CLOCK-related genes in response to photoperiod manipulations is different in diurnal and nocturnal mammals (Vosko et al. 2009), and so on. Some preliminary work indeed supports the possibility of using diurnal rodents to gain better understanding of the mechanisms related to circadian effects on mood. Specifically, a few recent studies show that diurnal sand rats consistently develop depression- and anxiety-like behavior when maintained in a short photoperiod environment (5 h light/19 h dark). These same effects can be induced by administration of melatonin in a regimen that mimics short photoperiods, and the behavioral deficits are ameliorated by bright light exposure or by treatment with antidepressant drugs (Ashkenazy et al. 2008, 2009; Einat et al. 2006; Krivisky et al. submitted). An additional study

showed that short photoperiods induce depression-like behavior in an additional diurnal rodent, the the diurnal Grass Nile rat (Arvicanthis Niloticus), suggesting a general phenomenon in diurnal rodents (Ashkenazy-Frolinger et al. 2010). These preliminary results indicate that diurnal rodents may be susceptible to similar circadian-related manipulations as humans and additional research is now designed to compare the effects of a variety of such manipulations in diurnal and nocturnal animals and examine behavioral, physiological, and molecular changes.

6 Conclusion

It is clear that the lack of appropriate and valid animal models for BPD hinders our ability to better understand the underlying pathophysiology of this devastating disease and to develop better new treatments for it. Different approaches and strategies can be used to achieve better models including the development of specific animals with targeted mutations, the development of new tests for domains of the disorder, the development of models and tests for endophenotypes, and the identification of the best model animals including specific strains of laboratory animals or unique nontraditional models.

It should, however, be emphasized that it is hard to imagine that any of these strategies will result in the "best model" when used in isolation. It is suggested that the important part of developing good and valid models might be the combination of all these approaches and the building of strong collaborative work between scientists with expertise in these different fields.

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Partial Rodent Genetic Models for Bipolar Disorder

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Contents

Abstract Bipolar disorder (BPD) is a complex clinical phenomenon. This episodic illness comprises at least four features/components: depression, mania, vulnerability to mood swings in euthymic BPD patients, and spontaneous cyclicity in at least some BPD patients. Currently, there is no rodent genetic model capable of encompassing the whole phenotype of BPD exists; however, recent genetic-behavioral studies have delineated partial models for some components of BPD, namely, depression, mania, and vulnerability or resilience to mood swings. p11 knockout (KO), vesicular monoamine transporter 2 (VMAT2) heterozygous KO, and neural

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cell adhesion molecule (NCAM) KO mice display anhedonia-like symptoms, and treatment with antidepressants rescues this anhedonia-related phenotype. Mutant CLOCK, glutamate receptor 6 (GluR6) KO, and extracellular signal-regulated kinase 1 (ERK1) KO mice exhibit mania-like behavioral clusters referred to as excessive behavioral excitement; at least some of the exhibited behaviors can be rescued through treatment with mood stabilizers or atypical antipsychotics. Neuronal glucocorticoid receptor (GR) overexpressing, B-cell lymphoma 2 (Bcl-2) heterozygous KO, and Bcl-2-associated athanogene (BAG1) heterozygous KO mice show vulnerability to mood swings. In contrast, neuronal BAG1 overexpressing mice display resilience to mood swings. These mutant mouse strains and the behavioral approaches used to characterize these strains offer an emerging set of research tools for the comprehensive understanding of various components of BPD, and the interrelation of these components at the molecular, cellular, and neuronal circuitry levels. These partial genetic models can also be used as complementary tools to augment other existing behavioral tests and paradigms in drug development for BPD.

Keywords Bipolar disorder · Mania · Depression · Antidepressants · Mood stabilizers · p11 · Vesicular monoamine transporter 2 (VMAT2) · Neural cell adhesion molecule (NCAM) · Extracellular signal-regulated kinase (ERK) · Glutamate receptor 6 (GluR6) · Glucocorticoid receptor (GR) · B-cell lymphoma 2 (Bcl-2) · Bcl-2 associated athanogene (BAG1)

1 Introduction

Animal models are essential for studying the molecular, cellular, and neuronal circuitry mechanisms underlying behaviors or behavioral clusters related to human neuropsychiatric diseases (Berton and Nestler 2006; Crawley 2008; Cryan and Holmes 2005; Cryan and Slattery 2007; Duman and Monteggia 2006; Einat 2006; Kato et al. 2007; O'Donnell and Gould 2007; Willner and Mitchell 2002). Indeed, such models are pivotal for investigating the therapeutic mechanisms underlying existing treatments, and for evaluating the efficacy of novel therapeutics. With regard to bipolar disorder (BPD), any model expected to capture the whole of the disease would require the following: (1) the animal would be biologically modeled to carry multiple gene alterations implicated by human genetic studies; (2) the behavioral displays of the model animals would cover multiple components of clinical phenomena associated with BPD; and (3) the behavioral alterations exhibited by the model animals would be at least partially responsive to chronic treatments with existing clinically effective antidepressants or mood stabilizers. These three aspects of model animals are often referred to in the literature as constructive, face, and predictive validity (Berton and Nestler 2006; Crawley 2008; Cryan and Holmes 2005; Cryan and Slattery 2007; Duman and Monteggia 2006; Einat 2006; Kato et al. 2007; O'Donnell and Gould 2007; Willner and Mitchell 2002. While animal models do exist that encompass facets of either depression or mania, to date no animal model of BPD encompassing the cyclic nature of its symptoms has been developed.

For the purposes of behavioral simulation and mechanistic studies, the clinical course and phenomena associated with BPD (Belmaker 2004; Goodwin and Jamison 2007) can be summarized into four components or features: depressive episode, manic episode, spontaneous mood swing or cyclicity, and vulnerability to triggerable/inducible mood changes in euthymic patients. The features of each component and the animal behavioral tests and paradigms to monitor these features will be discussed later.

Mood stabilizers are the treatment of choice for BPD and, although far from perfect, they are generally effective treatments for bipolar depression, mania, or mixed episodes, and are also used to prevent the recurrence of mood episodes (Belmaker 2004; Goodwin and Jamison 2007). Antidepressants are used in conjunction with mood stabilizers to treat bipolar depression; however, when used alone they carry the risk of cycle acceleration or agitation/dysphoria for some patients. With regard to animal models, a collection of antidepressant-sensitive and mood stabilizer (especially lithium)-sensitive behavioral tests are well documented in the literature (for reviews see Berton and Nestler 2006; Cryan and Holmes 2005; Cryan and Slattery 2007; Duman and Monteggia 2006; Einat 2006; Kato et al. 2007; O'Donnell and Gould 2007; Willner and Mitchell 2002). Some of these tests have been used to assess whether genetically altered animals display cross-species phenocopies of behavioral facets of BPD.

The term "cross-species phenocopy", used throughout this chapter and in other related articles, refers to the apparent phenotypical similarity between behavioral displays in model animals and simulated clinical symptoms or syndromes, regardless of the underlying biological causes (Shaltiel et al. 2008). Using this term acknowledges that, despite the behavioral similarity between model animals and human patients, the biological causes of such symptoms in model animals may or may not be similar. Unlike neurological disorders that cause seizures, movement abnormalities, or learning and memory difficulties, mood disorders (BPD or major depressive disorder (MDD)) affect a patient's subjective feelings or mood, which are the core symptoms of the illness and required for making a diagnosis. This core symptom, obviously, cannot be directly assessed in rodents. Thus, to reflect the limitations associated with animal models, terms, such as "manic mouse" or "depressed mouse" are avoided in the research literature; instead the terms "mania-like behaviors" or "depression-like behaviors," or "model for mania or depression" are used to highlight the fact that the behaviors of model animals phenocopy the observable diagnostic symptoms or behavioral displays related to mood alterations. The similarity or relevance of the phenocopied behaviors to human mood episodes are further validated, at least in most cases, by noting whether the animal behaviors respond to chronic treatment with antidepressants or mood stabilizers.

Over the years, several genetic mutant mouse strains have been examined using batteries of tests to assess the behavioral components of BPD. These mutant mice carry changes in selected genes previously implicated in mood disorders by human genetic and postmortem studies, or by animal studies on the neurochemical actions of antidepressants and mood stabilizers. Although none of the strains display a phenocopy covering all components of BPD, the data clearly demonstrate that altering these genes in turn alters behaviors related to BPD. Thus, these strains can be considered practical choices for in-depth mechanistic studies of depression

or mania as well as of vulnerability to mood swings; they are also useful for evaluating novel therapeutics in conjunction with other widely used animal paradigms assessing antidepressant- or mood stabilizer-sensitive behaviors. In humans, mood disorders manifest as a clinical syndrome. The symptoms of the syndromes are less specific and the same symptom can be present in different illnesses. The major advantage of using genetically altered animals is that mutant animals allow investigators to study behaviors as a cluster, not just the individual acts. Some of the most useful strains for investigating BPD will be discussed in this chapter.

2 Partial Models for Anhedonia and Depression (Table 1)

Depressed or irritable mood and anhedonia are the core symptoms of depression and unequivocally important for clinically diagnosing major depression (American Psychiatric Association 1997). Clinical anhedonia is defined as "markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)" (American Psychiatric Association 1997). According to this definition, one simple way to monitor cross-species phenocopies of anhedonic displays in rodents is to observe the animals' activity over a specific period of time in either their enriched (e.g. equipped with play objects) or their regular home cages. However, a home cage activity study requires special animal holding facilities or cabinets, video

Table 1 Partial genetic models for depression and anhedonia

Clinical features	$p11^{-/-}$	$Vmat2^{+/-}$	$NCAM^{-/-}$
Depressed mood	Cannot be assessed	Cannot be assessed	Cannot be assessed
Anhedonia	Less sucrose consumption in the SPT	Less sucrose preference in the SPT	Lack of sucrose preference in the SPT
Weight or appetite change	No data	No changes in food consumption or body weight	No data
Sleep disturbances	No data	No data	No data
Psychomotor activity change, agitation or retardation	More immobility in the TST and FST	More immobility in the TST and FST; less locomotion in the OFT	More immobility in the TST; more locomotion in a large cage and in the OFT
Lost physical strength	More immobility in the TST and FST	More immobility in the TST and FST; less locomotion in the OFT	Inconclusive
Low self esteem	Cannot be assessed	Cannot be assessed	Cannot be assessed
Cognitive disturbances	No data	No data	No data
Hopelessness	Cannot be assessed	Cannot be assessed	Cannot be assessed

SPT Sucrose or saccharin preference test, *TST* Tail suspension test, *FST* forced swim test, *OFT* open field test

tracking systems, and sophisticated computer software. These are not widely available to the research community. Alternatives do, however, exist. For instance, rodents love to run on the wheel. Indeed, wheel running, like psychostimulants, can induce conditional place preference (Lett et al. 2000), cause cross-tolerance to the rewarding effects of morphine (Lett et al. 2002), and stimulate deltaFosB expression in the reward pathway (Werme et al. 2002). Therefore, home cage wheel running can be used as part of hedonic-like activity measures (Engel et al. 2009).

Another behavior that can be monitored is that of food consumption. Rodents prefer to consume palatable food. As a result, the sweetened solution preference (vs. water) test has been widely used to examine anhedonia-like displays in rodents, although the test protocols vary from study to study. Chronic behavioral stress gradually reduces sweetened solution preference and this reduction can be prevented or reversed through treatment with antidepressants during the course of the stress (Willner 1997). Sucrose, sucralose (a noncaloric sweetener), or saccharin (a more potent noncaloric sweetener) are used to make the sweetened solution for the test. The TRPM5 (transient receptor potential cation channel, subfamily M, member 5) is expressed in taste receptor cells and is essential for sweet, bitter, and amino acid taste signaling. In a study conducted using both wild-type and TRPM5 knockout (KO) mice, de Araujo and colleagues found that both sucrose and sucralose induced consumption preference and activation of the dopamine-nucleus accumbens (NAc) reward system, and that sucrose, but not sucralose, induced similar effects in TRPM5 KO mice (de Araujo et al. 2008). The interpretation of this and other supporting data in their study suggest that overall food reward is mediated through two independent pathways: one relating to calorie-independent palatability initiated in the taste cells, and the other relating to taste-independent caloric load that bypasses the taste cells (de Araujo et al. 2008). In light of the findings from this study, the selection of sweeteners for the preference test should consider the reward-delivering pathways to be monitored.

Another option concerns the fact that rodents spend more time sniffing urine from the opposite sex than either water or novel odors. The female urine sniffing test (FUST) is a novel method for monitoring sexually related hedonic activity in rodents (Malkesman et al. 2009). In this test, water and female urine were presented to male rodents; the animals spent much longer sniffing female urine. While sniffing female urine, males also emitted ultrasonic vocalizations, and had significantly elevated dopamine levels in the NAc. In addition, mice that developed helplessness in the learned helplessness paradigm spent less time sniffing female urine, and treatment with antidepressants rescued these changes.

Nevertheless, the issue of appropriately defining an anhedonia-like phenotype in rodents is an issue that has yet to be resolved. Given that in humans the impact of anhedonia is sustained and spreads into broad aspects of patients' daily activity, and that in rodents each behavioral test has its limitations and confounding factors, one operational definition of an anhedonia-like phenotype in rodents is as follows: experimental animals display concurrent reductions in multiple activities that are known to be preferred by appropriate control animals, and these reductions cannot

be explained by a single or few causes alone, such as locomotive dysfunction, lack of explorative curiosity or neophobia, specific sensory alterations, low sexual drive, or loss of appetite. Thus, anhedonia-like behaviors should be evaluated as a behavioral cluster or pattern rather than a specific act in any given context.

Phenocopies of some other diagnostic symptoms of major depression can also be monitored in rodents. For instance, changes in body weight or appetite can be monitored. Home cage monitoring or tests such as the open field test can be used to evaluate psychomotor agitation or retardation. Home cage monitoring over a 24-h period can also be used to detect sleep disturbances (e.g., insomnia or hypersomnia). Similarly, fatigue or loss of energy can be evaluated using home cage activity, the open field, forced swim, and tail suspension tests, or treadmill running. However, tests to assess behaviors related to diminished ability to think or concentrate, or indecisiveness, need to be developed or adapted from other fields, refined, and validated for use in depression studies. Obviously, it would be very challenging to define and monitor displays related to low self-esteem or hopelessness. Some behavioral paradigms are thought to monitor behavioral despair (e.g., the forced swim or tail suspension tests and the learned helplessness paradigm). However, the link between rodent performance on these tests and the subjective human symptoms of depression – for instance, low self-esteem or hopelessness – require further examination.

Because no consensus has to date been established regarding how to define genetic models for depression or anhedonia, most investigators use a few behavioral tests, but not the comprehensive evaluation approach suggested above. Given the importance of anhedonia in diagnosing depression in humans, we here focus on those modeling anhedonia in mice.

p11 (also known as S100A10) is a member of the S100 calcium effector proteins (Svenningsson et al. 2006; Warner-Schmidt et al. 2009). In the brain, p11 mediates receptor trafficking (such as 5HTR1B and 5HTR4) as well as ion channels to the cell surface (Svenningsson et al. 2006; Warner-Schmidt et al. 2009). p11 also mediates the behavioral effects of antidepressants and antidepressant-like effects of a selective 5-HTR4 partial agonist (RS67333) on immobility in the tail suspension test and on thigmotaxis in the open field test (Svenningsson et al. 2006; Warner-Schmidt et al. 2009). A postmortem study revealed reduced p11 mRNA levels in multiple brain regions in suicide victims (Anisman et al. 2008). Interestingly, naïve p11 KO mice displayed increased immobility and thigmotaxis as well as reduced consumption of sucrose solution (Svenningsson et al. 2006). These results suggest that p11 KO mice may serve as a genetic model for depression with anhedonic features; this putative model is worthy of further characterization via additional tests and agents such as mood stabilizers and ketamine used to treat depression.

SLC18A2 (solute carrier family 18 (vesicular monoamine), member 2) encodes proteins and is also known as vesicular monoamine transporter 2 (VMAT2), transporting cytosolic monoamines into synaptic vesicles (Christiansen et al. 2007; Fukui et al. 2007). Treatment with reserpine, an irreversible VMAT inhibitor, depletes vesicular monoamine stores and precipitates depression in susceptible

individuals (Christiansen et al. 2007; Fukui et al. 2007). A haplotype of VMAT2 has been found to be significantly associated with depressive symptoms in elderly men (Christiansen et al. 2007). VMAT2 heterozygous (HET) KO mice were hypoactive in the open field test and displayed increased immobility in the forced swim and tail suspension tests (Fukui et al. 2007). Treatment with antidepressants reduced the immobility of VMAT2 HET KO mice. The mice also showed less preference for sweetened but not quinine solutions (Fukui et al. 2007). Thus, VMAT2 HET KO mice are another potential genetic model for depression with anhedonic features, and are worthy of further characterization.

Neural cell adhesion molecule (NCAM, also known as the cluster of differentiation (CD56)) is a cell surface homophilic binding glycoprotein involved in cell–cell adhesion. It has been implicated in signaling of growth factor receptors, such as fibroblast growth factor receptor (FGFR) and tyrosine receptor kinase B (TrkB, also known as neurotrophic tyrosine kinase, receptor, type 2 (NTRK2)), long-term potentiation (LTP), long-term depression (LTD), and learning and memory. An early study showed that soluble NCAM was increased in the CSF of depressed patients (Jorgensen 1988), and more recently a genetic study suggested that NCAM polymorphisms confer BPD risk (Arai et al. 2004). Furthermore, behavioral stress and treatment with antidepressants alter NCAM levels in the brain [for a review see Sandi and Bisaz (2007)]. Taken together, these data suggest that NCAM plays a role in mood regulation. There are three main NCAM isoforms resulting from alternative splicing of a single gene. Mice lacking all NCAM isoforms displayed increased immobility in the tail suspension test and reduced sucrose preference (Aonurm-Helm et al. 2008). Treatment with the antidepressants, citalopram and amitriptyline, rescued these phenotypes (Aonurm-Helm et al. 2008), suggesting that NCAM null mice are another potential genetic model for depression with anhedonic features.

3 Partial Models for Mania and Excessive Behavioral Excitement (Table 2)

Manic episodes are characterized by type of mood symptoms (either euphoric or irritable), thought processes (flight of ideas or racing thoughts) and content (inflated self-esteem or grandiosity), attention (distractibility), sleep (less need for sleep), and behavior (more talkative than usual or pressure to keep talking, increase in goal-directed activity or psychomotor agitation, and excessive involvement in pleasurable activities with a high potential for painful consequences) (American Psychiatric Association 1997; Belmaker 2004; Goodwin and Jamison 2007). For behavioral research purposes, attention, sleep, and behavioral impairments can be summarized in a phenotype known as excessive behavioral excitement (Engel et al. 2009; Shaltiel et al. 2008).

Although it seems model-able in rodents, no definitive test for assessing distractibility in a mania-related phenotype has yet been established. Nevertheless,

Table 2 Partial genetic models for mania and excessive behavioral excitement

Clinical features	mCLOCK	GluR6$^{-/-}$	ERK1$^{-/-}$
Elevated, expansive, or irritable mood	Cannot be assessed	Cannot be assessed	Cannot be assessed
Inflated self-esteem or grandiosity	Cannot be assessed	Cannot be assessed	Cannot be assessed
Flight of ideas or racing thoughts	Cannot be assessed	Cannot be assessed	Cannot be assessed
Increase in goal-directed activity	More activity in the OFT Less immobility in the FST More preference for sweet solutions in the SPT More reward sensitivity in the ICSS More preference in the CPP More escapes in the LHP	More activity in the OFT Less immobility in the FST More preference for sweet solutions in the SPT More sniffing in the FUST More activity in the SIAT More aggression in the RIT	More activity in the OFT Less immobility in the FST More wheel running activity More preference in the CPP
Excessive involvement in pleasurable activities that have a high potential for painful consequences	More risk-taking in the EPM More risk-taking in the RAT	More risk-taking in the EPM	More risk-taking in the EPM
Decreased need for sleep	More activity and less rest in home cage	More activity and less rest in home cage	More activity and less rest in home cage
Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)	No data	No data	No data

OFT open field test, *FST* forced swim test, *SPT* Sucrose or saccharin preference test, *ICSS* intracranial self-stimulation, *LHP* Learned helplessness paradigm, *EPM* Elevated plus maze, *RAT* Reward/Aversion Test, *FUST* female urine sniffing test, *SIAT* social interaction test, *RIT* resident-intruder test, *CPP* conditioned place preference test

sleep changes can be monitored through home cage observation, and several tests are suitable for monitoring cross-species phenocopies of "increase in goal-directed activity or psychomotor agitation". These include tests for open field activity, object exploration, social interaction, resident–intruder interaction, sexual activity, female urine sniffing, forced swim, sweetened solution preference, and home cage wheel running. There are also well-documented tests for measuring anxiety-like behaviors, such as center activity in the open field test, the elevated plus maze or zero maze test, the light/dark box, reward/aversion tests, and novelty-induced hypophagia. Recent data suggest that these tests are sensitive enough to measure

anxiolytic-like phenotypes in mutant mice, and that this phenotype can be rescued by treatment with mood stabilizers. Given that mood stabilizers do not produce anxiogenic effects in humans or anxiogenic-like effects in wild-type mice, the effects of mood stabilizers on anxiolytic-like phenotypes in mutant mice suggest that these tests may be useful in assessing risk-taking behaviors. Furthermore, combining the results of this battery of tests helps define the excessive behavioral excitement phenotype in rodents. One suggested definition of this phenotype is that the animal displays most, if not all, of these alterations, is hyperactive in multiple tests, displays increased goal-directed behavior in multiple tests or settings, displays increased risk-taking behaviors in multiple tests or settings, requires less rest or sleep in the home cage, and is distractible. The relevance of the excessive behavioral excitement phenotype to mania can be further validated by examining the response of this phenotype to treatment with mood stabilizers.

One partial genetic partial model for excessive behavioral excitement and mania is mutant CLOCK (mCLOCK) mice. CLOCK is a key component in the molecular circadian machine. Expression of CLOCK and other components of the circadian machine are not restricted to the suprachiasmatic nucleus, suggesting these proteins have broad functions (McClung 2007). These proteins have been implicated in the pathogenesis, pathophysiology, and therapeutic mechanisms of BPD in human genetic and postmortem studies and in animal studies [for a review see McClung (2007)]. mCLOCK mice carry a point mutation that causes protein inactivation (McClung et al. 2005). Research showed that these mice were hyperactive and more responsive to cocaine in both behavioral sensitization and conditioned place preference tests (McClung et al. 2005). Further studies revealed that the mice exhibited increased goal-directed activity, including reduced immobility in the forced swim test, disproportional increase in sucrose solution consumption in the sucrose preference test, and increased number of escapes in the learned helplessness paradigm (Roybal et al. 2007). The mice also displayed risk-taking behaviors, including increased activity in the center of an open field and in the open arms of an elevated plus maze, and reduced latency to approach crackers in a novel cage, even in the presence of bobcat urine. Lithium treatment rescued some of these behaviors, including altered immobility and risk taking in the open field and elevated plus maze tests. The data strongly support that mCLOCK mice may be a valid genetic model for mania and excessive behavioral excitement.

One proposed model for simulating the pathogenesis of mania involves the paradigm of repeated psychostimulant administration, which induces behavioral sensitization (Post 1992). Treatment with lithium partially attenuated the development of cocaine-induced behavioral sensitization (Post et al. 1984). Repeated, but not acute, administration of cocaine attenuated mRNA levels of glutamate receptor 6 (GluR6, also known as glutamate receptor, ionotropic, kainate 2 (GRIK2)) in striatum and cortex (Izawa et al. 2006).

mRNA levels of GluR6 were found to be lower in the postmortem entorhinal cortical tissue of individuals with BPD (Beneyto et al. 2007). The human GRIK2 gene is on 6q16.3–q21, a known "hot spot" for BPD risk genes implicated by linkage studies (Shaltiel et al. 2008). A recent preliminary study suggests that single

nucleotide polymorphisms (SNPs) of GRIK2 confer risk for BPD (Shaltiel et al. 2008). Given these indications of constructive validity, the phenotype of GluR6 KO mice was characterized (Malkesman et al. 2009; Shaltiel et al. 2008). These mice were found to be hyperactive on multiple tests, and displayed increased goal-directed behaviors in the forced swim, saccharine preference, female urine sniffing, resident-intruder, and social interaction tests. They also displayed increased risk taking activity in the elevated plus maze test, and slept/rested less during home cage activity monitoring. Chronic, but not acute, treatment with lithium rescued the hyperactive and risk-taking behaviors, as well as some of the increase in goal-directed behavioral phenotypes. These data illustrate that the GluR6 KO mouse strain is a potential genetic model for mania and excessive behavioral excitement.

Some human genetic data suggest that Disrupted in Schizophrenia 1 (DISC1) (Kato 2007) and RAS guanyl-releasing protein 1 (calcium and DAG-regulated) (RASGRP1) (Ferreira et al. 2008) may both be implicated in risk for BPD. DISC1 (Shinoda et al. 2007) and RASGRP1 are known modulators of the extracellular signaling regulated kinase (ERK) pathway. A postmortem study found that protein levels of the multiple components of the ERK pathway were lower in cortical tissue from victims of mental illnesses including BPD (Yuan et al. 2009). Several studies have shown that chronic treatment with the mood stabilizers, lithium or valproate, activated the ERK pathway, increased the expression of ERK regulated genes including B-cell lymphoma 2 (Bcl-2) and brain-derived neurotrophic factor (BDNF), and promoted the morphological function of ERK pathways, such as neurite growth, neurogenesis, and neuronal survival against a variety of insults (Creson et al. 2009; Einat et al. 2003; Engel et al. 2009; Hao et al. 2004; Hunsberger et al. 2009a; Yuan et al. 2001). ERK1 is one of two ERKs in the pathway. Multiple tests found that ERK1 ablation in mice resulted in hyperactivity (Engel et al. 2009; Mazzucchelli et al. 2002; Selcher et al. 2001), more locomotor activation in the amphetamine challenge test (Engel et al. 2009), increased response to morphine (Mazzucchelli et al. 2002), and cocaine in the place preference test (Ferguson et al. 2006), and enhanced development of cocaine-induced behavioral sensitization (Ferguson et al. 2006). ERK1 null mice also appeared to have increased goal-directed behavior in the active avoidance test (Mazzucchelli et al. 2002), the forced swim test (Engel et al. 2009), and home cage wheeling running (Engel et al. 2009); they also displayed increased risk-taking in the open arms of the elevated plus maze test (Engel et al. 2009) and more rearing in the open field (Engel et al. 2009). This hyperactive phenotype was rescued through treatment with valproate and olanzapine (an atypical antipsychotic with mood-stabilizing effects). Treatment with lithium, valproate, or olanzapine rescued increased response in the amphetamine challenge test (Engel et al. 2009). Together, the data provide reasonably strong evidence to support ERK1 null mice as a genetic model for mania and excessive behavioral excitement.

It is worth emphasizing that excessive behavioral excitement is a unique phenotype resulting from manipulation of certain genes expressed in the brain, though not all of them. For instance, GluR1 KO mice were hyperactive (Wiedholz et al. 2008), but showed reduced duration in the social investigation test (Wiedholz et al. 2008)

and more anxious-like behaviors in the elevated plus maze test (Mead et al. 2006). In addition, other mutant strains also display a few or several features of excessive behavioral excitement, but data regarding whether mood stabilizers rescue these phenotypes have not yet been reported. For example, mice overexpressing GSK-3β, a known direct and indirect target of lithium and valproate, were hyperactive in the open field and forced swim tests; however, it remains unknown whether these mice also display increased risk-taking and drive, and less sleep/rest in the home cage, or whether the phenotype responds to treatment with mood stabilizers (Prickaerts et al. 2006). Interestingly, knocking out the long form of NCAM resulted in a different phenotype from all-forms NCAM null mice (see discussion above). These 180 kDa null mice showed increased aggression in the resident–intruder test, less anxious-like behavior in the elevated plus maze test, and less immobility and more swimming in the forced swim test (Stork et al. 2000). Although the overall phenotype is very suggestive, whether or not the phenotype can be classified as excessive behavioral excitement related to mania cannot be further assessed unless data from treatment and additional behavioral studies become available.

4 Partial Models for Affective Vulnerability or Resilience (Table 3)

BPD is a recurrent illness; patients between mood episodes are considered to be in the euthymic phase. Euthymic BPD patients can respond to emotional, social–psychological, or physiological (such as jetlag and lack of sleep) stress/insults with a full-blown depressive or manic episode (Belmaker 2004; Goodwin and Jamison 2007). For instance, although psychostimulants can cause mood changes in healthy subjects, the same dose can result in full-blown mania in an euthymic BPD patient (Anand et al. 2000). Furthermore, monoamine depletion can cause mild mood disturbance in healthy controls, but a full-blown major depressive episode in euthymic patients with mood disorders (Ruhe et al. 2007). Thus, elucidating the genetic, molecular, and cellular mechanisms underlying these affective endophenotypes for BPD is essential for developing treatments that can prevent, or even cure, BPD.

Several behavioral paradigms using either acute or severe stress approaches (e.g., the learned helplessness paradigm) (Maeng et al. 2008) or chronic but relatively mild stress approaches [for a review see Willner (1995, 1997), Willner and Mitchell (2002)] are associated with anhedonia-like displays along with other behavioral abnormalities. Preliminary data also suggest that monoamine depletion can induce anhedonia-like displays. The amphetamine challenge test and psychostimulant-induced behavioral sensitization paradigms have been used as experimental models for the pathogenesis of mania [for a review see Einat (2006), O'Donnell and Gould (2007)]. Similarly, a paradigm of sleep deprivation-induced cluster of behavioral alterations has been reported for the pathogenesis of

Table 3 Partial genetic models for affective vulnerability or resilience

Clinical features observed in susceptible individuals	GRov	Bcl-2$^{+/-}$	BAG1ov	BAG1$^{+/-}$
Circadian shift causes mood changes	No data	No data	No data	No data
Psychostimulants trigger manic episodes	More sensitive to cocaine in the PIBSP	More sensitive to amphetamine in the PIBSP More locomotion in the AIH	Increased recovery in the AIH	More sensitive to cocaine in the PIBSP
Monoamine depletion causes depressive episodes	No data	No data	No data	No data
Stress triggers depression or mania	More immobility in the FST	No changes in the FST More vulnerability to helplessness in the LHP Less spontaneous recovery from helplessness in the LHP	Increased recovery from helplessness in the LHP	Less spontaneous recovery from helplessness in the LHP

GRov glucocorticoid receptor (GR) overexpressing mice, *BAG1ov* BAG1 overexpressing mice, *PIBSP* Psychostimulant induced behavioral sensitization paradigm, *FST* forced swim test, *AIH* amphetamine-induced hyperlocomotion test, *LHP* Learned helplessness paradigm

mania (Benedetti et al. 2008). Some of these paradigms or tests have been used to study suspected genes for affective vulnerability or resilience using genetically manipulated mice. However, such studies on affective vulnerability and resilience in animals are, overall, still in their early stages and more data are needed to further assess the promising potential models described below.

Dysfunction of the hypothalamic–pituitary axis (HPA) is known to contribute to the etiology of MDD and BPD (Wei et al. 2004). Neuronal glucocorticoid receptor (GR) overexpression (GRov) mice displayed increased anxiety-like behaviors in the elevated plus maze and light–dark box tests, and increased immobility in the forced swim test (Wei et al. 2004). These alterations were rescued through treatment with antidepressants (Wei et al. 2004). In addition, GRov mice displayed aggravated cocaine-induced behavioral sensitization (Wei et al. 2004). Taken together, these data support the GRov mouse strain as a promising potential model for affective vulnerability.

Although it was first discovered as a major antiapoptotic protein expressed throughout the body, Bcl-2 is now also known to play a major role in a variety of brain functions [for a review see Hunsberger et al. (2009a, b)]. Treatments with mood stabilizers and antidepressants upregulate Bcl-2 levels (Chen et al. 1999;

Creson et al. 2009); the upregulation by mood stabilizers is believed to occur via ERK/AKT-CREB-gene transcription mechanisms (Creson et al. 2009). Clinical studies have shown that Bcl-2 SNPs are associated with brain gray matter volume (Salvadore et al. 2009) and response to citalopram treatment (Hunsberger et al. 2009a, b). Lower Bcl-2 levels were also observed in the postmortem brain tissues of individuals with BPD (Kim et al. 2009). Furthermore, Bcl-2 heterozygous mice, which have approximately 50% of the Bcl-2 brain levels of wild-type mice, were more anxious-like (Einat et al. 2005) and exhibited enhanced amphetamine behavioral sensitization (Lien et al. 2008), suggesting that Bcl-2 HET KO mice are a promising potential model for affective vulnerability.

Bcl-2-associated athanogene (BAG1) is a Bcl-2-related protein known to function in ER and mitochondria and to modulate calcium homeostasis and intracellular signaling of steroid receptors including GRs. Chronic treatment with lithium and valproate upregulated hippocampal mRNA and protein levels of BAG1 and modulated BAG1-mediated GR nuclear translocation in primary neuronal cultures (Zhou et al. 2005). GR nuclear translocation is also known to be mediated by FK506 binding protein 5 (FKBP5), a gene implicated by some genetic studies in MDD, BPD, posttraumatic stress disorder (PTSD), and the therapeutic actions of antidepressants (Binder et al. 2008, 2004; Kato 2007; Lekman et al. 2008; Tsai et al. 2007; Willour et al. 2009). Mice with neuronal overexpression of BAG1 appeared normal in the open field and forced swim tests and displayed slight and significant increases in open arm activity in the elevated plus maze test, increased recovery from helplessness in the learned helplessness paradigm, increased recovery in the amphetamine-induced hyperlocomotion test, and attenuated response in the cocaine-induced behavioral sensitization test (Maeng et al. 2008). Conversely, BAG1 heterozygous knockout mice exhibited reduced recovery from helplessness and enhanced cocaine-induced behavioral sensitization (Maeng et al. 2008). Together, these data support that BAG1-overexpressing and BAG1 HET KO mice have features resembling affective resilience and vulnerability, respectively.

5 Cyclicity

Cyclicity – spontaneously alternating between mania and depression – is a unique feature of BPD, although a huge range of swing intervals exist among patients. Simulating this feature in rodents requires long-term activity monitoring with equipment, such as a video recording system or a running wheel. Wheel running activities, for instance, are known to alternate in female rodents along with the estrous cycle. Mitochondrial dysfunctions in BPD have been implicated by human genetic, peripheral tissue, and postmortem brain studies [for a review see Kato et al. (2007)]. Mice with neuronal expression of mutant mitochondrial DNA polymerase (mPOLG) were found to have an accumulation of biological changes resembling those in humans (Kasahara et al. 2006). Specifically, mPOLG transgenic mice displayed changes in activity patterns within the day–night cycle (Kasahara et al. 2006). Female mPOLG

transgenic mice showed marked increases in activities synchronized with the estrous cycle, and these changes were rescued by lithium treatment (Kasahara et al. 2006). One interpretation of these data is that mPLOG expression serves as an amplifier and modifier of long-range (several days) periodic activity; however, the genes and molecular machinery responsible for this cycling of mood and activity cycling have yet to be revealed.

6 Closing Remarks

BPD comprises at least four core features – depression, mania, mood vulnerability, and cyclicity – all of which remain to be fully understood at the molecular, cellular, and neuronal circuitry levels. These clinical features of BPD likely result from genetic polymorphisms, previous (especially early life) and ongoing environmental insults, as well as the interaction between the two. Studies using genetically manipulated animals are pivotal in evaluating the role of the gene being manipulated and its impact on behavioral alterations related to BPD, in elucidating the mechanisms leading to BPD-related behavioral alterations, and in assessing the potential efficacy of novel therapeutics for mania, depression, and mood episode recurrence. For this purpose, several partial genetic models for depression, mania, and affective vulnerability have been described with reasonable constructive validity, reasonable to comprehensive face validity, and strong predictive validity. These models do not simulate BPD as a whole. However, feature-by-feature studies and feature-specific models provide important information about the components of BPD. Obtaining this information is an essential step toward creating a comprehensive understanding of BPD and toward building a multiple-featured animal model of BPD in the near future.

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The Role of the Aminergic Systems in the Pathophysiology of Bipolar Disorder

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Abstract Bipolar disorder (BPD) is a major medical and social burden, but little is known about the specific pathophysiology of BPD. The key biogenic amines in the aminergic system include serotonin (5-HT), norepinephrine (NE), dopamine (DA), and acetylcholine (ACh). By analyzing these neurotransmitters, this chapter highlights three hypotheses in the pathophysiology of BPD: the biogenic amine hypothesis, the cholinergic–aminergic balance hypothesis, and the permissive hypothesis. Evidence from select studies of cerebrospinal fluid, postmortem subjects, neuroimaging, genetic factors, and pharmacological agents will be used to reconcile these hypotheses. Possible explanations for discrepancies in these hypotheses are given, and directions for future studies are suggested.

Keywords Acetylcholine · Biogenic amines · Bipolar disorder · Dopamine · Neurotransmitter · Norepinephrine · Serotonin

1 Introduction

Four major amine neurotransmitters – namely serotonin (5-HT), norepinephrine (NE), dopamine (DA), and acetylcholine (ACh) – have been implicated in bipolar disorder (BPD). By analyzing these neurotransmitters, this chapter highlights three hypotheses in the etiology of BPD: the biogenic amine hypothesis, the cholinergic–aminergic balance hypothesis, and the permissive hypothesis. The other neurotransmitters consistently connected to the pathophysiology of BPD include the GABAergic and glutamatergic systems, which are discussed in the next chapter.

The biogenic amine hypothesis suggests that abnormalities in the physiology and metabolism of biogenic amines, particularly catecholamines (NE and DA) and indoleamine (5-HT), are involved in the pathophysiology of BPD and major depressive disorder (MDD). This hypothesis began with the discovery that monoamine oxidase inhibitors (MAOIs) and certain tricyclic drugs had mood-elevating properties as well as dramatic effects on brain monoamine function. Monoamine neurotransmitters are further implicated in the etiology of BPD by the observation

that antidepressant drugs regulate intrasynaptic concentrations of 5-HT and NE. Furthermore, antihypertensive medications that deplete these monoamines sometimes precipitate depressive episodes, and DA agonists may trigger manic episodes in predisposed individuals (Baldessarini 1975).

The cholinergic–aminergic balance hypothesis proposes that an increased ratio of cholinergic to adrenergic activity may underlie the pathophysiology of depression, whereas the reverse occurs in mania. This association was identified by clinical observation that cholinesterase inhibitors, which inhibit degradation of ACh, may produce symptoms of depression (Janowsky and Overstreet 1995). Studies of the administration of physostigmine, an indirect stimulant of nicotinic and muscarinic receptors, have supported this hypothesis (Janowsky and Risch 1984). Methylphenidate, which increases levels of DA and to a lesser extent NE, intensifies manic symptoms in manic patients. Physostigmine and methylphenidate produce opposite effects in BPD when given alone and antagonistic effects when given simultaneously (Janowsky et al. 1973). The treatment of BPD with lithium, which provokes a cholinergic response and reduces manic symptoms, supports the contention that a balance between the cholinergic–aminergic systems may play a significant role in regulating mood (Goodwin and Jamison 2007).

The permissive hypothesis of BPD postulates that a deficit in central 5-HT neurotransmission is a necessary, but not sufficient, cause for affective disorders. Reduced central serotonergic neurotransmission permits the expression of BPD, but the phase of the illness is determined by catecholaminergic (i.e., NE and DA) neurotransmission. The manic phases are characterized by high levels of catecholaminergic neurotransmission, while the depressive phases are characterized by low levels of NE and DA, as well as reduced 5-HT neurotransmission. According to the permissive hypothesis, a pharmacological agent such as lithium corrects the cause of mania via both 5-HT enhancing abilities and anticatecholaminergic properties (Prange et al. 1974).

1.1 Neurobiological Methods

This chapter uses evidence from select studies of cerebrospinal fluid (CSF), postmortem subjects, neuroimaging, genetic factors, and pharmacological agents. Relatively little is known about brain pathology in BPD compared to other psychiatric disorders, and difficulties in recruiting drug-free manic patients for research studies are a major factor (Shiah and Yatham 2000). Most postmortem studies are complicated by data that include subjects who have committed suicide, had comorbid diagnoses, or lack retrospective diagnosis of BPD (Deep-Soboslay et al. 2008). The collection and analysis of metabolites in CSF is an alternative to sampling brain tissue.

Functional brain imaging studies cited in this chapter include positron emission tomography (PET) and single photon emission computed tomography (SPECT). PET produces a three-dimensional image of the brain, while SPECT creates

two-dimensional slices of the brain. PET provides images of the spatial distribution of a radiolabelled compound in a live subject. A ligand is a molecule with an affinity for a unique biological target, such as 5-HT receptors or transporters. The ability of the ligand to bind to a target is called binding potential (BP) and gives an estimate of target density.

BPD is highly heritable, and genetic factors are estimated to account for 60–85% of the liability for BPD (McGuffin et al. 2003; Smoller and Finn 2003). The prevalence of BPD is associated with number of risk alleles, and a combination of 19 risk alleles will increase the odds ratio of developing BPD 3.8-fold compared to the general population (Baum et al. 2008). Clarifying the precise role of genes in BPD will have treatment implications (Mamdani et al. 2004) and contribute to a better understanding of the pathophysiological mechanisms of BPD.

2 Serotonin

Serotonin was discovered in the brain more than 50 years ago and was almost immediately linked to psychiatric disorders (Woolley and Shaw 1954). A great many drugs currently used to treat psychiatric disorders such as depression, mania, schizophrenia, autism, obsessive–compulsive disorder, and anxiety disorders are thought to act, at least partially, through serotonergic mechanisms. 5-HT was implicated in the pathophysiology of manic-depressive illness as early as 1958 (Strom-Olsen and Weil-Malherbe 1958). Extensive evidence has accumulated on the role of 5-HT in depression, but relatively few studies have examined the role of 5-HT in the pathophysiology of BPD.

2.1 Cerebrospinal Fluid Studies

Studies measuring CSF levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, assume that 5-HIAA levels provide an index of brain 5-HT activity (Carpenter et al. 1998). This is a gross measure of 5-HT neurotransmission in the brain. However, lumbar CSF 5-HIAA concentrations appear to be closely associated with central 5-HIAA (Stanley et al. 1985) and 5-HT turnover (Carpenter et al. 1998). Most studies investigating CSF levels of 5-HIAA in manic patients are about 30 years old and were summarized in a thorough review article by Shiah and Yatham (2000). Studies comparing baseline CSF levels of 5-HIAA in manic patients with nondepressed controls produced inconsistent results. In contrast, studies that compared manic patients with depressed patients found that baseline CSF levels of 5-HIAA were by and large the same (Shiah and Yatham 2000). Four studies measured CSF 5-HIAA before and after blocking the transportation of 5-HIAA out of the CNS using probenecid, as this gives a better measure of central 5-HT activity. Two of these studies found lower levels of CSF 5-HIAA in both

manic and depressed patients when compared to controls. One study reported lower CSF 5-HIAA in mania compared to depressed patients and controls, and one study that did not include a control group found similar levels of CNS 5-HIAA in manic and depressed patients (Shiah and Yatham 2000). Overall, these results suggest that both mania and depression are associated with reduced central 5-HT function, as expected from the permissive hypothesis.

2.2 Postmortem Studies

Measuring 5-HT and 5-HIAA in postmortem brains of BPD patients is another strategy to assess the state of brain neurotransmitter function. To our knowledge, Young et al. (1994) conducted the only study to date that assessed 5-HT, NE, and DA, in addition to their metabolites, in a group with a well-documented history of BPD. The study found that 5-HT levels did not differ in any of the brain regions examined, but they did find higher levels of 5-HIAA in the frontal and parietal cortices in individuals with BPD compared to healthy controls (Young et al. 1994). In addition, they found lower 5-HT turnover (estimated by the 5-HIAA/5-HT ratio) in the temporal cortex, and a higher NE turnover in the temporal, frontal, and occipital cortices in BPD compared to controls (Young et al. 1994). These postmortem findings lend further support to the permissive hypothesis.

2.3 5-HT Receptors and Transporters: PET Imaging Studies

The changes seen in 5-HT neurotransmitter turnover in BPD should be reflected in changes to neurotransmitter receptors and transporters (Dean 2004). Based on pharmacological or molecular properties, about 14 types of 5-HT receptors have been identified, in addition to serotonergic transporters (5-HTT) that regulate neurotransmission through reuptake and removal of released 5-HT in the synaptic cleft. Previous studies have used peripheral platelets as models for brain 5-HT neurons in mood disorders, but the findings are conflicting (Shiah and Yatham 2000), and studies have failed to show correlations between platelets and brain 5-HT_2 receptors (Cho et al. 1999; Yatham et al. 2000).

Recent advances in imaging technology have made it possible to investigate changes in 5-HT receptors and transporters in vivo. A recent study using [^{18}F]-setoperone with affinity for 5-HT_{2A} and 5-HT_{2C} receptors found decreased 5-HT_2 BP in frontal, temporal, parietal, and occipital cortical regions of drug-free acutely manic patients compared to healthy controls (Yatham et al. 2010). The same ligand did not detect effects from treatment with the mood stabilizer valproate in a group of seven patients with acute manic BPD (Yatham et al. 2005). Although 5-HT_2 seems to be involved in the pathophysiology of BPD, it does not appear to be directly involved in the treatment effects of valproate.

Two studies using the 5-HT_{1A} receptor ligand [^{11}C]WAY-100635 reached contradictory conclusions. PET images of 12 unmedicated depressed patients found reduced 5-HT_{1A} BP in the raphe and mesiotemporal cortex relative to healthy controls (Drevets et al. 1999). This reduction was most prominent in the four patients with BPD and the four unipolar depressed who had relatives with BPD (Drevets et al. 1999). Using a larger sample of 32 currently depressed and medication-free BPD participants, Sullivan and colleagues found higher 5-HT_{1A} BP across all regions of interest, including raphe and temporal cortex (Sullivan et al. 2009), relative to healthy controls. Post hoc analysis found that the higher 5-HT_{1A} BP was specific to male patients with BPD compared to male healthy controls. Female patients with BPD did not differ in 5-HT_{1A} BP compared to female healthy controls in any brain region. This sex-effect could be specific to the neurotransmitter 5-HT (Walderhaug et al. 2007) and offer a possible explanation for the discrepancies between the [^{11}C] WAY-100635 studies, as Drevets and colleagues only had five male participants (Drevets et al. 1999).

5-HTT B in 18 currently depressed, unmedicated patients with BPD was investigated using the radioligand ^{11}C-DASB (Cannon et al. 2006). Relative to healthy controls, they found that 5-HTT BP was increased in the thalamus, dorsal cingulated cortex, medial prefrontal cortex, and insula and decreased in the brainstem at the level of the raphe nuclei (Cannon et al. 2006). In a sample that included 18 subjects with MDD, Cannon et al. (2007) found that individuals with BPD and MDD showed increased 5-HTT BP in the thalamus, insula, and striatum relative to healthy controls. Interestingly, they also found that individuals with BPD had reduced 5-HTT BP relative to both healthy controls and patients with MDD in the vicinity of the raphe nuclei (Cannon et al. 2007). This raises the possibility that 5-HTT abnormalities in the brainstem system could be related to the clinical differences between BPD and MDD. In contrast, Oquendo et al. (2007) reported reduced 5-HTT BP in all six brain regions examined (amygdala, midbrain, anterior cingulated cortex, hippocampus, putamen, and thalamus) in a sample of 18 medication-free BPD depressed patients relative to healthy controls, using [^{11}C](+)-McNeil5652, a different radioligand. Our knowledge of 5-HT receptors and transporters in the pathophysiology of BPD seems to change with every PET study published on the subject. Despite the diverging results from the PET studies described above, the findings signify an abnormal 5-HT receptor and transporter system in BPD.

2.4 Conclusion

Evidence from CSF, postmortem, and PET imaging studies supports a role for the 5-HT system in the pathophysiology of BPD and the permissive hypothesis. BPD is associated with reduced 5-HT turnover, and both mania and depression are associated with reduced 5-HT function. The recent advances in imaging technology are exciting, although PET studies might raise more questions than answers over the

next few years. Nevertheless, PET studies of 5-HT receptors and transporters to date point toward abnormalities in the 5-HT system of BPD patients.

3 Norepinephrine

The norepinephrine (NE) system was one of the first neurotransmitter systems examined in the pathophysiology of BPD. Since the 1960s, imbalances in the production and metabolism of NE have been postulated as an explanation for mood swings. A deficiency of NE is assumed to be associated with depression, and an excess of NE is associated with mania (Schildkraut 1965). In the past decades, this assumption has been extensively investigated. Much evidence has been found to support this, but a significant amount of contradictory findings exist (Ressler and Nemeroff 1999). It is now understood that deregulation of the NE system goes beyond a mechanistic model. The importance of how the NE system interacts with other neurotransmitter systems is now recognized by researchers (Wiste et al. 2008).

3.1 Metabolite Studies

Early studies of the role of NE in BPD focused on NE metabolites. One of the principal NE metabolites, 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), was extensively studied in CSF, plasma, and urine. MHPG levels have been found to be lower in depressed and higher in manic states of BPD in these body fluids (Schildkraut 1965; Jimerson et al. 1981; Koslow et al. 1983; Muscettola et al. 1984; Azorin et al. 1990). Similar findings have been reported regarding CSF NE, where elevations have been documented in mania and reductions in depression (Post et al. 1978; Swann et al. 1983). Low CSF MHPG and 5-HIAA may predict the likelihood of a suicide attempt and its lethality (Sher et al. 2006; Galfalvy et al. 2009). These findings are consistent with the primary assumptions of the amine and permissive hypothesis. However, negative findings have also been reported in plasma and urinary MHPG, and some of these inconsistencies may be due to the contribution of peripheral NE metabolites to the measurements (Kopin 1985). Symptom heterogeneity in BPD subjects might be another reason for these inconsistencies. One study found that increased arousal symptoms might explain increased CSF NE metabolite levels in some cases of bipolar depression (Redmond et al. 1986). Reduced urinary MHPG may be present only in BPD-I and not in BPD-II depressed patients (Muscettola et al. 1984; Schatzberg et al. 1989). Overall, these data suggest substantial heterogeneity among patients with BPD, which may account for some inconsistent and contradictory findings to date. Carefully designed studies in this patient population are needed.

3.2 Tyrosine Hydroxylase in Locus Coeruleus NE Neurons

NE neurons are primarily located in the locus coeruleus (LC) and project widely throughout the entire cortex. Tyrosine hydroxylase (TH) is the rate-limiting enzyme in the production of the NE and other catecholamines. Studying TH immunoreactivities (TH-ir) may provide indirect information of NE neuron activity in producing NE transmissions. In the past decades, postmortem studies have shown reduced TH-ir in LC in bipolar depressed suicide victims, which is consistent with similar findings in previous studies of MDD (Wiste et al. 2008). Further investigations revealed relatively higher TH-ir in violent suicide victims of BPD and MDD compared to nonviolent ones (Gos et al. 2008). The available data on TH-ir have indirectly but strongly supported insufficient NE production in neurons of the LC in suicidal depressed BPD patients.

3.3 Genetics

Research efforts have emphasized an association between BPD and specific genes. Among these, an association between catechol-*o*-methyltransferase (COMT) variant and BPD has been repeatedly reported (Rotondo et al. 2002; Zhang et al. 2009), especially in ultra rapid-cycling BPD (Kirov et al. 1998; Papolos et al. 1998). As COMT is one of the several enzymes that degrade NE and other catecholamines, these findings provide genetic evidence for studies of NE and its metabolite levels in their parallel relationship to BPD mood status (Zumarraga et al. 2010). Bipolar depressed patients with the TH gene variant (TH*2/2) may show low depressive scores, but this is a weak association (Perez de Castro et al. 1995; Serretti et al. 1998). The DOPA decarboxylase gene also seems to be weakly associated with BP (Borglum et al. 1999). However, these findings are not always replicated (Kunugi et al. 1997). The NE transporter (NET) genes have never been associated with BPD (Stober et al. 1996; Chang et al. 2007), indicating that not all components in the NE system bear equal weight in its pathology.

3.4 Medication for BPD: Mood Stabilizers

Medications for BPD provide strong evidence supporting the role of NE regulation in the mechanisms involved in the treatment of BPD. Valproate is a widely used mood stabilizer that may increase TH mRNA, an indicator of TH synthesis, via both acute and chronic treatment, though it has no effect on NET or α2A autoreceptor mRNA (Sands et al. 2000). A concentration-dependent threshold effect of valproate in regulating TH mRNA and protein levels in the LC has been reported recently (D'Souza et al. 2009). Lithium, the treatment of choice for BPD, is associated with

significant decreases in CSF MHPG (Wilk et al. 1972; Swann et al. 1987). Quetiapine, a potent inhibitor of the NET with effects on serotonergic and dopaminergic systems, has been successfully used in treating BPD (Ketter et al. 2010; Pae et al. 2010). Similar results were discovered with Ziprasidone, another atypical antipsychotic (Rosa et al. 2008; Bowden et al. 2010). These findings indicate that mood stabilizers might exert antimanic effects by downregulating NE activity in BPD.

3.5 *Medication for BPD: Antidepressants*

Those antidepressants that have demonstrated efficacy in treating bipolar depression appear to do so by adjusting the NE system along with other neurotransmitter systems. Such modifications could be related to their effects in converting depression to hypomania or mania (Koszewska and Rybakowski 2009; Tondo et al. 2009). Increased NE levels may occur by inhibiting monoamine oxidase as seen in MAOIs (Krishnan 2007), or inhibiting NE reuptake transporters as seen in tricyclics and other antidepressants (Thase and Denko 2008). Some studies have reported that chronic use of selective serotonin reuptake inhibitors (SSRIs) may lead to β-adrenergic receptor downregulation and TH/TH mRNA reduction (Baron et al. 1988; Nestler et al. 1990). Moreover, paroxetine has been unequivocally demonstrated, both in vivo and in vitro, to be a relatively potent NE reuptake inhibitor (Owens et al. 1997). The involvement of the NE system in the treatment mechanisms of antidepressants is greater than previously thought.

3.6 *Conclusion*

In summary, the original assumption in the aminergic and permissive hypotheses regarding a dysregulated NE system in the pathology of BPD has generally been supported by preclinical and clinical studies. On the other hand, inconsistent findings have also been noted (Ressler and Nemeroff 1999). These inconsistencies reflect the profoundly complicated nature of the pathology of BPD and call for in-depth investigation in this area. For example, recruiting patient subjects based on clustered symptoms would clarify the variable results in MHPG studies (Redmond et al. 1986). Finally, the NE system is not the only neurotransmitter system involved in the pathology of BPD. Evidence suggests that the deregulation of the NE system might lead to bipolar symptoms in susceptible individuals with a background of concurrent abnormalities of other neurotransmitters. This observation supports the general concept of the permissive hypothesis. Sophisticated study designs and advanced technology will further improve our knowledge of the role the NE system plays in the etiology of BPD.

4 Dopamine

The role of the dopamine (DA) system in the pathophysiology of BPD has received little scientific attention compared to the 5-HT and NE systems, although it represents a very promising substrate for further research. In recent years, there has been increasing agreement that the original serotonergic and noradrenergic hypotheses do not fully explain the neurobiology of BPD or the mechanisms of action of effective treatments. Perhaps one of the most defining characteristics of BPD is motor changes, ranging from near catatonic immobility during depression to profound hyperactivity in manic states (Parker et al. 1993; Goodwin and Jamison 2007). Also, anhedonia or "hyperhedonic" states are central features of bipolar depression and mania, respectively. The midbrain DA systems play critical roles in regulating not only motor activity but also motivational and reward circuits. It is clear that motivational variables can influence motor activity both qualitatively and quantitatively. Furthermore, there is considerable evidence that the mesolimbic DA pathway plays a crucial role in selecting and orchestrating goal-directed behaviors, particularly those elicited by incentive stimuli (Nestler et al. 2002; Goodwin and Jamison 2007).

4.1 Cerebrospinal Fluid Studies

The strongest and most consistent biochemical finding from clinical studies implicating the dopaminergic system in depression is reduced homovanillic acid (HVA), the major DA metabolite in CSF (Manji and Potter 1997; Goodwin and Jamison 2007). There is also evidence for decreased rate of CSF HVA accumulation in subgroups of depressed patients, including those with marked psychomotor retardation versus agitation (Willner and Scheel-Kruger 1991). Furthermore, depression occurs in up to 40% of patients with idiopathic Parkinson's disease, a neurological condition usually resulting from DA deficiency. Depression may precede motor symptoms in Parkinson's disease. Case reports have even documented the disappearance of Parkinson's disease symptoms during a manic episode (Larmande et al. 1993; Scappa et al. 1993).

4.2 Pharmacological Studies

Pharmacological data support the hypothesis that manipulation of the DA system is capable of modulating mood disorders. There is strong pharmacological support for a major involvement of the DA system in the switch process to (hypo)mania (Goodwin and Jamison 2007). DA agonists appear to be effective antidepressants and are capable of precipitating mania in some patients with BPD (Manji and Potter 1997;

Goodwin and Jamison 2007). It has been postulated that DA abnormalities are involved in the hyperactivity associated with the severe stages of mania, whereas NE is associated with hypomania as observed in BPD-II (Manji and Lenox 2000). Furthermore, medications such as pimozide that selectively block DA receptors have profound antimanic efficacy. Mania can also be interrupted by the cholinesterase inhibitor physostigmine, which raises ACh levels within the CNS (Garver and Davis 1979). Using a catecholamine-depleting strategy via the use of the tyrosine hydroxylase inhibitor α-methyl-*p*-tyrosine (AMPT) in lithium-treated euthymic patients with BPD, Anand et al. (1999) suggested a dysregulated signaling system where adaptation to catecholamine depletion results in an over-compensation, or "rebound hypomania," due to impaired homeostatic mechanisms. These findings imply a critical balance between the neurotransmitter systems in BPD, lending support to the permissive and the cholinergic–aminergic balance hypotheses.

4.3 Neuroimaging Studies

Structural neuroimaging data suggest brain abnormalities in patients with BPD in DA-rich regions, including the basal ganglia (Baumann and Bogerts 2001) and areas within the prefrontal cortex [e.g., anterior cingulated, subgenual, orbital, and dorsolateral prefrontal cortices (Drevets et al. 1998; Lopez-Larson et al. 2002)]. Functional imaging, such as PET and SPECT, has confirmed that activation of these areas is abnormal during neurocognitive challenging tasks in patients with BPD (Yurgelun-Todd et al. 2000; Gruber et al. 2004), making these candidate regions to pursue using targeted pharmacological agents. PET studies show reduced D1 receptor BP in frontal cortex, while striatal D2 receptor density seems normal in all phases of nonpsychotic BPD (Gonul et al. 2009), including drug-free BPD (Wong et al. 1985; Pearlson et al. 1995). On the other hand, psychotic patients with BPD show higher D2 receptor densities in the caudate. However, this correlates with the degree of psychosis and not mood symptoms.

4.4 Conclusion

Compared to other neurotransmitter systems, there are fewer studies suggesting primary dopaminergic abnormalities in BPD. It has been suggested that BPD is associated with an abnormality of DA function, but not due to defects in the DA system itself (Goodwin and Jamison 2007; Gonul et al. 2009). Rather, abnormalities in the mechanisms involved in dampening and fine-tuning dopaminergic signals might be essential in the pathophysiology of BPD. Recent data support this contention, suggesting that BPD may be associated with polymorphisms affecting the functioning of the G protein-coupled receptor kinase 3 (GRK-3),

where a mutation in GRK may result in overshooting of multiple neurotransmitter systems, thereby producing excessive excursions from the norm (Goodwin and Jamison 2007). The few functional neuroimaging studies to date have not revealed differences in the amount of DA release and density of DA receptors between nonpsychotic patients with BPD and healthy controls. Still, treatment with mood stabilizers might change DA release, possibly related to enhanced modulation of the prefrontal cortex over subcortical structures. Evidence suggests that enhancing DA activity may be useful, at least in improving cognition in depressed patients with BPD (Burdick et al. 2007). Further research is clearly needed to elucidate the involvement of the DA system in the pathophysiology and treatment of BPD.

5 Acetylcholine

For more than a century, ACh has been postulated to be a factor in the regulation and etiology of affect. As early as 1889, Willoughby reported a case in which pilocarpine, now known to be a muscarinic cholinergic agonist, was used to alleviate acute mania. Most evidence supporting the involvement of the cholinergic system in BPD comes from neurochemical, behavioral, and physiological studies in response to pharmacological manipulations, and most research has focused on muscarinic neuropharmacology (Dilsaver 1986; Overstreet 1993; Furey and Drevets 2006). Abnormal levels of ACh have been reported in the erythrocytes of BPD, prompting researchers to believe that an imbalance between cholinergic and catecholaminergic activity is important in the pathophysiology of BPD. Decreased cholinergic activity has been found in mania and cholinergic hypersensitivity in depression (Janowsky et al. 1972; Dilsaver 1986; Owens et al. 1991).

5.1 Pupilometry and Medications in BPD

The cholinergic–aminergic balance hypothesis postulates that the relative inferiority of noradrenergic compared to cholinergic tone is associated with depression, whereas the reverse is associated with mania (Janowsky and Overstreet 1995). Studying the effects of cholinergic agonist drugs on pupil size in BPD patients has revealed a decreased cholinergic tone during mania. Severe manic patients required higher concentrations of pilocarpine to elicit a 50% reduction in pupil size. Consistently, improvements in mania after lithium or valproate treatments were closely correlated with decreases in pilocarpine requirements to elicit pupillary contraction (Sokolski and DeMet 1999, 2000). Therefore, lithium and valproate treatment may possibly potentiate brain cholinergic neurotransmission (Lenox and Manji 1998; Jope 1999). However, the therapeutic activity of other antidepressant and antimanic drugs does not consistently parallel effects of the cholinergic system.

A number of these agents, including MAOIs and second-generation antidepressants, lack any interaction with cholinergic receptors (Rudorfer et al. 1984).

5.2 Cholinesterase Inhibitors

Further evidence implicating the cholinergic system in BPD comes from the antimanic properties of cholinergic agonists and the modulation of manic symptoms by the cholinesterase inhibitor physostigmine (Manji and Lenox 2000; Muller-Oerlinghausen et al. 2002). Pilot trials with cholinesterase inhibitors and muscarinic agonists suggest that stimulating the muscarinic receptors may produce an antimanic effect, possibly by activating muscarinic M4 receptors (Bymaster and Felder 2002). Studies administering physostigmine intravenously showed modulation of manic symptoms toward depression (Davis et al. 1978; Khouzam and Kissmeyer 1996). Physostigmine administration has also been shown to precipitate depression in euthymic BPD patients maintained on lithium (Oppenheim et al. 1979) and in healthy controls (Janowsky and Risch 1984). Also, the direct muscarinic agonist arecoline produces depressive symptoms in euthymic BPD patients off lithium and in healthy controls (Nurnberger et al. 1983, 1989). Furthermore, depressive symptoms are often a complication of acetylcholinesterase inhibitor treatment in Alzheimer's disease.

5.3 Conclusion

Overall, data seem to be consistent with Janowsky's original proposal that cholinergic–adrenergic balance may play a role in modulating affective behavior. However, the role of ACh and how it relates to BPD and other mood disorders remain a relatively underexplored area. In particular, few studies have addressed the role of nicotinic ACh in affective disorders. Studies at the cellular, physiological, and behavioral levels have shown that a wide range of antidepressants, including tricyclics, SSRIs, and atypical antidepressants, all act as noncompetitive antagonists of nicotinic ACh receptors at clinically relevant doses (Hennings et al. 1997; Slemmer et al. 2000; Lopez-Valdes and Garcia-Colunga 2001; Shytle et al. 2002). Thus, nicotinic antagonism may be another important component for antidepressant efficacy. However, the therapeutic responses observed with antidepressant and antimanic pharmacological agents have not been reliably associated with effects on the cholinergic system. Advances in molecular genetics and brain imaging could potentially help clarify the role of ACh in BPD. Furthermore, studying the effects of antidepressant and mood-stabilizing medications on the central cholinergic nervous system could give additional support for the involvement of ACh in the etiology and expression of BPD.

6 Conclusion

Three hypotheses that attempt to explain BPD have evolved in the past 50 years: the biogenic amine hypothesis, the cholinergic–aminergic balance hypothesis, and the permissive hypothesis. Biochemical and pharmacological studies have implicated biogenic amine systems, as well as neuropeptides, neuroendocrine systems, glial cells, and GABAergic and glutamatergic systems, as discussed in the other chapters.

The biogenic amine hypothesis is attractive because of its simplicity and inferences for therapy, but a number of questions remain unanswered. Most evidence supporting this hypothesis is indirect; estimates of neurotransmitters can be inferred by measuring metabolites in CSF. Measurements of 5-HT and 5-HIAA in CSF and postmortem brains show lower levels in manic and depressed patients compared to healthy controls; yet studies comparing manic and nondepressed patients have inconsistent results. MHPG was found to be decreased in depressed and increased in manic states of BPD. PET studies of BPD patients revealed abnormal 5-HT receptor and transporter systems in various brain regions. Antidepressants produce a number of effects other than increasing 5-HT and NE that have not been accounted for. The mechanisms of converting depression to hypomanic or manic episodes are not entirely clear. Furthermore, there are few tests available to verify a biochemical deficiency, and, if present, it may be an effect from, as well as a cause of, BPD (Shiah and Yatham 2000). These criticisms may also apply to the cholinergic–aminergic balance hypothesis and the permissive hypothesis.

There is evidence to support the cholinergic–aminergic balance hypothesis, but problems with the theory arise when pharmaceutical agents other than lithium are used to manipulate the cholinergic system. MAOIs, for example, lack interaction with cholinergic receptors. Anticholinergic drugs have mixed reports of efficacy in treating depression. Sensitivity to mood-lowering effects of cholinergic drugs appears to depend on the presence of underlying psychiatric disorders, as seen in the administration of physostigmine to precipitate depression in euthymic BPD patients. Overall, pathophysiological significance of ACh in relation to BPD requires further investigation (Goodwin and Jamison 2007).

The permissive hypothesis of BPD postulates that depression is characterized by low 5-HT, NE, and DA function, whereas mania is characterized by low 5-HT and high NE and DA function. The permissive hypothesis cannot be rejected based on a collective impression from the studies discussed in this chapter. Although the permissive hypothesis is unlikely to be true in an absolute sense, it introduces an important concept of interactions between the neurotransmitters in the pathophysiology of BPD. Future studies should also be aware of a possible sex difference in the way 5-HT deficiency is expressed in men and women. A new model of the pathophysiology of BPD could emerge from the foundation of these hypotheses and may integrate the role of all known mood regulators. It is plausible that naturally or pharmacologically induced changes in one neurotransmitter can cause relevant perturbations in downstream neurochemical modulators and neurotransmitters or

in second messengers, since all these neurotransmitters appear to exert important regulatory influence on the expression of BPD. Evaluation of these complex interactions will likely yield promising results with respect to understanding the pathophysiology of BPD and can facilitate preventive and therapeutic measures.

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The Neurobiology of Bipolar Disorder: From Circuits to Cells to Molecular Regulation

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Contents

Abstract Over the past 15 years, postmortem studies of the corticolimbic system in subjects with bipolar disorder (BPD) have demonstrated a variety of abnormalities affecting the gamma aminobutyric acid (GABA)ergic system. Although some of the changes are similar to those seen in individuals with schizophrenia, there are pronounced differences in the regulation of complex networks of genes involved in the expression of GAD_{67}, a key marker for functionally differentiated GABAergic interneurons. Overall, these changes vary not only according to diagnosis, but also subregion and layer, suggesting that the activity of GABA cells in complex neural circuits are differentially affected by the unique extrinsic and intrinsic inputs that they receive at different points along a circuit like the trisynaptic pathway. Our ability to understand the functional implications in terms of complex molecular changes will ultimately influence our ability to develop novel treatments for BPD.

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1 Introduction

In recent years, postmortem studies of bipolar disorder (BPD) have defined abnormalities in corticolimbic circuitry (for a review, see Benes 2009) and have further demonstrated that there are abnormalities at both the cellular and molecular levels that probably influence the ability of this circuitry to function normally. The use of laser microdissection (LMD) to "deconstruct" complex circuits, such as the trisynaptic pathway in the hippocampal formation, has uncovered robust changes in the expression of genes associated with gamma aminobutyric acid (GABA)ergic inhibition, as well as other functional categories of genes such as the regulation of cell cycle and DNA repair, which may help to control their functional differentiation in BPD. As discussed below, changes in the expression of genes in the hippocampus of subjects with BPD appear to be circuitry-based, site-specific, and diagnosis-dependent.

2 The Corticolimbic GABA System in Psychosis

There is now compelling evidence that a GABA defect occurs in corticolimbic regions of patients with psychotic disorders (for a review, see Benes 2009). Decreased expression of transcripts for the 67 kDa isoform of glutamate decarboxylase, or GAD_{67}, has become one of the most replicated postmortem findings in schizophrenia research (Benes et al. 2007; Guidotti et al. 2000; Hashimoto et al. 2003; Veldic et al. 2005; Volk et al. 2000) and BPD (Benes et al. 2007; Guidotti et al. 2000; Veldic et al. 2005). Notably, changes have been preferentially found in the superficial layers of the dorsolateral prefrontal and the anterior cingulate cortices (for a review, see Benes 2010). In the latter region, changes in GAD_{67}

Table 1 Subregional changes in hippocampus of bipolar subjects

	AD	CA4	CA3/2	CA1
Nonpyramidal neurons[a]			↓↓	
TH-IR varicosities[b]			↓↓	
$GluR_{5,6,7}$-IR[c]			↓	↓
Dopamine D1 mRNA[d]			↓	
$GAD^{67/65}$ mRNA[e]			↓↓↓↓	

[a]Benes et al. (1998)
[b]Benes and Todtenkopf (1999)
[c]Benes et al. (2001)
[d]Pantazopoulos et al. (2004)
[e]Benes et al. (2007)

expression have been selectively found in layer II (Woo et al. 2004, 2007). In the hippocampus, however, there is a subregional preference for decreased expression of GAD_{67} in sectors CA2/3. As shown in Table 1, other markers for the GABA, glutamate, and dopamine systems have also been observed in CA3/2 of subjects with BPD (Benes, 2010).

3 Hippocampal Circuitry and Modulation by GABA Cells

The finding of preferential abnormalities in sectors CA3/2 of the hippocampus has provided an important clue as to the larger circuitry that may be involved in the pathophysiology of psychotic disorders. Sectors CA3 and 2 are integral sites within the trisynaptic pathway, a complex network of extrinsic and intrinsic fiber systems that terminate at various points along this circuit as it courses toward sector CA1 (Benes et al. 2008). The trisynaptic pathway includes a specific fiber projection that runs from the granule cell layer in the area dentate and terminates on the dendrites of pyramidal neurons within the stratum radiatum of sectors CA3/2. These latter neurons, in turn, send Schaffer collaterals to the stratum radiatum of sector CA1 where they terminate on the dendrites of pyramidal neurons. These neurons send projections to the subiculum, entorhinal cortex, and dorsolateral prefrontal area (for a review, see Rosene and Van Hoesen 1987).

GABA cells are found throughout the trisynaptic pathway, particularly the stratum oriens and stratum radiatum; GABA cells are the exclusive neuronal cell type in these laminae (Benes and Berretta 2001). As shown in Table 2, the expression of mRNA for GAD_{67} is most robustly reduced in sector CA3/2, particularly in the stratum oriens of subjects with BPD where the decrease was approximately tenfold when analyzed with microarrays, but as high as 25-fold when quantitative real-time polymerase chain reactions (qRT-PCR) were used (Benes et al. 2007). It seems likely that the regulation of GAD_{67} expression may influence the function of the GABA cell phenotype, as this protein is a critical marker for inhibitory interneurons. Virtually all interneurons that express GAD_{67} mRNA co-express the 65 kDa isoform (Stone et al. 1999), indicating that changes in GAD expression may also be present in several or perhaps even in all interneuron subtypes.

Table 2 Microarray study of GAD_{67} in hippocampus of BPDs

		CA 2/3		CA 1	
		Fold change	*P*-value	Fold change	*P*-value
Stratum radiatum	BPD vs CON	NC	NC	NC	NC
Stratum pyramidale	BPD vs CON	–2.74	0.048	NC	NC
Stratum oriens	BPD vs CON	–9.59	0.000048	NC	NC

The data shown represent the fold changes and *P*-values for messenger RNA (mRNA) for GAD67 in laser microdissected layers stratum radiatum, stratum pyramidale, and stratum oriens from sectors CA3/2 and CA1 of the hippocampus in subjects with bipolar disorder (BPD) when compared to normal controls (CON)

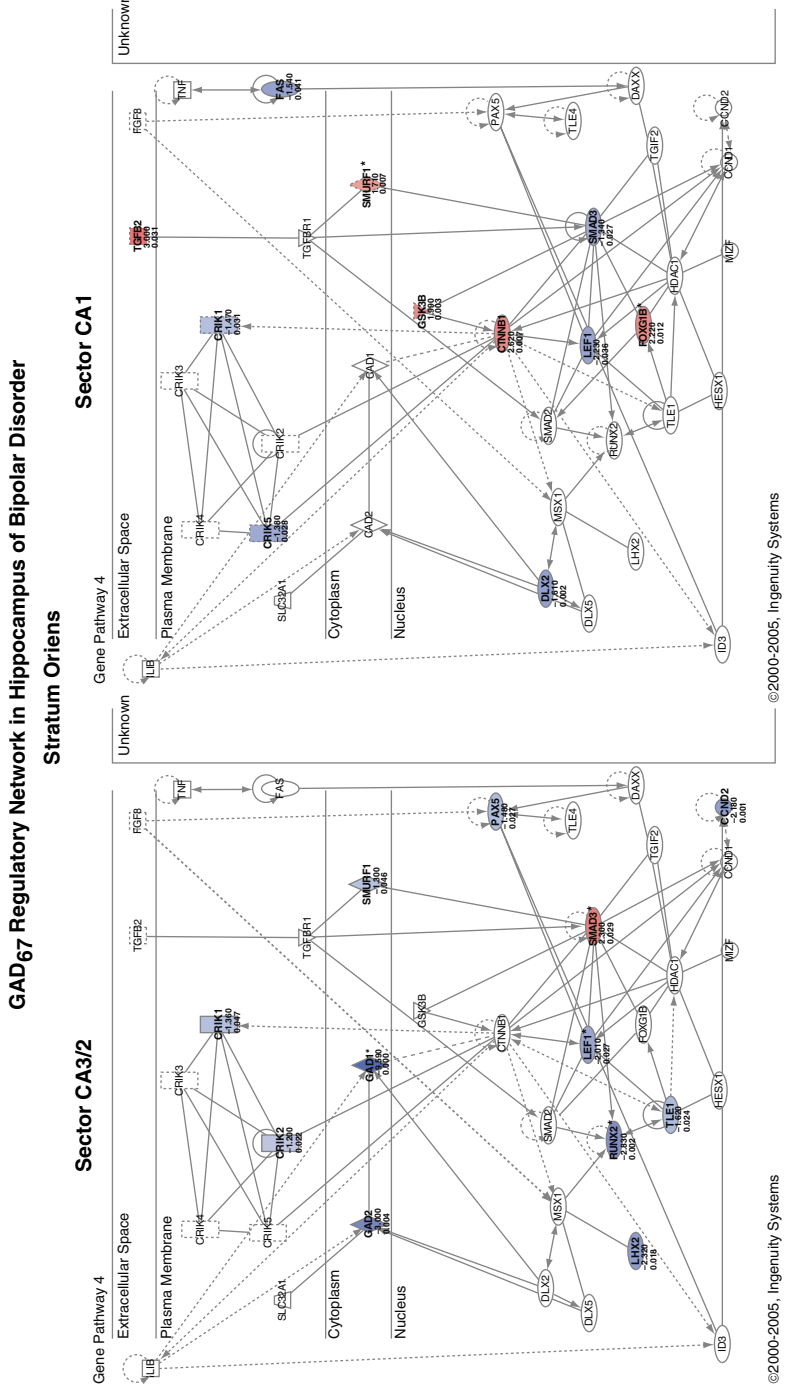
4 Regulation of GAD_{67} Expression

To learn more about the expression patterns of GAD_{67}, a combination of LMD and microarray-based gene expression profiling was used to identify whether there are functional clusters of genes that show significant changes in expression in parallel with GAD_{67}. These functional clusters included genes associated with synaptic transmission, voltage-gated channels, calcium metabolism, intermediary metabolism, protein synthesis and degradation, transcription, translation, cell cycle regulation, and DNA repair. These functional gene clusters were analyzed in specific loci along the trisynaptic pathway defined by their locations within different layers and sectors of the hippocampus. Sectors CA3/2 and CA1 were "deconstructed" into the component layers: stratum radiatum, stratum pyramidale, and stratum oriens. Neurons in the stratum radiatum and stratum oriens are almost exclusively GABAergic in nature, and this segregation of interneurons was exploited so that genes related to the regulation of GAD_{67} could be separately examined. A network association analysis was used to establish relationships of GAD_{67} with other potential genes in the functional gene clusters.

This strategy revealed that there is a unique network of 25–30 different genes that are associated with the regulation of GAD_{67} expression in the human hippocampus (Fig. 1). The pattern of gene expression changes noted within this network in individuals with BPD varies on the basis of hippocampal layer and sector (Fig. 1). For example, the pattern of expression changes in these genes is fundamentally different in the stratum oriens of CA3/2 compared to the stratum oriens of CA1 in subjects with BPD. The most pronounced decreases of GAD_{67} expression, as well as other genes within this network, occurred preferentially in the stratum oriens of CA3/2 in individuals with BPD. As discussed above, this is consistent with other work using a variety of markers and methodological approaches showing a preponderance of postmortem abnormalities at this same locus in both individuals with BPD and schizophrenia (Benes 2010; Benes and Berretta 2001).

5 The Role of Glutamate Receptors and Channels in GAD_{67} Regulation

CABA cell dysfunction inferred from our gene expression profiling studies in seems to involve glutamatergic receptors, possibly the ones modulated by afferents from the Basolateral amygdala (BLa) (Acsady et al. 1998). For example, the glutamate receptor subunits 1–5 of the kainate receptor (GRIK1-5) play a critical role in early development by influencing the differentiation of GABA cells and their functional integrity within the trisynaptic pathway (Maingret et al. 2005). In individuals with BPD (Benes et al. 2008), a downregulation of kainate receptor subunits has been observed in the stratum oriens of CA3/2 and could be part of a larger mechanism involved in regulating neuronal excitability along GABA cell


GAD67 Regulatory Network in Hippocampus of Bipolar Disorder
Stratum Oriens
Sector CA3/2
Sector CA1
Gene Pathway 4
Extracellular Space
Plasma Membrane
Cytoplasm
Nucleus
Unknown
TNF
FAS
TGFB2
TGFBR1
FGFB
CRIK1
CRIK2
CRIK3
CRIK4
CRIK5
SLC29A1
GAD1
GAD2
SMURF1
GSK3B
CTNNB1
LEF1
SMAD2
SMAD3
RUNX2
MSX1
LHX2
DLX2
DLX5
TLE1
TLE4
FOXG1B
HDAC1
TGIF2
DAXX
PAX5
MZF
HESX1
CCND1
CCND2
ID3
TLR
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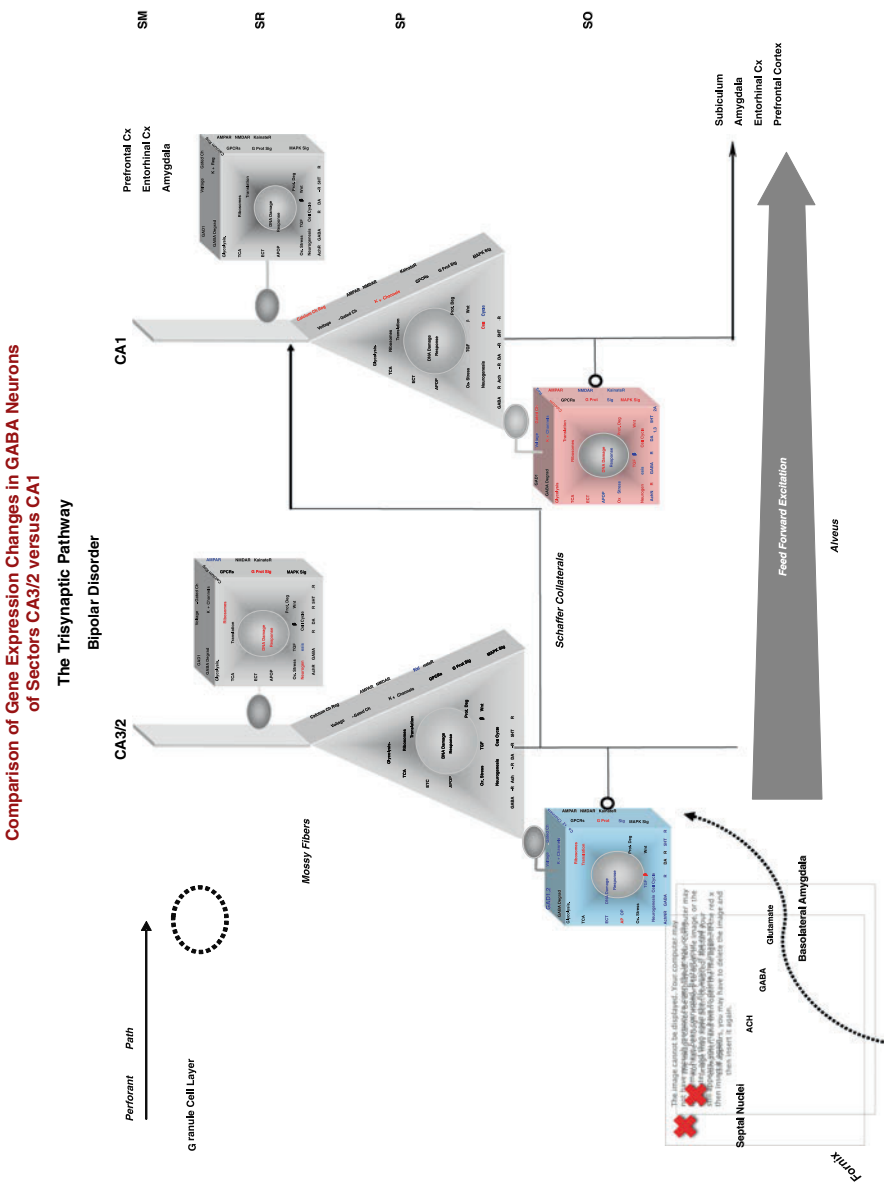
dendrites (Schaefer et al. 2007). Such an effect could involve changes in the regulation of (Ih) channels, as individuals with BPD showed a significant downregulation of the gene (HCN4) at the SO-CA3/2 locus. Ih is a hyperpolarization-dependent nonspecific cationic channel (Robinson and Siegelbaum 2003); it is associated with attenuation of after-hyperpolarizing currents (Chen et al. 2001; Lauri et al. 2005) and the activation of GABA cells (Gisabell et al. 2009). The downregulation of the GRIKI-5 and HCN4 gene in BPD is consistent with abnormal in GABA cell activation may occur in this disorder (Benes et al. 2008).

Kainate receptors are also critical for generating gamma oscillations (Fisahn et al. 2004). A significant decrease in the expression of mRNA for the GRIK1 and GRIK2 receptor subunits (i.e., GluR5 and 6, respectively) has been observed in the stratum oriens CA3/2 locus of subjects with BPD. Interestingly, Ih channels also show decreased expression at this same site in individuals with BPD. This channel is thought to be involved in pacemaker activity (Robinson and Siegelbaum 2003) and has the potential to reset the phase currents that comprise oscillatory rhythms (Yang et al. 2007). Together with kainate receptors, Ih channels expressed by "horizontal," fast-spiking interneurons located in the region of the oriens–alveus (Maccaferri and Lacaille 2003) may contribute to the generation of gamma (Traub et al. 2003) and theta (Cobb et al. 2003; Dugladze et al. 2007) oscillations. Both kainate receptors and Ih channels can influence the long-range synchronization (Traub et al. 2004) of GABA currents in pyramidal neurons (Palva et al. 2000). Oscillatory rhythms are thought to be important in establishing the cognitive relevance of hippocampal output (Whittington et al. 2001).

In BPD, GABA cells within the stratum oriens of CA3/2 might be particularly impaired in their ability to provide inhibitory modulation because this is the exclusive neuronal cell type in the SO, where the kainate receptor subunits and Ih channels show significantly decreased expression. Such changes could promote diminished firing of GABA cells (Lauri et al. 2005; Lupica et al. 2001). In the CA1 of subjects with BPD, the expression of kainate receptor subunits is also decreased; however, dramatic increases in the expression of genes associated with a broad range of metabolic signaling and transcriptional and translational clusters are also present. Together with normal expression of GAD_{67} in individuals with BPD, the GABA cells found at this locus may be hyperactive and capable of exerting higher than normal levels of inhibitory modulation on the pyramidal neurons in the stratum oriens of CA1.

Figure 2 postulates that the overall flow of excitatory activity between CA3/2 and CA1 may be increased in BPD. In the CA1 of subjects with BPD, however, GAD_{67}

Fig. 1 The regulatory network for GAD_{67} mRNA expression in the stratum oriens (SO) of sectors CA3/2 (*left*) and CA1 (*right*) of subjects with BPD. The genes showing either increases (*red*) or decreases (*blue*) in expression are quite different within the two sectors of the patient group. GAD1 and 2 genes are significantly decreased in the stratum oriens of CA3/2, but not in CA1. In CA3/2, most of the GAD_{67} network genes showed a significant decrease in expression, suggesting that the functional differentiation of GABAergic interneurons may be diminished. In CA1, however, genes that are involved in promoting growth and differentiation (i.e., TGFβ2, SMURF1, CTNNB1, and GSK3β) were all upregulated, suggesting that functional differentiation of inhibitory interneurons at this locus may be well maintained [adapted from Benes et al. (2008)]


Comparison of Gene Expression Changes in GABA Neurons
of Sectors CA3/2 versus CA1
The Trisynaptic Pathway
Bipolar Disorder
CA3/2
CA1
SM
SR
SP
SO
Prefrontal Cx
Entorhinal Cx
Amygdala
Subiculum
Amygdala
Entorhinal Cx
Prefrontal Cortex
Schaffer Collaterals
Mossy Fibers
Feed Forward Excitation
Alveus
Perforant Path
G ranule Cell Layer
Septal Nuclei
ACH
GABA
Glutamate
Basolateral Amygdala
Fornix

expression is normal and genes associated with intermediary metabolism show prominent increases in activity. Taken together, these changes are consistent with a model in which the inhibitory modulation of pyramidal neurons firing in the CA1 may be decreased as a result of hyperactive interneurons in the stratum oriens of this sector. The critical question is whether these changes can compensate for those seen in SO of CA 3/2.

6 Medication Effects in Bipolar Disorder

Psychotropic effects have the potential to increase intersubject variability of gene expression profiling for individuals with schizophrenia and/or BPD. Prominent qualitative differences have been between these two groups, but it is difficult to specifically relate them to one or another class of medications to which they were exposed. For example, neither antipsychotic medications nor mood stabilizers appear to influence GAD_{67} expression. An earlier study found that GAD_{65}-containing terminals showed antipsychotic medication dose-related increases, suggesting that these medications may contribute to compensatory sprouting of GABAergic terminals, particularly in the stratum oriens of CA3/2 (Benes and Todtenkopf 1998). In the medial prefrontal cortex, rats that received chronic haloperidol treatment showed marked increases in the number of GABA-containing terminals forming axosomatic contacts with pyramidal neurons (Vincent et al. 1994). In addition, mRNA for GAD_{65} showed no significant changes in individuals with either BPD or schizophrenia, suggesting that exposure to antipsychotic medications might have increased its expression to normal levels. In the study by Benes et al. (2008), most of the individuals with schizophrenia or BPD included in the study were treated with both antipsychotic medications and mood stabilizers. The fact that gene expression profiles in the two groups were fundamentally different despite

Fig. 2 A network association analysis revealed that several genes involved in the regulation of GAD_{67} expression in GABA cells located at key loci within the trisynaptic pathway were strikingly different in subjects with BPD. In sector CA3/2, the overall expression pattern was consistent with dysfunction of GABA cells in the stratum oriens and insufficient amounts of inhibitory modulation to the Schaffer collaterals of pyramidal neurons. This change could be associated with an increased flow of excitatory activity toward the apical dendrites of pyramidal neurons in the stratum radiatum of CA1. Gene expression profiling in the stratum oriens of CA1 of individuals with BPD demonstrated that there was no decrease in the expression of GAD_{67}. At the same time, the overall regulation of intermediary metabolism, TGFβ and Wnt signaling, transcription and translation, as well as the regulation of cell cycle and DNA repair, all tended to be significantly increased at this locus in individuals with BPD. Taken together, these findings suggest that GABA cells at this key locus of the trisynaptic pathway may be capable of providing sufficient, or perhaps even enhanced, amounts of inhibitory modulation to pyramidal neurons of this sector. It is possible that an increase in feed forward excitation along the Schaffer collaterals may increase the excitation of GABA cells in the stratum oriens of CA1 via the recurrent collaterals of pyramidal neurons

overlapping treatments suggests that most of these changes were not related to psychotropic treatment alone. It is possible that these drugs interact in disease-specific ways with functional clusters of genes, like those showing changes in the schizophrenic and BPD subjects.

Finally, since may patients with psychotic disorders smoke cigarettes, decreased expression of various nicotinic receptor subunits could have potentially contributed to the induction of changes in GABA cell regulation in subjects with schizophrenia (Adler et al. 1998) and BPD (McEvoy and Allen 2002). Because individuals with BPD do not smoke as heavily as those with schizophrenia (clinical observation), they might be expected to show less striking changes in nicotinic receptor expression; however, this group showed more subunits with decreased expression than individuals with schizophrenia, suggesting that nicotine ingestion alone cannot account for the receptor expression changes noted here. Could this receptor system play a role in GABA cell dysfunction in BPD?

7 Conclusions

In summary, a cross-sectional analysis of gene expression profiling at key sites along the trisynaptic pathway that almost exclusively contain GABAergic interneurons may account for at least some of the abnormalities in this transmitter system that have been detected in BPD. Overall, the results suggest that genes in hippocampal GABA cells show significant changes in expression that vary not only according to psychiatric diagnosis but also according to location along the trisynaptic pathway. As shown in Fig. 2, the patterns of connectivity are particularly different for GABA cells in the stratum oriens of sector CA3/2 and CA1 (Benes et al. 2007). The explanation for these differences is likely to be found in the nature of the extrinsic and intrinsic connections that exist within each locus. For example, in the stratum oriens of CA3/2, inputs from the BLa and septal nuclei, which show uniquely important terminations at this site, may help to establish gene expression changes that are also unique to this locus (for a review, see Benes et al. 2008). The extrinsic and intrinsic afferent fiber systems that modulate the activity of GABA cells within the trisynaptic pathway probably contribute significantly to the maintenance of function in these interneurons (Zhu et al. 1999).

These results further suggest that cellular endophenotypes for BPD may be determined by multiple factors that include not only unique susceptibility genes but also the specific ways in which these genes affect the integration of hippocampal GABA neurons with extrinsic and intrinsic afferent fiber systems of the trisynaptic pathway. The expression of genes associated with GAD_{67} regulation is fundamentally different in individuals with BPD than in those with schizophrenia. This suggests that the dynamics of feed forward excitation along the trisynaptic pathway are probably quite different in the two disorders. In BPD subjects where GABA cell dysfunction is largely restricted to the stratum oriens of CA3/2, GABA cells in other loci like the stratum oriens of CA1 may be able to respond more

effectively to excitatory activity transmitted to this sector from CA3/2. A key question that must be asked is how such an arrangement might influence the properties of rhythmic activity generated within the hippocampus of BPD subjects. The extensive and intricate data obtained from a study that combines LMD, microarray-based gene expression profiling, and network association algorithms can provide novel insights into how a complex circuit like the trisynaptic pathway may be regulated in BPD.

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Signal Transduction Pathways in the Pathophysiology of Bipolar Disorder

Jeremy W. Gawryluk and L. Trevor Young

Contents

Abstract Signal transduction pathways and genes associated with cellular life and death have received much attention in bipolar disorder (BPD) and provide scientists with molecular targets for understanding the biological basis of BPD. In this chapter, we describe the signal transduction pathways involved in the molecular biology of BPD and the indications for the mechanisms of disease and treatment. We discuss the BPD literature with respect to the disease itself and the effects of mood stabilizer treatment on cellular receptors, including G-protein-coupled receptors, glutamate receptors, and tyrosine receptor kinase. We also discuss the

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intracellular alterations observed in BPD to second messenger systems, such as cyclic adenosine monophosphate (cAMP), protein kinase A, phosphoinositide pathways, glycogen synthase kinase-3, protein kinase B, Wnt, and arachidonic acid. We describe how receptor activation and modulation of second messengers occurs, and how transcription factors are activated and altered in this disease (e.g., the transcription factors β-catenin, cAMP response element binding protein, heat shock transcription factor-1, and activator protein-1). Abnormalities in intracellular signal transduction pathways could generate a functional discrepancy in numerous neurotransmitter systems, which may explain the varied clinical symptoms observed in BPD. The influence of mood stabilizers on transcription factors may be important in connecting the regulation of gene expression to neuroplasticity and cellular resilience.

1 Introduction

Bipolar disorder (BPD) is a commonly occurring psychiatric illness characterized by recurrent episodes of mania, hypomania, mixed states, and depression that affect approximately 1–3% of the population worldwide (Belmaker 2004; Kupfer 2005; Merikangas et al. 2007). Historically, signal transduction pathways and their associated genes that encode proteins important for cellular life and death have received much attention in BPD (Martinowich et al. 2009). These intracellular pathways are responsible for the coordination of a cellular response resulting from extracellular information (Ross 1989). Hence, abnormalities in these pathways may produce a functional discrepancy in several neurotransmitter systems, which may explain the varied clinical symptoms observed in BPD, such as recurrent course, mood fluctuations, psychotic features, neurovegetative symptoms, and cognitive impairment (Bauer et al. 2003). Higher order brain functions, such as behavior, cognition, and mood, are perilously reliant on the proper functioning of signal transduction processes (Ross 1989). In addition, the onset of mood stabilizers' pharmacological and clinical effects is slow, and this suggests that their therapeutic mechanism of action requires changes to cellular and molecular processes. Signal transduction pathways offer scientists a host of potentially important molecular targets for understanding in the biological basis of BPD. In this chapter, we describe the signal transduction pathways involved in the molecular biology of BPD and the indications for the mechanisms of disease and treatment.

2 Signal Transduction Pathway Abnormalities in BPD

Some studies have examined signal transduction pathways and gene expression regulation in BPD (Bauer et al. 2003; Manji and Lenox 2000). Many neurotransmitter receptors are coupled to guanine-nucleotide binding proteins (G-proteins) that generate second messengers or, alternatively, are linked to ion channels.

The extracellular signals are integrated, amplified, and transmitted to specific intracellular enzymes, i.e., effectors, that catalyze a broad array of second messengers that act on protein kinases (Ross 1989). This specific kinase activation regulates diverse intracellular processes, including gene expression, and links transient signals to neurobiological changes (Ross 1989).

Clinical investigations have suggested signal transduction system abnormalities in BPD. In vivo and in vitro studies have demonstrated the pharmacological efficacy of mood stabilizers, especially lithium, and suggest that these may play a neuroprotective role that may include reduced excitotoxicity via augmented glutamate uptake, and regulation of a number of second messenger systems, such as adenylate cyclase [cyclic adenosine monophosphate (cAMP)], phosphoinositide [protein kinase C (PKC)], and glycogen synthase kinase-3 (GSK-3) (Schloesser et al. 2008).

3 Receptor Types

3.1 G-Protein-Coupled Receptors

G-proteins have received much attention in BPD. Animal studies have shown that lithium attenuates the function of several G-proteins such as the stimulatory subtype (Gαs) (for a review see Beaulieu et al. 2009). Gαs levels (but not Gαi, Gαo, or Gβ) are increased in frontal, temporal, and occipital cortices from BPD patients (Friedman and Wang 1996; Young et al. 1991; Young et al. 1993). Furthermore, Young et al. (1993) demonstrated that adenylate cyclase (AC) activity and Gαs levels are elevated by lithium, suggesting functional importance. In contrast, Dowlatshahi et al. (2000) observed diminished occipital cortex Gαs levels in lithium-treated BPD patients (Table 1). Friedman and Wang (1996) used a specific binding assay for G-proteins – [[35]S]GTPγS – and showed that brains from individuals with BPD had enhanced serotonin receptor to G-protein coupling.

Studies have not connected BPD with alterations to the gene encoding for Gαs (Fan et al. 2009; Ferreira et al. 2008; Sklar et al. 2008), and likewise the gene-expression levels for Gαs are not changed in the postmortem BPD brain (Young et al. 1996). However, some evidence suggests abnormal interactions between neurotransmitter receptors and G-protein signal transduction pathways (Dean et al. 2009). For example, G-protein-coupled serotonergic (reviewed by Catapano and Manji 2006) and dopaminergic receptors (Pearlson et al. 1995; Wong et al. 1997) are overactive in BPD patients. Studies have identified polymorphisms in serotonergic 5HT2A receptors, with C516T, C135T, and A1438G having been noted as the most common (Chee et al. 2001; McInnis et al. 2003; Ranade et al. 2003). Interestingly, abnormalities in 5HT1A receptor binding in BPD patients are reversed by chronic lithium administration (Goodwin et al. 2008).

Table 1 G-protein signaling in bipolar disorder

Tissue	Δ	Result
Brain		
Cortex	+	Gαs (Young et al. 1991; Young et al. 1993)
	=	Gαi, Gαq, Gβ (Young et al. 1991; Young et al. 1993)
	=	Gαs mRNA levels (Young et al. 1996)
	+	Coupling of serotonin receptors to G-proteins (Friedman and Wang 1996)
	−	Gαs in lithium-treated subjects (Dowlatshahi et al. 2000)
	−	Gβ, Gγ and GRK3 (Rao et al. 2009b)
Blood		
Leukocytes	+	3[H]Gpp(NH)p binding during mania (Schreiber et al. 1991)
	+	Gαs levels in unmedicated depressed patients (Young et al. 1994)
	+	Gαs and Gαi levels during mania (Avissar et al. 1997)
	−	Gαs and Gαi levels in patients during depression (Avissar et al. 1997)
	+	Gαs mRNA levels in unmedicated patients (Spleiss et al. 1998)
Platelets	+	Gαs 45- and Gαs 52-kDa during euthymia (Mitchell et al. 1997)
	+	[35S]GTPγS binding to Gαs, Gαi and Gαq/11 (Hahn et al. 2005)
Transformed lymphoblast	=	Gαs levels in lithium-responsive patients (Alda et al. 2005)

(+) increased levels, (−) decreased levels, (=) no change compared to healthy control group

D1 and D2, the G-protein-coupled dopaminergic receptors, have been shown to have a polymorphic association in BPD – for instance, the D1 receptor at A48G (Rybakowski et al. 2009). Massat et al. (2002) found an association between the D2 receptor and BPD. G-protein receptor kinase 3 (GRK3) has also received attention in BPD; a new study demonstrated a significant decrease in mRNA and protein levels of G-protein β3, G-protein γ, and GRK3 in the postmortem prefrontal cortex of BPD patients (Rao et al. 2009b). GRK3 levels were decreased in lymphoblastoid cell lines derived from BPD patients and this correlated with the severity of an individual's illness (Shaltiel et al. 2006). These studies provide both conceptual and experimental evidence that alterations to Gα levels and function may play an important role in the biological basis of BPD.

Further support of altered dopaminergic signaling has arisen from investigations of prostate apoptosis response-4 (Par-4). A synaptic promoter of apoptosis, Par-4, is upregulated in response to pro-apoptotic stimuli, as it interacts with PKC (Diaz-Meco et al. 1996) to interfere with the prosurvival activity of NFkB. Par-4 forms a complex with the dopamine D2 receptor and may be a significant regulatory factor in dopamine signaling. Mutant mice with impaired Par-4 signaling displayed increased depressive-like behaviors (Park et al. 2005), and individuals with BPD have diminished Par-4 levels (Glantz et al. 2010).

3.2 Glutamatergic Neurotransmission

Several lines of evidence implicate cellular and synaptic abnormalities in the pathophysiology of BPD, including postmortem studies of low glial cell number in the prefrontal cortex (Ongur et al. 1998; Rajkowska 2000) and abnormal

prefrontal cortex volume (Blumberg et al. 2006; Drevets et al. 1997). Glial cells play an important role in glutamatergic neurotransmission. The excitatory neurotransmitter glutamate (Glu) is released into the synaptic cleft, taken up by glial cells, converted to glutamine (Gln), and is cycled back to neurons (Rothman et al. 2003; Pellerin and Magistretti 2004). Neuroimaging studies have shown increased levels of Glu plus Gln and lactate levels in discrete subregions of the prefrontal cortex in adult patients with BPD (Yildiz-Yesiloglu and Ankerst 2006). Lan et al. (2008) reported that nuclear magnetic resonance imaging in the dorsolateral prefrontal cortex in BPD showed elevated Glu levels. More recently, Ongur et al. (2008) evaluated the Glu/Gln ratios in the anterior cingulate cortex and parieto-occipital cortex in individuals with BPD and found increased Glu/Gln ratio in both regions, supporting the hypothesis of glutamatergic involvement in the pathophysiology of BPD. In this context, the balance between Glu-Gln conversion in glia and Gln-Glu conversion in neurons appears disrupted due to a breakdown in neuronal–glial interactions in BPD (Ongur et al. 2008).

Additionally, NMDA receptors are ionotropic Glu receptors that, when stimulated by Glu, allow the passage of calcium into the cell, promoting activation of CAMKIV. This may activate nitric oxide synthases (NOS1 and NOS3), thereby leading to increased nitric oxide production, which is related to increased oxidative damage to proteins and DNA. Supporting this scenario, increased nitric oxide levels have been demonstrated in BPD patients (Savas et al. 2006; Savas et al. 2006; Selek et al. 2008).

3.3 Tyrosine Receptor Kinase

Tyrosine receptor kinases (TRKs) have a single hydrophobic transmembrane spanning domain with an intracellular C-terminal kinase region and an extracellular N-terminal ligand-binding region. Several TRKs are classified into subfamilies based on their structural properties and ligand specificity (Arevalo and Chao 2005; Chao 2003; Chao et al. 2006). This superfamily includes many receptors for growth factors and hormones, such as nerve insulin-like growth factor and brain-derived neurotrophic factor (BDNF) receptors.

Growth factor effects are mediated through the activation of TRKs (Chao 2003) as each factor interacts with a specific receptor subtype. For example, nerve growth factor (NGF) binds to TrkA; BDNF and neurotrophin-4 (NT4) bind to TrkB; neurotrophin-3 (NT3) stimulates TrkC (Chao 2003). Neurotrophins activate TRK and p75NTR receptors and affect several signaling pathways. Specifically, the p75NTR receptor modulates three signaling pathways: (1) NF-κB activation results in gene transcription, including those promoting neuronal survival; (2) activation of the Jun kinase pathway similarly affects gene transcription, some of which encourage apoptosis; (3) Rho family of GTPases' activation regulates actin dynamics, including growth cone motility. In addition, TRKs control three distinct signaling pathways: (1) Ras activation triggers the MAP kinase-signaling cascade, promoting

neuronal differentiation and outgrowth; (2) PI3 kinase activation through Ras or Gab1 promotes cell survival and growth; (3) phospholipase-C-γ1 (PLC-γ1) activation activates calcium- and PKC-regulating pathways that support synaptic plasticity. Ultimately, these pathways interact with transcription factors – i.e., cAMP response element binding protein (CREB) and β-catenin – to control gene expression (Chao 2003; Chao et al. 2006).

Growth factors have been extensively studied in BPD (for a review see Kapczinski et al. 2009). BDNF contributes to neuronal survival, structure, function (Neves-Pereira et al. 2002; Neves-Pereira et al. 2005), and long-term memory (Post 2007). BPD patients have diminished serum BDNF levels during mania (Cunha et al. 2006; Machado-Vieira et al. 2007) and depression (Cunha et al. 2006). Data from euthymic individuals are conflicting. Reports have shown that BDNF levels are either decreased (Monteleone et al. 2008) or unaltered compared to healthy controls (Cunha et al. 2006). Interestingly, a negative correlation between serum BDNF levels and psychopathology scores has been reported in BPD (Cunha et al. 2006). Patients with BPD-I, regardless of treatment, have lower BDNF serum levels, and this may imply that low serum BDNF levels are maintained by therapeutics; this supports the notion that these levels may be a biomarker for BPD mood episodes (de Oliveira et al. 2009). Dunham et al. (2009) reported that (pro)BDNF expression in the hippocampus is decreased in subjects with BPD and major depression. Growth factors are associated with neuroplasticity and contribute to brain resilience. The findings described above demonstrate the importance of these factors in the pathophysiology of BPD.

4 Second Messenger Targets

Subsequent to the activation of receptors, second messengers are generated that modulate intracellular protein phosphorylation and ultimately regulate cellular function. The extent of a protein's phosphorylation reflects a balance between the opposing actions of protein kinases and phosphatases and is the by-product of a multitude of signal transduction pathways (Zarate and Manji 2008). Several studies have reported changes to second messenger systems in BPD. These are summarized in Fig. 1 and Tables 1–4.

4.1 Cyclic Adenosine Monophosphate and Protein Kinase A Pathway

cAMP is produced via stimulatory Gαs activation of AC (Beaulieu et al. 2007). The chief target for cAMP is cAMP-dependent protein kinase, also known as protein kinase A (PKA) (Fig. 1). Upon PKA activation, many additional proteins that can

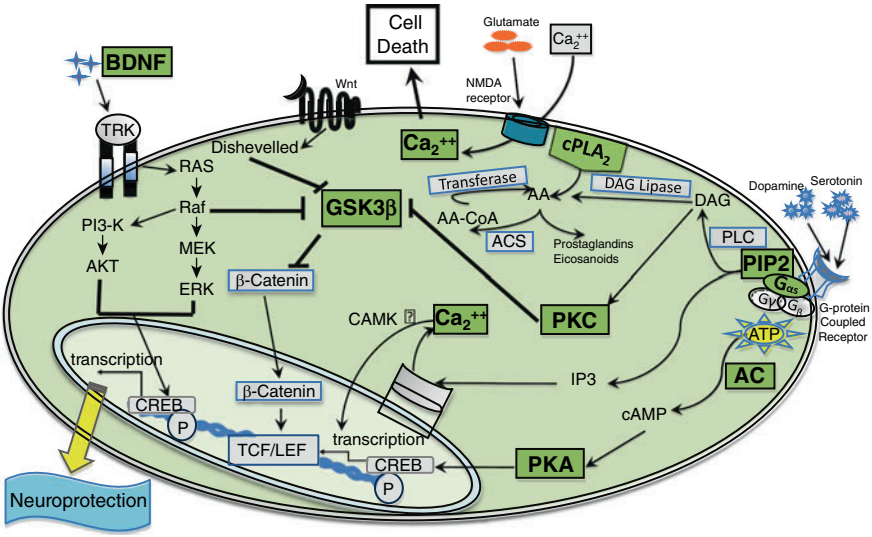

Fig. 1 Signal transduction pathways implicated in BPD. Factors in *green boxes* indicate involvement in BPD

Table 2 cAMP and PKA signaling in bipolar disorder

Tissue	Δ	Result
Brain		
Cortex	+	AC activity (Ebstein et al. 1982)
	+	Forskolin-stimulated cAMP production (Young et al. 1991; Young et al. 1993)
	+	PKA levels in temporal cortex (Spaulding et al. 1993)
	−	[^{3}H]cAMP binding to PKA (Rahman et al. 1997)
	+	Maximal and basal cAMP-dependent PKA activity (Fields et al. 1999)
	−	PKA EC50 (Fields et al. 1999)
Blood		
Platelets	+	PKA catalytic subunit in mania and depression, but not in euthymia + Rap1 in mania, depression and euthymia (Perez et al. 2000)
	+	cAMP-stimulated PKA activity in unmedicated euthymic and depressed bipolar patients have significantly higher (Tardito et al. 2003)
Transformed lymphoblast	+	PKA catalytic subunit and −[^{3}H]cAMP binding (Karege et al. 2004b)
	+	Basal PKA activity (Karege et al. 2004b)
	+	PKA catalytic subunit levels (Karege et al. 2004b)

(+) increased levels, (−) decreased levels, (=) no change compared to healthy control group

modulate gene expression are phosphorylated. This pathway is a vital step in connecting transient variations in neurotransmitter signaling to lasting neurobiological changes (Beavo et al. 1974).

Evidence suggests that basal and receptor-activated AC activity is increased in BPD patients (summarized in Table 2). Augmented levels of post-receptor stimulated AC activity (Ebstein et al. 1982) and increased levels of forskolin-stimulated

Table 3 Phosphoinositide pathway in bipolar disorder

Tissue	Δ	Result
Brain		
Cortex	+	levels of Gαq/11 and PLC levels (Taylor and Exton 1991)
	+	PKC levels (Wang and Friedman 1996)
	−	Inositol levels in prefrontal but not occipital cortex or cerebellum (Shimon et al. 1997)
	−	PI-coupled G-protein activation (Mathews et al. 1997)
Blood		
Biopsy-derived tissue	−	Calcium levels in response to stimulation of olfactory receptor (Hahn et al. 2005)
Platelets	+	PIP2 levels in patients during depression (Brown et al. 1993)
	+	PKC activity in patients during mania (Friedman et al. 1993)
	−	PIP2 levels in lithium-treated patients during euthymia (Soares and Mallinger 1996; Soares et al. 1997; Soares et al. 2000; Soares et al. 1999)
	+	PKC-β1 and -β2 activity and mRNA levels in unmedicated pediatric BPD (Pandey et al. 2008)
	+	Intracellular calcium (Dubovsky et al. 1986)
	+	Intracellular calcium in patients during mania and depression (Dubovsky et al. 1994)
	+	Thapsigargin-induced cytosolic calcium (Hough et al. 1999; Kato et al. 2003; Perova et al. 2010)
Serum	+	Total and ionized calcium levels (El Khoury et al. 2002)
Transformed lymphoblast	+	Basal calcium levels in patients with BPD-1 (Emamghoreishi et al. 2000)
	+	Calcium mobilization by LPA stimulation (Perova et al. 2008)
	−	Calcium levels after LPA or thapsigargin in lithium-treated patients (Wasserman et al. 2004)

(+) increased levels, (−) decreased levels, (=) no change compared to healthy control group

Table 4 Neurotrophic factors in bipolar disorder

Tissue	Δ	Result
Brain		
Hippocampus	−	(pro)BDNF and p75 expression (Dunham et al. 2009)
Blood		
Serum	−	BDNF levels in depression and mania (Cunha et al. 2006)
	=	BDNF levels in euthymia (Cunha et al. 2006)
	−	BDNF levels in unmedicated patients (Machado-Vieira et al. 2007)
	−	BDNF levels euthymia (Monteleone et al. 2008)
	−	BDNF levels in drug-free and medicated patients (de Oliveira et al. 2009)
	−	BDNF levels in late stage of the disorder but not in early stage (Kauer-Sant'Anna et al. 2009)

(+) increased levels, (−) decreased levels, (=) no change compared to healthy control group

cAMP production have been identified in postmortem brains from BPD patients (Young et al. 1991; Young et al. 1993). As well, in peripheral mononuclear leukocytes from individuals with BPD, there are changes in receptor and/or post-receptor sensitivity in the cAMP system without modifications to receptor number

(reviewed by Bezchlibnyk and Young 2002). In platelet samples from treated euthymic BPD patients, cAMP-stimulated phosphorylation of Rap-1, a cAMP substrate that regulates cell adhesion, was increased when compared to healthy individuals (Perez et al. 2000). Zanardi et al. (1997) demonstrated that lithium treatment augments basal and cAMP-stimulated protein phosphorylation. In addition, diminished levels of cytosolic PKA regulatory subunits have been identified in postmortem brain samples from patients with BPD (Rahman et al. 1997).

In the temporal cortex of patients with BPD, PKA activity is increased (Spaulding et al. 1993). Following an analysis of specific PKA subunits, augmented activity may result from a state-related disparity (Fields et al. 1999). PKA levels, activity, and the levels of several downstream markers in peripheral cells are elevated in BPD patients in various mood states both before and after treatment (Karege et al. 2004b; Perez et al. 1999; Tardito et al. 2003). As well, platelets from both unmedicated euthymic and depressed patients with BPD have greater cAMP-stimulated PKA activity compared to healthy subjects (Tardito et al. 2003). Even though depressed and manic patients with BPD have elevated PKA catalytic subunit levels, as compared to both euthymic BPD patients and healthy individuals, all BPD patients, regardless of state, have increased Rap1 levels (Perez et al. 2000). Lymphoblast cells from BPD patients have elevated PKA activity, PKA catalytic subunit levels, and pCREB expression, and significantly less [^{3}H] cAMP binding to PKA regulatory subunits compared with controls (Karege et al. 2004b). This group also reported that euthymic BPD patients have elevated basal PKA activity, PKA catalytic subunit levels, and pCREB expression (Karege et al. 2004a). These studies suggest that cAMP and affiliated PKA activation are involved in BPD.

4.2 Phosphoinositide Pathway (PLC: IP3–Ca^{++}–CAMK; DAG–PKC)

The phosphoinositide (PI) signaling pathway commences with G-protein-coupled receptor activation by neurotransmitter. Ultimately, receptor binding leads to PLC-catalyzed cleavage of a plasma membrane inositol-containing phospholipid, phosphatidylinositol 4,5-bisphosphate (PIP2), into two second messenger products: inositol 1,4,5-trisphosphate (IP3) and 1,2-diacylglycerol (DAG) (Perez et al. 1999) (Fig. 1). Binding of IP3 to its receptor on the endoplasmic reticulum (ER) stimulates the release of intracellularly stored calcium from the smooth ER into the cytosol (Berridge et al. 1983). Calmodulin (CaM), a calcium-binding protein, mediates many of calcium's intracellular effects toward various target proteins, such as protein kinases, like the CaM kinase family (CaMKs). The isoforms I and IV of CaMK are involved in mediating transcriptional activation of gene expression through the phosphorylation of transcription factors such as CREB (reviewed by Bezchlibnyk and Young 2002). Calcium is a widespread second messenger, and it

is important to note that IP3-mediated intracellular calcium release is only one way that intracellular calcium concentrations are increased. Intracellular calcium levels are critical to cellular function in that excessive accumulation can promote apoptosis, whereas moderate elevations may trigger the release of neurotransmitters from neuronal presynaptic boutons (Schloesser et al. 2008).

IP3 activation induces calcium release from the smooth ER into the cytosol (Berridge et al. 1983). It has become increasingly appreciated that calcium contributes to synaptic transmission, synaptic plasticity, cell survival, and excitotoxicity (reviewed in Kato 2008b). Dubovsky et al. (1986) first reported that platelet intracellular calcium concentrations are increased in BPD patients, and that these increases are measureable during both manic and depressive states (Dubovsky et al. 1994). Total serum and ionized calcium have also been reported to be elevated in euthymic lithium-treated BPD patients (El Khoury et al. 2002). More recently, intracellular calcium levels were examined from biopsy-derived olfactory neurons from euthymic patients with BPD; these patients responded with lower calcium levels to odorant stimulation compared to healthy control subjects (Hahn et al. 2005). Elevations to basal calcium concentrations have been reported from transformed B-lymphoblasts in BPD-I compared to levels measured from individuals with BPD-II, major depression, and healthy controls. These changes to calcium levels are associated with abnormalities in receptor coupling and AC activity (Emamghoreishi et al. 2000). Thus, calcium homeostasis is affected in all mood states of BPD (for a summary of these results, see Table 3).

Agonist-induced calcium entry by thrombin, serotonin, and platelet activating factor is elevated in cells derived from BPD patients (Kato 2008a; Kato 2008b). In addition, thapsigargin-induced cytosolic calcium response is increased in peripheral blood cells from patients with BPD (Kato et al. 2003; Perova et al. 2010). Perova et al. (2008) showed increased calcium mobilization following lysophosphatidic acid (LPA) stimulation in B-lymphoblast cells from patients with BPD-I. Because LPA provokes calcium entry through a DAG-dependent TRPC3-like channel, these findings suggest that calcium homeostatic disturbances may be due to alterations in the DAG-gated TRPC3 channels. Interestingly, lithium attenuates LPA-stimulated and thapsigargin-induced calcium mobilization in B-lymphoblast cell lines from patients with BPD-I (Wasserman et al. 2004). Various transmembrane proteins that allow the entry of calcium into a neuron, such as *N*-methyl-D-aspartate (NMDA) receptor, α-amino-3-hydroxyl-5-methyl-4-isoxazolepropioic acid (AMPA)/kainate receptor, and voltage-dependent calcium channels may also contribute to abnormal calcium signaling in neurons. Indeed, much evidence supports alterations to genes for these receptors and channels in the postmortem BPD brain (Kato et al. 2007), and some of the strongest evidence from genome-wide association studies came from the gene encoding a subunit for the L-type voltage-dependent calcium channel (Sklar et al. 2008).

Alterations to the PI pathway in BPD have been examined in many studies (reviewed in Kato 2008a and summarized in Table 3). Shimon et al. (1997) demonstrated that levels of inositol are decreased in BPD patients in the prefrontal but not in the occipital cortex or cerebellum. Gαq/11 and PLC levels (Taylor and Exton 1991) were increased in the occipital cortex; however, the levels of

PI-coupled G-protein activation were reduced significantly in this region (Mathews et al. 1997) and suggest an adaptive response resulting from deficient PI-signaling activity in the disorder (Bezchlibnyk and Young 2002). Lymphoblastoid cells and lymphocytes from patients with BPD also have decreased levels of inositol (Belmaker et al. 2002), inositol monophosphatase 2 (IMPA2) mRNA (Nemanov et al. 1999; Yoon et al. 2001), and IMPase activity (Shamir et al. 1998). Studies have also measured membrane PI levels, in particular PLC's major substrate, PIP2. Brown et al. (1993) observed elevated PIP2 levels in BPD patient platelets during a depressed mood. In contrast, the levels of PIP2 are reduced in lithium-treated BPD patients during euthymia (Soares et al. 1997; Soares and Mallinger 1996; Soares et al. 1999; Soares et al. 2000).

DAG, the second cleavage product from PIP2, activates PKC and belongs to another family of kinases (Perez-Gordones et al. 2009). DAG leads to the translocation of PKC from the cytosol to the plasma membrane, where it binds phosphatidylserine and calcium. These actions reduce auto-inhibition, leading to PKC phosphorylation of different proteins. PKC also acts in sites other than the plasma membrane, such as the cytoskeleton, perinuclear location, and the nucleus (Perez-Gordones et al. 2009).

PIP2 hydrolysis generates a second messenger, DAG, that functions as an allosteric activator of PKC (Newton and Ron 2007). DAG is metabolized by its conversion to phosphatidic acid by the DAG kinases (DAGK) (Crotty et al. 2006). Even mild impairment to DGK function can dysregulate PKC signaling. Recently, two independent genome-wide association studies identified the gene for DAGK as a risk gene for BPD. The activity and levels of PKC are increased in platelets and cerebral prefrontal cortex, respectively, during mania in BPD patients (Friedman et al. 1993; Hahn and Friedman 1999; Wang and Friedman 1996). Several studies have demonstrated that lithium and valproate reduce PKC levels in animal models, cell cultures, and platelets of lithium-treated patients (reviewed in Zarate and Manji 2008). In contrast, Pandey et al. (2008) used platelets from unmedicated pediatric BPD patients to show that PKC activity and subunit expression – βI and βII, but not α or Δ – were significantly decreased in both membrane and cytosolic fractions. Furthermore, pharmacotherapy with mood stabilizers for 8 weeks resulted in significantly elevated PKC activity but did not affect PKC isozyme expression in patients with BPD (Pandey et al. 2008). These data suggest that PKC expression and activity may be associated with the molecular biology of BPD, and that pharmacological treatment corrects PKC activity and improves clinical symptoms. Table 3 summarizes these findings.

4.3 The Regulation of Glycogen Synthase Kinase-3 by Protein Kinase B (Akt) and Wnt

The enzyme glycogen synthase kinase 3 (GSK3) is a serine/threonine protein kinase with two isoforms, α and β, that are involved in cellular processes, such as proliferation, differentiation, and in neurons, axogenesis and synaptogenesis

(Gould et al. 2006). This chapter will discuss GSK3β, as this isoform has been implicated in the pathophysiology of BPD. The protein substrates that are phosphorylated by GSK3β include members from classes such as metabolism, signaling, structure, and transcription factors; thus, the regulation of GSK3β activity is significant (Rowe and Chuang 2004). As an example, GSK3β has high expression in the adult brain and phosphorylates a number of cytoskeletal proteins, such as Tau, MAP1B, and MAP2 (Salinas and Hall 1999). GSK3β-mediated MAP1B phosphorylation is associated with the stabilization of axonal microtubules (Lucas et al. 1998). Furthermore, GSK3β promotes the intrinsic apoptotic-signaling pathway by regulating transcription factors that direct the expression of pro- and anti-apoptotic proteins, by promoting structural changes that occur to a cell in apoptosis, and by promoting mitochondrial dysfunction (Beurel and Jope 2006). In this framework, many signaling pathways are implicated in inactivating GSK3β, including the phosphoinositide 3-kinase (PI-3K) and Wnt pathways (Zarate and Manji 2008).

Activation of TRK receptors by growth factors dimerizes and activates PI-3K through its autophosphorylation at tyrosine residues. The membrane-associated phospholipid, PIP2, is subsequently phosphorylated by activated PI-3K to generate PIP3, which activates the protein-serine/threonine kinase Akt (Beaulieu et al. 2007). Akt functions to phosphorylate cell survival proteins, for example, GSK3α and GSK3β, which are inactivated through the phosphorylation of either serine residue serine 21 (GSK3α) or serine 9 (GSK3β) (Beaulieu et al. 2007). The Wnt signaling pathway also affects the activation state of GSK3. The Wnt protein family comprises more than 15 secreted glycoproteins (Wodarz and Nusse 1998) that bind to and activate extracellular frizzled family receptors. This action intracellularly transduces the message via disheveled protein and results in the inhibition of GSK3β (Gould and Manji 2002b). GSK3β inhibition promotes the activation of transcription factors, including β-catenin, HSF-1, AP-1, and CREB. These intracellular targets provide neuroprotection by authorizing specific genes.

GSK3β has received much interest in BPD, owing to robust evidence that lithium and valproate increase GSK3β phosphorylation, and thus lead to its inhibition (reviewed in Rowe et al. 2007). The means by which lithium augments GSK3β phosphorylation levels is not understood. One possibility is the PI3K/Akt pathway. Studies have demonstrated that lithium treatment increases BDNF levels in cell culture (Hashimoto et al. 2002) and in an animal model of mania (Frey et al. 2006) via the Trk-B receptor signaling pathways of PI3K/Akt and MEK/ERK (Chalecka-Franaszek and Chuang 1999; Einat et al. 2003). Lithium provides protection against excitotoxicity, and these effects are mimicked by other GSK3 inhibitors, transfection with GSK3 isoform-specific siRNA, and dominant-negative mutants (Liang et al. 2007), suggesting that this facet of lithium's actions is mediated via GSK3. Valproate also inhibits GSK3β by increasing its phosphorylation levels through activation of the Wnt pathway, as evidenced by elevated β-catenin mRNA and protein levels (Chen et al. 1999b; Phiel and Klein 2001).

Numerous investigations have studied the relationship of GSK3 single nucleotide polymorphisms (SNPs) and BPD. In Korean and Caucasian populations, no

significant differences were observed for SNPs of GSK3 between individuals with BPD and controls (Benedetti et al. 2004; Lee et al. 2006; Nishiguchi et al. 2006). One study did find a trend toward an association between T/C polymorphism and BPD; however, upon closer examination, the strong connection was found between the T-50C polymorphism and females with BPD-II (Szczepankiewicz et al. 2006). These reports imply that GSK3 mutations are not associated with BPD, excluding females with BPD-II. Postmortem brain studies also have not found differences in levels of GSK3β, β-catenin, or Dvl-2 between BPD, other psychiatric illness, and controls (Beasley et al. 2001).

It is well recognized that mood stabilizers promote GSK3 phosphorylation. One might expect that GSK3 mutations may predict BPD treatment efficacy. Upon examination, Benedetti et al. (2005) found that the −50 C/T SNP mutation improved the recurrence index (frequency of episodes pre- and post-lithium treatment) following lithium administration. However, later studies were unable to predict lithium's efficacy in BPD-I from genotype and allele frequencies (Michelon et al. 2006), and the T-50C polymorphism was not related to lithium prophylaxis (Szczepankiewicz et al. 2006).

4.4 Arachidonic Acid

Arachidonic acid (AA; 20:4$n-6$) is another second messenger that plays a role in BPD. AA is a nutritionally essential polyunsaturated fatty acid located chiefly in the stereospecifically numbered (Sn)-2 site of membrane phospholipids. AA is hydrolyzed by phospholipase A2 (PLA2) that is coupled to receptor-mediated signaling from stimulation of cholinergic, dopaminergic, glutamatergic, and serotonergic neurons (Axelrod 1990). A recognizable second messenger (Bazinet 2009), AA, can function as a ligand for numerous transcriptional factor receptors including hepatic nuclear factor-4a (Hertz et al. 1998), liver X (Ou et al. 2001), peroxisomal-proliferator-activator (Devchand et al. 1996), and prostaglandin (Kuehl et al. 1970). Some of this released AA may be metabolized into prostaglandin H2 by cyclooxygenase-1 (COX-1) or -2 (COX-2), to generate protective epoxyeicosatrienoic acids via cytochrome P450 epoxygenase or to generate toxic leukotrienes via lipoxygenase (Funk 2001). Prostaglandin H2 can be metabolized into prostaglandin E2 by prostaglandin synthase or into thromboxane A2 by thromboxane synthase (Needleman et al. 1976). The messaging actions of AA are not fully elucidated in BPD (Bazinet 2009); however, they appear to contribute to the modulation of blood flow (Gordon et al. 2007), excitotoxicity (Barbour et al. 1989), neurogenesis (Maekawa et al. 2009), neuroinflammation (Farooqui et al. 2007; Orr and Bazinet 2008), and circadian rhythm (Chen and Bazan 2005). AA and its metabolites regulate apoptosis, neuronal activity, signal transduction, transcription, and many other functions within the brain (Kim et al. 2009).

For example, chronic administration of a subconvulsant dose of NMDA to rats increased cerebral AA turnover, protein and mRNA levels of cytosolic PLA2 IVA,

AP-2 DNA binding activity, AP-2a and AP-2b protein, and cytokine levels (Chang et al. 2008; Rao et al. 2007). Lithium and valproate downregulate components of the cerebral AA cascade. These affected pieces include AA turnover in brain phospholipids, calcium-dependent AA-selective cytosolic PLA2 IVA and its transcription factor AP-2 (lithium only), acyl-CoA synthetase (valproate only), COX-1 (valproate only), COX-2, and NFkB (valproate only) (Kim et al. 2009). Chronic lithium administration foils AA cascade marker increases in rat models of excitotoxicity and neuroinflammation (Basselin et al. 2006; Basselin et al. 2007). The postmortem BPD brain demonstrates increased expression levels of cPLA2 and COX-2 in the prefrontal cortex (Kim et al. 2009). Furthermore, a recent study reported increased markers of excitotoxicity and neuroinflammation in the frontal cortex of individuals with BPD (Rao et al. 2009a).

AA can avert apoptotic processes by preserving the pro-apoptotic protein BAD, specifically by not permitting its dephosphorylation and hence inhibiting its translocation from the cytoplasm to the mitochondria, where it can displace Bax, leading to apoptosis (Zha et al. 1996). Kim et al. (2010) observed increased BAD protein and mRNA levels in the postmortem brains of BPD patients; combined with previous findings that cPLA2 expression is increased in BPD (Kim et al. 2009) these results suggest that these increases may induce AA release and support early pro-apoptotic steps. The same researchers also observed significant decreases in protein and mRNA levels of anti-apoptotic factors [B-cell lymphoma-2 (Bcl-2), BDNF] and of synaptic markers (synaptophysin and drebrin), and increases in pro-apoptotic factors (Bax, BAD, active caspase-3 and -9) in the postmortem prefrontal cortex of individuals with BPD (Kim et al. 2010). These data suggest an abnormality in the apoptotic-signaling pathway in BPD.

In addition to data arising from AA studies, numerous other studies have demonstrated changes to apoptotic factors and their mediated responses in BPD. These alterations (Kim et al. 2009b) include DNA damage in peripheral blood cells from BPD patients (Andreazza et al. 2007), elevated activity of pro-apoptotic serum (Politi et al. 2008), and mitochondrial dysfunction (Shao et al. 2008). Reports have suggested that pharmacological agents used in BPD treatment promote DNA repair (Gasiorowski and Brokos 2001), and that lithium and valproate inhibit glutamate-induced DNA fragmentation (Shao et al. 2005). These medications repress caspase-3 activity while stimulating the expression of Bcl-2, attenuating a cell's apoptotic propensity (Chuang 2004). Chronic lithium administration enhances neurogenesis in rat hippocampus, as demonstrated by elevated Bcl-2 levels and the percentage of new neurons (Chen et al. 2000; Chen and Chuang 1999).

5 Transcription Factors

Following receptor activation and modulation of second messengers, transcription factors are activated to bind to specific DNA sequences and thereby control the transfer (or transcription) of genetic information from DNA to mRNA.

Transcription factors may execute this action alone or in combination with other proteins in a complex, by activating or repressing the recruitment of RNA polymerase to explicit genes. This chapter will focus on the transcription factors β-catenin and CREB (Mamdani et al. 2008).

5.1 β-Catenin

β-catenin is a proto-oncogene product in the canonical Wnt-1 pathway. It is regulated through its phosphorylation by casein kinase 1 (CK1) at the Ser-45 site and by GSK3 at Thr-41, Ser-37, and Ser-33 sites. Phosphorylation of β-catenin targets this protein for ubiquitination and degradation by the proteasome system (McCarty 2009). The activation of the Wnt pathway promotes Wnt proteins to bind to a family of cell-surface receptors known as Frizzled. These receptors activate intracellular disheveled proteins that inhibit GSK3 and result in decreased β-catenin phosphorylation, and hence stabilize this transcription factor (Hedgepeth et al. 1997). The stabilization of β-catenin allows for its accumulation in the cytoplasm and its subsequent translocation into the nucleus, so that it can interact with transcription T-cell factor/lymphoid enhancer factor (TCF/LEF) and promote specific gene expression (Barker 2008; Eastman and Grosschedl 1999). Leng et al. (2008) investigated the effect of lithium and/or valproate on β-catenin levels and TCF/LEF-dependent transcription in cerebellar granule cell line and found that lithium or valproate treatment increased LEF activity five- to sevenfold, but their co-treatment potentiated LEF activity.

5.2 cAMP Response Element Binding Protein

CREB is located in the nucleus and is typically present in its inactive form. It is activated by phosphorylation at Ser-133 by protein kinases, including those that are downstream targets of aforementioned signaling pathways (PKA, MAPKs such as RSK1–3, and CaMKs) (Meyer and Habener 1993). Following CREB protein phosphorylation (pCREB), it binds to a discrete location in the promoter region of target genes, known as the cAMP-response element (CRE). This binding generates mRNA, the blueprint for new protein synthesis (Shaywitz and Greenberg 1999). This step couples quickly changing neurotransmitter levels and receptor binding to the generation of proteins that can permanently transform the function of discrete brain regions. CREB also vitally contributes to the maintenance of normal synaptic transmission and plasticity such as those processes involved in hippocampal long-term potentiation and memory (Kinney et al. 2009). Many growth factors and stress result in CREB's regulation by some of the previously mentioned pathways, including BDNF, MEK/ERK, and GSK-3β (reviewed by Rowe and Chuang 2004). CREB can augment anti-apoptotic protein expression, for example,

the members of the Bcl-2 family (Finkbeiner 2000) and BDNF (Freeland et al. 2000). Because BDNF induces CREB activation and CREB upregulates BDNF expression, this provides a feedback-loop in the cell survival-signaling pathway. Chronic lithium treatment modifies CREB activity in excitotoxic circumstances by thwarting Glu-induced loss of pCREB and CRE-driven gene expression (Kopnisky et al. 2003).

Additional support is provided from the effect of pharmacotherapy on transcription factor activity. Nibuya et al. (1996) found that chronic antidepressant administration elevated rat hippocampal CREB protein and mRNA levels, and the binding of CREB to the CRE. Dowlatshahi et al. (1998) demonstrated raised temporal cortex CREB levels in patients with major depressive disorder treated with antidepressants compared with untreated patients. Zubenko et al. (2002) also reported a relationship between CREB1 polymorphism and major depressive disorder. These data are not consistent, as studies that have investigated antidepressant responses have reported diminished pCREB levels. Sulser (2002) reported that antidepressant treatment reduces the expression of CREB1, as well as the efficacy of CREB1 to initiate transcription, and this may occur as a result of hindered DNA binding ability. Considering that lithium has also dual effect on CREB, in this chapter we will describe both findings (Wang et al. 2001). Chen et al. (1999a) demonstrated that chronic lithium treatment decreased CREB phosphorylation in rat cerebral cortex and hippocampus. More recently, Boer et al. (2008) found decreased CRE/CREB-direct gene expression following chronic treatment with lithium in hippocampus, cortex, hypothalamus, and striatum in a transgenic mouse model, and similarly reduced CREB phosphorylation. Lithium's effect on CREB phosphorylation agrees with the literature that this compound reduces cAMP signaling (Divish et al. 1991). Chronic lithium administration dulls agonist-stimulated cAMP production and can control expression of individual AC isoforms and cAMP-dependent protein kinase activities in rat brain and in platelets from lithium-treated BPD subjects (Boer et al. 2007; Manji et al. 1995). The CREB-c-activator, transducer of regulated CREB, has recently been noted as a novel lithium target, as lithium boosts cAMP-induced CREB-direct gene transcription (Boer et al. 2008; Heinrich et al. 2009). These data agree with previously published results from the temporal cortex of individuals with BPD (Dowlatshahi et al. 1998).

The CREB family is a member of the leucine zipper family of DNA-binding proteins capable of recognizing the CRE. CREB1 is situated on chromosome 2q32.3-q34 in one of two isoforms (CREB347/CREB327) that vary by a 14-bp deletion (Daniel and Habener 1998). CREB2 or ATF4 is found on chromosome 22q13.1 and inhibits CRE-dependent transcription (Karpinski et al. 1992). The CREB3 gene, also known as LUMAN, may function as a transcriptional activator that is comparable to CREB1. Mamdani et al. (2008) studied the genetic variants associated with lithium responders, and their results suggest that the CREB1-1H SNP and CREB1-7H SNP may be linked to BPD and/or to lithium response. These findings maintain the involvement of CREB in lithium response and the molecular biology of BPD.

5.3 Heat Shock Transcription Factor-1 and Activator Protein-1

Other transcription factors have been reported in the BPD literature, including heat shock transcription factor-1 (HSF-1) and activator protein-1 (AP-1). GSK3β negatively regulates HSF-1 as both HSF-1 DNA binding and transcription are negatively correlated with GSK3β activity (Bijur and Jope 2003; Xavier et al. 2000). Lithium is a potent GSK3β inhibitor and therefore may affect the HSF-1 pathway. Indeed, lithium increased HSF-1 DNA binding activity and induced HSP70 upregulation in a rat ischemia model (Ren et al. 2003).

AP-1 is a member of the Jun, Fos, CREB and activating transcription factor (ATF) families and is also regulated by GSK3β, which phosphorylates c-Jun and thus reduces AP-1-binding activity (Boyle et al. 1991). Data have demonstrated that lithium can elevate AP-1 activity in cultured cells (Asghari et al. 1998). Spiliotaki et al. (2006) measured the nuclear protein level of c-fos, JNK, and AP-1-DNA-binding in BPD patients during euthymic and depressed states. Depressed patients had lesser levels of c-fos, JNK, and AP-1-DNA-binding than controls, whereas euthymic patients only had diminished JNK levels, thus suggesting a potential mood–state relationship for this pathway.

6 Conclusion

Abnormalities in intracellular signal transduction pathways may produce a functional discrepancy in several neurotransmitter systems, which may explain the varied clinical symptoms of BPD. Studies have shown that G-protein-coupled serotonergic and dopaminergic neurotransmitter systems are overactive in BPD; specifically, levels of Gas and AC are elevated in these patients. In addition, experiments have demonstrated that the brain's chief excitatory neurotransmitter, Glu, is increased in prefrontal cortex from patients with BPD. In terms of receptors, TRK plays a role in BPD for modulating neurotrophic levels, especially of BDNF. This protein has been noted to contribute to the survival and function of neurons, and its levels are diminished in both serum and brain from patients with BPD. The second messenger system is also altered in BPD. For example, the levels and activity of PKA and PKC are increased, as well as the levels of intracellular calcium. This cation's levels mediate several cellular functions, including receptor coupling, AC activity, neurotransmitter release from presynaptic boutons, and apoptosis. One of the downstream targets important for cellular survival is GSK3 β. It has received much attention in BPD due to lithium's strong inhibition of this protein, which activates many transcription factors, including CREB. Lithium also corrects PKC and BDNF levels. In addition, lithium elevates the expression of β-catenin, HSP-1, and CREB, whereas valproate increases the AP-1, DNA-binding, and expression of β-catenin. The influence of mood stabilizers on transcription factors may be important in connecting the regulation of gene expression to

neuroplasticity and cellular resilience. These studies have heuristically influenced the direction of BPD research to the contemporary investigation of cerebral energy metabolism as it relates to augmented oxidative stress/damage with ensuing neuronal death.

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Synaptic Plasticity in the Pathophysiology and Treatment of Bipolar Disorder

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Contents

Abstract Emerging evidence suggests that synaptic plasticity is intimately involved in the pathophysiology and treatment of bipolar disorder (BPD). Under certain conditions, over-strengthened and/or weakened synapses at different circuits in the brain could disturb brain functions in parallel, causing manic-like or depressive-like behaviors in animal models. In this chapter, we summarize the

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regulation of synaptic plasticity by medications, psychological conditions, hormones, and neurotrophic factors, and their correlation with mood-associated animal behaviors. We conclude that increased serotonin, norepinephrine, dopamine, brain-derived neurotrophic factor (BDNF), acute corticosterone, and antidepressant treatments lead to enhanced synaptic strength in the hippocampus and also correlate with antidepressant-like behaviors. In contrast, inhibiting monoaminergic signaling, long-term stress, and pathophysiological concentrations of cytokines weakens glutamatergic synaptic strength in the hippocampus and is associated with depressive-like symptoms.

Keywords BDNF · Bipolar disorder · Cytokine · Mood stabilizer · Stress · Synaptic plasticity

1 Introduction

There is an urgent need to identify the functional mechanisms associated with bipolar disorder (BPD) in order to develop novel and effective therapeutics. This has led investigators to explore synaptic function, and recent studies from our and other laboratories have consistently suggested that synaptic plasticity of the glutamatergic system may be the convergent mechanism for the treatment of BPD (Carlezon and Nestler 2002; Du et al. 2004a, 2008; Manji et al. 2003; Zarate et al. 2006).

Indeed, Berman et al. (2000) reported the first placebo-controlled, double-blind trial to assess the effects of a single dose of the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine in seven patients with major depressive disorder (MDD). Zarate et al. (2006) subsequently described that a single intravenous dose of ketamine showed robust, rapid, and long-lasting antidepressant effects in patients with treatment-resistant MDD; the same investigators are currently assessing the therapeutic effects of ketamine in patients with bipolar depression. These studies bring new hope for the development of fast-acting medications for BPD.

In addition, accumulating evidence from preclinical studies suggests that α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor (AMPAR) antagonists attenuate several "manic-like" behaviors, mimicking BPD, produced by amphetamine administration. Studies demonstrating that AMPAR antagonists reduce amphetamine/cocaine-induced hyperactivity and hedonic behavior (Dalia et al. 1996; Layer et al. 1993; Li et al. 1997b; Mead and Stephens 1999; Tzschentke and Schmidt 1997) provide compelling behavioral support for the notion that AMPARs play key roles in regulating affective behavior. A recent study from our laboratory found that the structurally dissimilar antimanic agents lithium and valproate both reduced synaptic expression of AMPAR subunits GluR1 and GluR2 at synapses in vivo and in vitro in the hippocampus (Du et al. 2003, 2004a, 2008). In contrast, the antidepressant agents imipramine, lamotrigine, and

riluzole enhanced surface AMPAR expression and phosphorylation of GluR1S845 in the hippocampus in vivo (Du et al. 2007). These data suggest that glutamatergic synaptic plasticity may be the convergence point for the treatment of BPD.

More recently, the traditional monoamine focus for mood disorders has been extended to encompass their downstream signaling targets for regulation of synaptic plasticity. In this chapter, we will summarize recent findings regarding the modulation of synaptic plasticity by pharmacological, environmental, hormonal, and biological factors, and their correlative effects on mood-associated behaviors. We will specifically focus on the regulation of synaptic plasticity in the hippocampal and prefrontal cortical brain regions because these two regions are closely related to mood disorders and the data are well established.

2 Synaptic Plasticity in Psychoneurobiology

Broadly, synaptic plasticity is the ability of the synapses to respond and adapt to neuronal activity and environmental stimuli in order to remodel neurotransmitter release, synaptic strength, and synaptic stability (Citri and Malenka 2008; Malenka 2003a). More than 100 billion neurons function in the adult human brain, and each neuron interconnects with thousands of synapses. A single behavioral action may therefore be translated into the activation of a large number of synapses in the relevant neuronal circuits. It is believed that behavioral experiences or medications can modify synapses, thereby strengthening some neuronal pathways within a circuit, and weakening others (Kessels and Malinow 2009; Shepherd and Huganir 2007). Therefore, the major goals of modern psychoneurobiology and psychopharmacology must encompass the identification of brain synaptic plasticity and the circuits modified by experience or medicines that lead to changes in mood-associated behaviors.

Synaptic plasticity has been extensively studied via long-term potentiation (LTP), which is typically induced by high-frequency stimulation (HFS) of excitatory input leading to rapid elevation of calcium in postsynaptic dendritic spines (Blundon and Zakharenko 2008; Bramham 2008). This essential calcium influx at most excitatory synapses is provided by activating AMPARs and, subsequently, NMDA-type glutamate receptors; this occurs in combination with the contributions from voltage-gated calcium channels and mobilization of calcium from intracellular stores. LTP can last for weeks and months and can be evoked by both HFS and chemicals. It is well established that maintenance of LTP involves at least two phases, including early LTP and late LTP. Early LTP, which lasts about 1–2 h, requires phosphorylation of existing proteins (i.e., GluR1S845 or GluR1S831) and protein trafficking at synapses, but not new protein synthesis. Late LTP, like long-term memory, depends on protein synthesis (Blundon and Zakharenko 2008; Bramham 2008).

Although the mechanisms of LTP and long-term depression (LTD) have not been completely elucidated, it is widely accepted that AMPAR trafficking is key to these phenomena, especially during early phase LTP (Kessels and Malinow 2009;

Shepherd and Huganir 2007). Trafficking of AMPA-type glutamate receptors serves as a prevalent mechanism underlying activity-induced changes in synaptic transmission. AMPARs comprise four homologous subunits (GluR1–4), which assemble into various heteromeric tetramers. In the adult hippocampus, most AMPARs contain GluR1 or GluR3 subunits in combination with GluR2, which confers calcium impermeability. However, phosphorylation of the GluR1 receptors by protein kinase A (PKA), protein kinase C (PKC), and calcium/calmodulin-dependent protein kinases (CAMKII) is highly regulated, and several signal transduction cascades can produce short- and long-term changes in the expression of AMPAR subunits at the synaptic surface (Kessels and Malinow 2009; Shepherd and Huganir 2007). In particular, phosphorylation of GluR1 at serine 845 leads to the insertion of AMPARs into the neuronal membrane and the wide opening of AMPAR ion channels, thus serving as a marker for synaptic strength in various psychological conditions (Kessels and Malinow 2009; Shepherd and Huganir 2007).

LTP is associated with both rapid (in minutes) and more delayed (in hours or days) changes in gene expression (Davis and Laroche 1998). After HFS, several constitutively expressed transcription factors, including cyclic-AMP/calcium responsive-element binding protein (CREB) and Elk-1, are activated, leading to enhanced transcription of a functionally diverse group of immediate early genes. CREB is also a key factor and is an associated gene for depression. The protein synthesis-dependent consolidation plays an essential role in various forms of long-term synaptic plasticity and animal behaviors (Kandel et al. 2001). The long-term changes usually lead to the strengthening of the synapses structurally or the formation of the new synapses (Bredt and Nicoll 2003; Hu et al. 2008; Massaro et al. 2009). In addition to the association between synaptic plasticity and learning and memory, a growing body of data suggests that synaptic plasticity is the key regulator for psychiatric disorders and drug addiction. Indeed, synaptic plasticity is a fundamental mechanism for neuronal communication.

3 Synaptic Plasticity Is a Common Target of the Mood Stabilizers Lithium and Valproate

Lithium and valproate are structurally dissimilar mood stabilizers which are used to treat mania for decades. Accumulating data demonstrate that mood stabilizers regulate several intracellular signaling pathways that regulate synaptic plasticity, including PKC, PKA, mitogen-activated protein (MAP) kinase, glycogen synthase kinase 3ß (GSK-3ß), and intracellular calcium (Lee 2006; Manji et al. 2003). In this context, it is notable that a growing body of data indicates that synaptic plasticity, and particularly AMPAR trafficking, might be involved in the pathophysiology and treatment of mood disorders.

Recent studies found that the mood stabilizers lithium and valproate appear to attenuate glutamatergic function via multiple mechanisms. Repeated administration of lithium appears to promote the uptake of glutamate from the synapse

(Dixon and Hokin 1998), alter the function of glutamate receptors (Du et al. 2004b, 2008; Gould et al. 2008; Nonaka et al. 1998), and reduce the function of intracellular signaling cascades (Manji et al. 1999). Chronic treatment with lithium also leads to a decreased AMPA/NMDA ratio, which is mainly caused by reduction of AMPARs at the synapses (Du et al. 2008). In addition, both lithium and valproate reduced AMPAR GluR1 and GluR2 levels at synapses of hippocampal neurons. This reduction in synaptic GluR1/2 by lithium and valproate was due to attenuated phosphorylation of GluR1 at a specific PKA site (residue 845 of GluR1), which is crucial for AMPAR insertion (Du et al. 2004a, 2008). Notably, both lithium and valproate inhibit GSK-3, and lithium, valproate, and other GSK-3 inhibitors demonstrate both antimanic and antidepressant efficacy in animal models of mood-associated behaviors (Gould et al. 2004; Kapus et al. 2008). Lithium's antidepressant effects were inhibited by the AMPAR antagonist GYKI52446 (Gould et al. 2008). Rats receiving hippocampal infusions of AMPA-specific inhibitors exhibited significant reductions in manic behaviors as assessed through the amphetamine-induced locomotion and conditioned place preference (CPP) paradigms, both of which are well-validated animal models of mania (Du et al. 2008). In contrast, the tricyclic antidepressant (TCA) imipramine, which can provoke mania in patients, increases synaptic expression of GluR1 in the hippocampus in vivo. Thus, it appears that mood stabilizers may exert their effects by regulating AMPA synaptic strength in the hippocampus.

4 Modulation of Synaptic Plasticity by the Monoaminergic Systems: Serotonin, Norepinephrine, and Dopamine

Modulatory transmitters such as norepinephrine, serotonin, dopamine, and acetylcholine are all involved in regulating, inducing, or maintaining LTP (Bramham et al. 1997; Bramham and Srebro 1989; Harley 2004; Kulla and Manahan-Vaughan 2002; Stanton and Sarvey 1985a, b; Straube et al. 2003; Swanson-Park et al. 1999). These extrinsic inputs typically have diffuse, global patterns of innervation to the corticolimbic system. Neuronal firing activity in these systems is tied to mood-associated behaviors. Furthermore, these classic modulatory transmitters can affect gene expression by affecting PKA and CREB activity. Recently, a theory of altered neuroplasticity as a neurophysiologic condition for mood disorders was proposed (Bramham 2007; Pittenger and Duman 2008). Below, we discuss the regulation of synaptic plasticity by monoaminergic systems.

4.1 Serotonin

Antidepressants modulate synaptic plasticity, particularly LTP (Kasper and McEwen 2008; Pittenger and Duman 2008); however, the effect of antidepressants

on hippocampal synaptic plasticity remains unclear (Holderbach et al. 2007; Massicotte et al. 1993; Matsumoto et al. 2005; Stewart and Reid 2000; Wang et al. 2008). Chronic application of fluvoxamine during the stress protocol prevented the facilitation of LTD induced by exposure to chronic mild stress and increased LTP induction (Holderbach et al. 2007). In addition, imipramine, fluoxetine, and other antidepressants increase the phosphorylation of GluR1 at S845 and S831, both of which serve as markers for the occurrence of LTP (Du et al. 2007; Svenningsson et al. 2007; Szabo et al. 2009).

Accumulating data have shown that serotonin affects LTP and LTD in slice preparations. The effect differs by receptor subtype, timing, and interaction with other factors. Serotonin and serotonergic subreceptors can either facilitate or block LTP as well as LTD, depending on subreceptor specificity, neuronal type, location of plasticity induction, and frequency of application (Abe et al. 2009; Edagawa et al. 1999, 2000; Inaba et al. 2009; Machacek et al. 2001; Normann and Clark 2005; Ryan et al. 2008; Sanberg et al. 2006). Serotonin is also a potential candidate for modulating synaptic plasticity with novel stimuli (Kemp and Manahan-Vaughan 2004), and it is thought to play an important role in mood and anxiety disorders. Previous studies reported that serotonin releasers facilitate the response of dentate granule cells to perforant path stimulation (Winson 1980), an effect thought to be mediated by the 5-HT1a receptor (Levkovitz and Segal 1997). Recent studies also found that stimulation of basolateral amygdaloid serotonin 5HT2C promotes the induction of LTP in the dentate gyrus of the rat hippocampus (Abe et al. 2009). In rodents, the 5HT1A receptor may also mediate perforant path dentate LTP induced by novel environments (Sanberg et al. 2006). Although the effect of serotonin on LTP depends on receptor subtype and neuronal type, most evidence suggests that enhancing serotonergic signaling facilitates the formation of LTP in the perforant path.

4.2 Norepinephrine

The stress hormone norepinephrine plays a central role in regulating emotions via brain β-adrenergic receptors (Cahill and Perlman 1994; Ferry and McGaugh 2000). During stress, norepinephrine is released by neurons originating from the locus coeruleus and lateral brain stem tegmentum to many brain regions, including the hippocampus and the amygdala, both of which are key to mood-associated behaviors (Carrasco and Van de Kar 2003). Norepinephrine and β-adrenergic stimulation show profound effects on facilitation of LTP induction in the hippocampus CA1 region (Gelinas et al. 2008; Gelinas and Nguyen 2005; Katsuki et al. 1997; Sarvey et al. 1989). Recent studies also show that norepinephrine signaling induces phosphorylation of the Ser845 and Ser831 sites of GluR1 both in vitro and in vivo. Norepinephrine and phosphomutant mice with knockin mutations on the GluR1 phosphorylation sites have similar defects in norepinephrine-facilitated LTP and norepinephrine-enhanced contextual memory tasks (Hu et al. 2007).

4.3 Dopamine

Previous studies strongly suggest that dopamine promotes the induction of LTP at CA1 synapses in the rat hippocampus after exposure to a novel spatial environment (Li et al. 2003). Furthermore, dopamine release in the hippocampus enhances LTP and learning, suggesting a link between synaptic plasticity and rewarding circuitry (Li et al. 2003; Lisman and Grace 2005). Recent studies revealed that the critical factor regulating LTP and LTD induction in the hippocampus is the level of tonic background of dopamine (Kolomiets et al. 2009; Matsuda et al. 2006). LTP induction in the hippocampus–prefrontal cortex (PFC) pathway is disrupted by PFC dopamine fiber de-enervation with 6-hydroxydopamine and pretreatment with dopamine D1 receptor inhibitor in vivo (Gurden et al. 2000). D1 receptor activation facilitates calcium influx and activates signaling cascades, including PKA, which subsequently phosphorylates AMPAR GluR1 at S845 and promotes the insertion of AMPARs into the synapses (Greengard et al. 1999; Sun et al. 2008). Taken together, the evidence suggests that dopamine signaling enhances and facilitates the formation of LTP in the hippocampus and PFC.

5 Brain-Derived Neurotrophic Factor Is a Key Modulator of Synaptic Plasticity

Brain-derived neurotrophic factor (BDNF), an important neurotrophin highly expressed in the brain, is best known for its role in regulating synaptic plasticity and its neuroprotective effects against various hazardous stimuli (Kuipers and Bramham 2006; Popoli et al. 2002). Several lines of evidence also suggest that BDNF is involved in depression (Kuipers and Bramham 2006; Popoli et al. 2002). For instance, the expression of BDNF is decreased in depressed patients, and antidepressants up-regulate its expression (Duman 2004; Hashimoto et al. 2004). Furthermore, infusion of BDNF into the rodent brain resulted in antidepressant effects in animal models of depression (Shirayama et al. 2002). It is also interesting to note that human genetic studies found that individuals with BPD who have the Val/Met, rather than the Val/Val form of BDNF, had a more favorable response to lithium, suggesting that the prophylactic effects of lithium could be increased in patients with lower BDNF activity (Frey et al. 2006; Yu et al. 2009). In support of this theory, the mood stabilizers lithium and valproate were found to increase BDNF expression in the rat brain, suggesting that BDNF's neurotrophic effects may contribute to its therapeutic efficacy (Frey et al. 2006; Yu et al. 2009).

BDNF also contributes to a range of adaptive neuronal responses at the synapses including LTP, LTD, certain forms of short-term synaptic plasticity, and homeostatic regulation of intrinsic neuronal excitability. The unique role that BDNF plays as a major regulator of synaptic transmission and plasticity within the neurotrophin family fits with the widespread distribution of BDNF and the

colocalization of BDNF and its receptor, TrkB, at glutamatergic synapses (Lu et al. 2008; Lynch et al. 2007). The molecular mechanisms and function of BDNF in modulating LTP have been well established in the hippocampus. BDNF activates distinct mechanisms to regulate the induction, early maintenance, and late maintenance phases of LTP (Lu et al. 2008; Lynch et al. 2007). BDNF modulates LTP by inhibiting synaptic fatigue, which is a reduction in excitatory postsynaptic potential (EPSP) amplitude observed in response to theta burst stimuli (Lu et al. 2008; Lynch et al. 2007). Inhibition of BDNF signaling by TrkB-Fc to sequester extracellular TrkB ligands enhanced synaptic fatigue and impaired both the induction and early maintenance of LTP at CA3–CA1 synapses in adult rat hippocampal slices (Figurov et al. 1996). In an analysis of BDNF knockout mice, two groups independently reported impaired early LTP in mice homozygous or heterozygous for BDNF (Korte et al. 1995; Patterson et al. 1996). These studies suggest that BDNF is a key modulator of synaptic plasticity in vivo.

6 Neural and Synaptic Plasticity During Chronic Stress

Corticosteroids, such as prednisone and dexamethasone, are commonly prescribed medications that suppress the immune system and decrease inflammation, but are associated with psychiatric and cognitive side effects (Daban et al. 2005; Marshall and Garakani 2002). Hypomania and mania are the most common mood changes during acute corticosteroid therapy. However, depression appears to be more common than mania during long-term treatment with corticosteroids (Laakmann 1988; Sonino and Fava 2001). Similar results were reported in patients with Cushing's syndrome (Laakmann 1988; Sonino and Fava 2001). A decline in declarative and working memory has also been reported during corticosteroid therapy (Daban et al. 2005; Laakmann 1988; Sonino and Fava 2001). Mood and cognitive symptoms are dose-dependent and frequently occur during the first few weeks of therapy. Controlled trials suggest that lithium can prevent mood symptoms associated with corticosteroids (Daban et al. 2005).

Glucocorticoids enter the hippocampus and exert their function through mineralocorticoid and glucocorticoid receptors. In vivo, behavioral stressors cause long-lasting potentiation of NMDA receptor (NMDAR)- and AMPAR-mediated synaptic currents via glucocorticoid receptors selectively in PFC pyramidal neurons. This effect is accompanied by increased surface expression of NMDAR and AMPAR subunits in acutely stressed animals (Maggio and Segal 2009; Setiawan et al. 2007; Venkova et al. 2009). Furthermore, behavioral tests indicate that working memory, a key function that relies on recurrent excitation within networks of PFC neurons, is enhanced by acute stress via a glucocorticoid receptor-dependent mechanism (Yuen et al. 2009).

The stress hormone corticosterone exerts marked effects on learning and memory. It can both facilitate and impair these functions, suggesting that short-term versus long-term treatment may exert opposite effects (Sandi and Pinelo-Nava 2007). Interestingly, corticosteroid hormones profoundly affect AMPAR function, synaptic transmission, and plasticity via genomic and nongenomic pathways. These rapid, nongenomic effects of corticosterone are mediated via high-affinity mineralocorticoid receptors that act to enhance AMPAR miniature excitatory postsynaptic current (mEPSC) frequency and facilitate synaptic potentiation (Maggio and Segal 2009; Setiawan et al. 2007; Venkova et al. 2009). In one model, corticosterone increases associated with a stress paradigm significantly increased LTP in the hippocampal CA1 regions (Alzoubi et al. 2005; Yang et al. 2004). These effects were believed to occur through nongenomic mechanisms. Long-lasting effects were mediated via glucocorticoid receptors that enhance AMPAR-mediated mEPSC amplitude, impair NMDAR-mediated LTP, and facilitate LTD (Alzoubi et al. 2005; Yang et al. 2004). Recent studies also found that corticosteroids regulate AMPAR insertion on the neuronal membrane, providing a molecular mechanism for LTP and LTD (Campioni et al. 2009; Conboy and Sandi 2010; Martin et al. 2009). Therefore, acute, short-term corticosterone enhanced the formation of LTP; however, long-term treatment inhibited the formation of LTP and facilitated formation of LTD. Notably, acute increases in stress hormones lead to mania, and long-term stress leads to depression (Conboy and Sandi 2010; Pittenger and Duman 2008; Popoli et al. 2002).

7 Proinflammatory Cytokines in Regulating Synaptic Plasticity: Potential Implications for Mood Disorders

The interactions between the immune and central nervous system (CNS) in various pathological conditions such as brain trauma, mood disorders, and neurodegenerative diseases have been well studied. Considerable evidence suggests that cytokines also play an important physiological role in normal CNS function at both the cellular and molecular level. The relative abundance of proinflammatory cytokines in specific brain areas involved in regulating learning and memory, such as the hippocampus, suggests their potential role in synaptic plasticity. (Carlezon and Nestler 2002; Du et al. 2004a, 2007, 2008; Kendell et al. 2005; Malenka 2003b; Sun et al. 2005; Wolf et al. 2004).

7.1 Regulation of Synaptic Plasticity by Tumor Necrosis Factor-α

Altered levels of tumor necrosis factor (TNF)-α have been found in several neuropathological states associated with learning and memory deficits, such as depression

and Alzheimer's disease, thus raising the intriguing possibility that TNF-α may play a putative role in regulating neuroplasticity. Indeed, pathophysiological levels of TNF-α have been shown to inhibit LTP in the CA1 region, as well as the dentate gyrus of the rat hippocampus (Butler et al. 2004; Cunningham et al. 1996; Tancredi et al. 1992). More specifically, TNF-α has been shown to inhibit LTP in a biphasic manner; inhibition of early phase LTP by TNF-α depends on a p38MAPK process, whereas late phase LTP inhibition is p38MAPK-independent (Butler et al. 2004). Further studies also found that TNF-α inhibition of LTP is mediated via TNFR-1 and mGluR5 receptor-activated pathways (Cumiskey et al. 2007).

Although most studies suggest that TNF-α has deleterious effects on synaptic plasticity, recent evidence shows that physiologically low levels of TNF-α may play an important role in neurodevelopment, as well as in regulating homeostatic synaptic plasticity, namely "synaptic scaling" (Golan et al. 2004; Stellwagen and Malenka 2006). TNF-α released from glial cells in response to decreased neuronal activity potentiates membrane trafficking of synaptic AMPARs, and thus synaptic strength, and is therefore critical for homeostatic adjustment of neuronal excitability. Conversely, removal of TNF-α from brain slices results in weakened synapses (Beattie et al. 2002), suggesting that glially released TNF-α plays an important role both in adjusting synaptic strength and in maintaining it at appropriate levels. This TNF-α-induced AMPAR membrane trafficking depends on activation of TNF-R1 receptors and is selective for calcium-permeable AMPAR subunits.

7.2 Regulation of Synaptic Plasticity by IL-1

In addition to its well-known role in immunoregulating inflammatory processes, emerging evidence suggests that IL-1 may modulate synaptic plasticity and behavioral systems. Early studies have suggested that IL-1 inhibits LTP induction in hippocampus (Cunningham et al. 1996; Murray and Lynch 1998). In accordance with this finding, several cognitive-behavioral studies in animals have repeatedly shown that high pathophysiological levels of IL-1 have a detrimental effect on hippocampal-dependent memory and learning processes (Barrientos et al. 2002; Bellinger et al. 1993; Curran and O'Connor 2001; Gibertini et al. 1995; Goshen et al. 2008; Oitzl et al. 1993; Pugh et al. 1999), while stress-induced inhibition of hippocampus-dependent conditioning can be reversed by IL-1ra, an IL-1 receptor antagonist (Maier and Watkins 1995; Pugh et al. 1999, 2000). Recent studies observed that increased IL-1 levels disrupted an LTP-associated spinal learning paradigm (Avital et al. 2003). Although most findings to date indicate that IL-1 has deleterious effects on synaptic function and memory, recent evidence suggests that, like TNF-α, it may also be required for the physiological regulation of hippocampal plasticity. IL-1 also inhibited the formation of LTP in the hippocampus, and

phosphorylation as well as trafficking of AMPARs (Lai et al. 2006; Ross et al. 2003).

7.3 Regulation of Synaptic Plasticity by IL-6

IL-6 inhibits LTP induction without affecting previously established LTP via the MAP kinase/ERK pathway (MAPK-ERK) (Li et al. 1997a; Tancredi et al. 2000). In addition, IL-6 is up-regulated after LTP induction, and neutralizing IL-6 after HFS strengthens LTP maintenance (Balschun et al. 2004; Jankowsky et al. 2000). Taken together, these findings suggest that IL-6 appears to play a role in synaptic plasticity and may be required for fine-tuning the consolidation of long-term synaptic plasticity and hippocampal-dependent learning (Balschun et al. 2004; McAfoose and Baune 2009).

8 Brain Imaging Studies of Patients with BPD Demonstrate Changes in Neural Plasticity in the Brain Circuits Associated with Mood Disorders

BPD is associated with considerable structural impairment, potentially due to changes in cellular resilience and neuroprotection. Reduced gray matter volume in the ventral/orbitalmedial PFC and amygdala has been described (Brambilla et al. 2005; Konarski et al. 2008). One recent study noted volumetric reductions in discrete fronto-limbic cortex areas in individuals with BPD compared to healthy controls (Savitz and Drevets 2009). Several independent researchers have noted reduced subgenual PFC in individuals with BPD; this decrease is also associated with therapeutic response (Drevets et al. 1997; Hirayasu et al. 1999; Sharma et al. 2003). Similarly, volumetric and density abnormalities have been described in other areas of the PFC including the ventral and the ventromedial PFC, the orbitofrontal cortex, the posterior cingulate cortex, and the frontal gyri (Adler et al. 2004; Lyoo et al. 2004; Nugent et al. 2006).

Increased white matter hyperintensities (WMH) is a consistently replicable neuroimaging finding in individuals with BPD compared to healthy controls (Altshuler et al. 1995). This finding has been linked to a higher prevalence of cognitive dysfunction and greater severity of symptoms in mood disorders (Salvadore et al. 2008). Notably, evidence suggests that WMH represent damage to the structure of brain tissue and may disrupt neuronal connectivity (Sheline 2000). In addition, multiple episodes of BPD are associated with greater ventricular volumes (Strakowski et al. 2002), but not with gray matter loss in periventricular structures in BPD (Brambilla et al. 2001; Strakowski et al. 2002). Magnetic resonance spectroscopy (MRS) studies conducted over the last decade have also

reported widespread abnormalities in gamma aminobutyric acid (GABA), Glx (a combined measure of glutamate and glutamine), and glutamate levels in patients with BPD. MRS studies have also noted abnormalities in GABA and glutamate levels in mood disorders; these may be closely related to synaptic activity and reuptake of neurotransmitters in the interplay between glia and neurons in the PFC (Bhagwagar et al. 2007; Dager et al. 2004; Frey et al. 2007).

9 Synaptic Plasticity Models for Mood Disorders and Future Directions

Ample evidence from preclinical and clinical research indicates that synaptic plasticity is involved in the pathophysiology of mood disorders, and that many of the factors related to mood disorders including antidepressants, mood stabilizers, monoamine systems, hormonal changes, neurotrophin, cytokines, and electroconvulsive therapy have both direct and indirect effects on synaptic plasticity. Given that BPD is such a complex disease, it is not surprising that many molecules involved in the network of signaling cascades that regulate synaptic plasticity play a role in its pathophysiology.

The data reviewed in this chapter summarize the possible molecular mechanisms whereby biological or environmental stimulants enhance glutamatergic synaptic strength in the hippocampus or PFC, and how this correlates with mood-associated behaviors. In contrast, biological or environmental stimulants lead to decreased synaptic strength in the hippocampus, and this correlates with depressive-like behaviors. For example, increased serotonin, norepinephrine, dopamine, BDNF, acute corticosterone, and antidepressants lead to enhanced synaptic strength in the hippocampus and also correlate with antidepressant-like behaviors. However, inhibiting monoaminergic signaling and long-term stress weaken glutamatergic synaptic strength in the hippocampus and are associated with depressive-like symptoms.

Therefore, we propose the synaptic plasticity model as a convergent mechanism for mood disorders. However, many questions remain to be answered in this research area: (1) does this consistent correlation between synaptic plasticity and hippocortical path to mood-associated behaviors provide sufficient evidence to serve as a convergent biological mechanism? and (2) does the convergent biological mechanism provide a new avenue for drug screening?

Given these findings, further research with medications that specifically affect synaptic plasticity is warranted. Furthermore, more direct targeting of synaptic plasticity might be a strategy for the treatment of BPD, as this strategy would bypass defects in critical circuits required for monoaminergic antidepressants to exert their therapeutic effects. This line of research holds considerable promise and might lead to the next generation of rapid-acting antidepressants and antimanic agents, which could help to reduce the initial morbidity and mortality associated with this disorder.

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Mitochondrial Dysfunction and Bipolar Disorder

Tadafumi Kato

Contents

Abstract The mitochondrial dysfunction hypothesis was proposed to integrate various findings in bipolar disorder (BPD). This hypothesis is supported by possible roles of maternal inheritance, comorbidity with mitochondrial diseases, the mechanism of action of mood stabilizers, magnetic resonance spectroscopy, mitochondrial DNA mutations, gene expression analysis, and phenotypes of animal models. Mitochondrial dysfunction is not specific to BPD but is common to many neurodegenerative disorders. It would be reasonable to assume that neurons regulating mood are progressively impaired during the course of BPD. Further studies are needed to clarify which neural systems are impaired by mitochondrial dysfunction in BPD.

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Abbreviations

acetyl-CoA	Acetyl-coenzyme A
ATP	Adenosine triphosphate
Bag-1	Bcl-2-Associated athanogene
CPEO	Chronic external ophthalmoplegia
ER	Endoplasmic reticulum
GABA	γ-Aminobutyric acid
GSK-3β	Glycogen synthetase kinase-3β
IP3	Inositol triphosphate
LARS2	Mitochondrial leucyl tRNA synthase
MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes
MIRAS	Mitochondrial recessive ataxia syndrome
MRS	Magnetic resonance spectroscopy
mtDNA	Mitochondrial DNA
NAA	*N*-acetylaspartate
NAD	Nicotinamide adenine dinucleotide
UPR	Unfolded protein response

1 Introduction

As shown in this book, many possible systems and pathways contribute to the etiology and pathophysiology of bipolar disorder (BPD), including calcium signaling, monoaminergic abnormalities, γ-aminobutyric acid (GABAergic) dysfunction, signal transduction pathways, neural plasticity, biological rhythms, and so on. However, it is still difficult to integrate all of these findings into one clear picture. The mitochondrial dysfunction hypothesis integrates these findings to comprehensively understand the neurobiology of BPD (Kato and Kato 2000).

Since this hypothesis was first proposed, additional data have been reported (Fattal et al. 2006; Jou et al. 2009; Kato 2007; Quiroz et al. 2008; Rezin et al. 2009; Shao et al. 2008; Stork and Renshaw 2005; Young 2007). Although many findings support this hypothesis, others do not. Thus, it is still a hypothesis and needs to be tested further. In this section, the history and current status of the mitochondrial dysfunction hypothesis in BPD are summarized.

2 What are Mitochondria?

Eukaryotic cells have functionally and structurally distinctive structures named organelles. Organelles include the nucleus, mitochondrion, chloroplast (plants only), endoplasmic reticulum (ER), Golgi body, lysosome, phagosome, secretory vesicle, peroxisome, and so on. A group of diseases caused by dysfunction of each organelle is designated by the name of organelle; for example, peroxisomal disease, lysosomal disease, and mitochondrial disease. Among organelles, the mitochondrion is known as an organelle that synthesizes adenosine triphosphate (ATP) as an energy source (Lane 2006). A mitochondrion is surrounded by inner and outer membranes, and its internal space is referred to as the matrix. A mitochondrion varies in shape among cell types and continuously undergoes fission and fusion.

Mitochondria play a central role in respiration, a reaction to generate ATP from glucose within an organism. Mitochondria take up pyruvate made from glucose in cytosol and change it into acetyl-coenzyme A (acetyl-CoA). Acetyl-CoA is finally metabolized into water and carbon dioxide through the citric acid cycle. In this process, ATP and hydrogen are generated. Hydrogen is transferred into the electron transport chain (respiratory chain) with a carrier molecule, nicotinamide adenine dinucleotide (NAD). In the electron transport chain, hydrogen is separated into an electron and a proton, and electrons transport the proton outside the mitochondrial matrix through the large protein complexes named complex I, complex III, and complex IV. This chain reaction generates a proton gradient across the mitochondrial inner membrane, giving the mitochondrial matrix a negative charge. This ion gradient generates ATP. ATP synthase (complex V; F1-ATPase) synthesizes ATP using this proton gradient. However, this proton gradient is also used for calcium uptake.

3 Mitochondrial DNA

In addition to a nuclear genome, a mitochondrion has its own DNA named mitochondrial DNA (mtDNA); mtDNA is maternally inherited, possibly because it originates from symbiotic bacteria.

mtDNA is a circular double-stranded DNA molecule with a length of approximately 16 kb. There are hundreds of copies of mtDNA within a cell. In comparison with nuclear DNA, it is a compact molecule with no intron and encodes protein subunits of the respiratory chain, tRNA and rRNA. The protein complex of the respiratory chain is formed by the assembly of protein subunits of nuclear origin and mtDNA-derived protein subunits. The genes for enzymes required for mtDNA maintenance are encoded in the nuclear genome (Kato 2001).

mtDNA evolves faster than the nuclear genome, and its sequence has large inter-individual variation. The diseases caused by mtDNA mutations make up a major group within mitochondrial diseases. These include those caused by maternally

inherited point mutations of mtDNA and somatic mtDNA deletions caused by mutations of nuclear genes responsible for mtDNA maintenance. The latter are autosomally transmitted. In both cases, mutations coexist with wild-type mtDNA. This phenomenon – coexistence of mutant and wild-type mtDNA – is referred to as heteroplasmy, and causes variations of mutation rates among tissues resulting in variations of clinical phenotypes even within the same pedigree.

A representative mitochondrial disease caused by maternally inherited point mutations of mtDNA is mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); this disease also shows wide-ranging phenotypes among individuals.

A representative mitochondrial disease caused by mutations of nuclear genes is chronic external ophthalmoplegia (CPEO), characterized by ptosis, ophthalmoparesis, and the accumulation of multiple mtDNA deletions in muscles. At least four causative genes have been reported [ANT1, Twinkle, POLG1 (previously named POLG), and POLG2]. Among them, POLG1 mutations are the most frequent. The phenotype of diseases caused by POLG1 mutations is also wide-ranging and includes Parkinson's disease, diabetes mellitus, cerebellar ataxia, and peripheral neuropathy (Horvath et al. 2006).

4 Relationship with the Endoplasmic Reticulum

The Endoplasmic Reticulum (ER) has multiple functions, such as synthesis and folding of secreting proteins or membrane proteins, synthesis of phospholipid and cholesterol, and storage and release of calcium ions. When inositol triphosphate (IP3) is generated on neurotransmitter stimulation, it binds to the IP3 receptor on the ER membrane and calcium is released from the ER.

When unfolded proteins are accumulated in the ER, it is referred to as "ER stress." This triggers a series of reactions called the "ER stress response" and includes the unfolded protein response (UPR), which increases molecular chaperones, ER-associated degradation, translation suppression, and apoptosis. Transcription factors indispensable for this reaction include ATF6 and XBP1. The ATF6 protein is located on the ER membrane and is activated by proteolysis. On the other hand, XBP1 mRNA is located in the cytosol, spliced onto the ER membrane by IRE1 protein, and then activated (Yoshida et al. 2001). UPR, and XBP1 in particular, may play a role in BPD (Hayashi et al. 2009; Kakiuchi et al. 2003; So et al. 2007). Brain-derived neurotrophic factor (BDNF)-induced XBP1 splicing affects neurite extension (Hayashi et al. 2007), and XBP1 is thought to play a role in BDNF-induced differentiation of GABAergic neurons (Hayashi et al. 2008).

Mitochondria and the ER are in close contact, and calcium released through the IP3 receptor is taken up by the mitochondrial calcium uniporter. The molecular identity of the mitochondrial calcium uniporter is still controversial (Kirichok et al. 2004). The sigma-1 receptor is enriched in this contact site, stabilizes the IP3 receptor, and affects calcium signaling from the ER to mitochondria (Hayashi

and Su 2007). A number of psychotropic drugs bind to this receptor; for instance, haloperidol is an antagonist and fluvoxamine is an agonist.

IP3-induced calcium release is key to neuroplasticity and mitochondrial calcium regulation also plays a role in neuroplasticity (Mattson 2007; Quiroz et al. 2008).

5 The Foundations of the Mitochondrial Dysfunction Hypothesis

5.1 Possible Role of Maternal Inheritance

Twin, adoption, and family studies have all highlighted the role of genetic factors in BPD. Classic studies suggested that male-to-male transmission is rare in BPD. Based on these findings, the possibility of X-linked inheritance was considered. However, Winokur and Pitts suggested that X-linkage alone could not explain this pattern of inheritance and, in the mid-1960s, when mtDNA was just discovered (Nass et al. 1965), thought cytoplasmic inheritance was a possibility (Winokur and Pitts 1965).

Thirty years later, McMahon and colleagues revisited gender differences in the transmission of BPD in families collected for linkage analysis; maternally transmitted families were more frequent than paternally transmitted families and more affected relatives were found in maternal than paternal relatives. These results suggested that mtDNA or genomic imprinting might play a role in BPD (McMahon et al. 1995). The same investigators further analyzed mtDNA polymorphisms in pedigrees with maternal transmission. They found that four polymorphisms were over-represented in the probands, but the difference was not statistically significant after correcting for multiple testing (McMahon et al. 2000). These nominally associated polymorphisms included only one variant changing amino acid sequence: A10398G. This polymorphism was later reported to alter mitochondrial calcium levels (Kazuno et al. 2006). Although one report supported the association of A10398G with BPD (Kato et al. 2001), others did not (Kirk et al. 1999; Munakata et al. 2004). Kirk and coworkers also sequenced the whole mtDNA genome in 25 probands of maternally inherited pedigrees but found no mutations linked with BPD (Kirk et al. 1999).

Findings in twin studies showing that monozygotic twins have higher concordance rates than dizygotic twins do not support the major role of maternally inherited mtDNA mutations/polymorphisms. It is difficult to conclude whether maternal inheritance plays a role in the transmission of BPD based solely on segregation analysis because this type of analysis is susceptible to observation bias, ascertainment bias, and gender differences in the prevalence of mood disorders (Kato et al. 1996). In addition, the significance of early association studies in small patient populations is difficult to ascertain. Thus, it is still not clear whether maternal transmission of mtDNA plays a role in BPD.

5.2 Comorbidity with Mitochondrial Diseases

In 1992, Suomalainen and colleagues presented data on a patient with CPEO with severe depression (Suomalainen et al. 1992). Other affected relatives also had depression. CPEO is clinically defined by detection of multiple deletions of mtDNA or ragged red fibers in muscles. In this patient, however, an autopsy showed an accumulation of mtDNA deletions also in the brain, which suggested that accumulation of mtDNA in the brain may cause mood disorders.

Subsequently, data on a number of patients with mood disorder and mitochondrial disease were reported (Fattal et al. 2006; Kato 2001). More than half the patients with mitochondrial recessive ataxia syndrome (MIRAS) caused by POLG1 mutations had psychiatric symptoms, including depression (Hakonen et al. 2005). Mood disorders are reported in CPEO families caused by three genes: ANT1, Twinkle, and POLG1 (Mancuso et al. 2004; Siciliano et al. 2003; Spelbrink et al. 2001). Those cases are rarely diagnosed by DSM criteria using structured interviews. In a study using DSM-IV criteria, all four patients with CPEO in a pedigree had BPD before the onset of CPEO (Siciliano et al. 2003). A study using a structured interview showed that 17% of the 36 patients with mitochondrial diseases had BPD and 54% had major depression (Fattal et al. 2007). In addition, the mothers of children with mitochondrial diseases more frequently had depression than those of children with other diseases (Boles et al. 2005). These findings suggested that mood disorders can appear as either one of the symptoms of mitochondrial diseases or as a milder, incomplete form of mitochondrial diseases.

5.3 Mechanism of Action of Mood Stabilizers

Because lithium is an alkaline metal ion, its effect on the ion transport system drew attention, and its effect on signal transduction systems was subsequently closely investigated. These studies elucidated lithium's molecular effects. However, lithium has wide-ranging effects. In contrast to other small compounds, it is impossible to produce a derivative that has part of its effects and test efficacy because lithium is a simple ion. Lack of established animal models of BPD have also hampered the study of the mechanism of action of lithium. Thus, it is difficult to conclude which of these effects is indispensable for its clinical action.

Because valproate is also an established mood stabilizer, several studies have focused on the common actions of these two compounds. An especially remarkable discovery was that both mood stabilizers robustly up-regulate Bcl-2, an antiapoptotic protein on the mitochondrial outer membrane (Chen et al. 1999). Recent studies further support that lithium and valproate commonly enhance mitochondrial function and protect against mitochondria-mediated toxicity (Bachmann et al. 2009).

In addition to the effects on mitochondria, both mood stabilizers deplete inositol intracellularly (Hallcher and Sherman 1980), inhibit glycogen synthase kinase-3β

(GSK-3β; Klein and Melton 1996), up-regulate BDNF (Fukumoto et al. 2001), increase Bcl-2 associated athanogene (Bag-1; Zhou et al. 2005), inhibit glutamate receptor trafficking (Du et al. 2003), and activate notch signaling (Higashi et al. 2008). All of these molecular effects may participate in the action of mood stabilizers on neural plasticity, such as neuroprotective effects, enlargement of the growth cone, and increase of neurogenesis (Quiroz et al. 2008). These effects of mood stabilizers further suggest that BPD is associated with cellular vulnerability. Indeed, one study showed that olfactory epithelium derived from patients with BPD was vulnerable to cell death (McCurdy et al. 2006).

5.4 Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a method for in vivo chemical analysis using a clinical MR scanner (Dager et al. 2008). Several nuclei such as ^{31}P, ^{1}H, ^{7}Li, ^{13}C, and ^{19}F have been applied to the study of BPD.

Some early ^{31}P-MRS studies showed decreased phosphomonoester, a precursor of membrane phospholipid in the euthymic state (Kato et al. 1993), decreased phosphocreatine in the depressive state (Kato et al. 1994), and decreased intracellular pH in the euthymic state (Kato et al. 1993). Among these findings, the decrease in phosphomonoester was replicated in another study (Deicken et al. 1995), but other findings were either not tested or not replicated. A proton MRS study showed that lactate was increased in the brain (Dager et al. 2004). Decreased GABA detected by proton MRS was also reported (Bhagwagar et al. 2007). The finding of reduced *N*-acetylaspartate (NAA) in BPD is controversial (Dager et al. 2008). Among these findings, decreased phosphocreatine and accumulation of lactate have been reported in CPEO.

5.5 Mitochondrial DNA Mutations

Based on a report of comorbidity of depression with CPEO, Stine and colleagues searched for mtDNA deletions in the postmortem brains of patients with BPD using Southern blot analysis but found none (Stine et al. 1993). However, a subsequent study using quantitative polymerase chain reaction methods showed that mtDNA deletions had accumulated in two patients with BPD and one patient with major depression, though the accumulated levels were around 0.5%, much smaller than levels seen in the muscles of patients with CPEO (Kato et al. 1997). However, subsequent studies using different brain samples and experimental techniques detected no mtDNA deletions in BPD (Fuke et al. 2008; Kakiuchi et al. 2005; Sabunciyan et al. 2007). Thus, the region of the brain accumulating mtDNA deletions may be only a small part of the mtDNA deletions.

Munakata and colleagues sequenced the whole mtDNA of six patients with BPD having somatic symptoms suggestive of mitochondrial disease and found that one patient had a homoplasmic mutation, 3644C. This was more frequently seen in patients with BPD (Munakata et al. 2004). However, this finding should be investigated in an independent sample set.

5.6 Gene Expression Analysis

Konradi and colleagues performed comprehensive gene expression analysis in the postmortem hippocampus and found that mitochondria-related genes were globally down-regulated in BPD (Konradi et al. 2004). This finding was replicated by other investigators (Iwamoto et al. 2005; Sun et al. 2006; Vawter et al. 2006). Sample pH and agonal factors profoundly affected the expression level of mitochondria-related genes (Li et al. 2004) and, therefore, it was suggested that this finding may be affected by lower pH in the postmortem brains of patients with BPD (Iwamoto et al. 2005; Vawter et al. 2006). Another suggestion was that mitochondria-related genes were up-regulated in patients with BPD compared with pH-matched controls (Iwamoto et al. 2005; Vawter et al. 2006). Despite this controversy, no differences in pH values were found between patients with BPD and controls in the original report. Decreased pH may also reflect the pathology in BPD (Sun et al. 2006). More recently, Rollins and colleagues studied the relationship between mtDNA polymorphisms and pH in postmortem brains and found that brain postmortem pH was associated with a super haplogroup of mtDNA (U, K, UK) (Rollins et al. 2009). This finding is consistent with the hypothesis that the reduced pH seen in some brain samples of patients with BPD might reflect mitochondrial dysfunction.

Munakata and colleagues searched for the mitochondria-related genes significantly altered in patients with BPD and found that LARS2, encoding mitochondrial leucyl tRNA synthase, was significantly up-regulated in the postmortem brains of patients with BPD (Munakata et al. 2005). LARS2 was up-regulated in the hybrid cells carrying the mtDNA 3243G mutation, which impairs aminoacylation of tRNALEUUUR. Thus, the 3243 mutation was quantified in the postmortem brains and was found to be accumulated in two patients with BPD and one patient with schizophrenia (Munakata et al. 2005). These patients carried the same mutation in the liver, suggesting that this is a heteroplasmic mutation distributed throughout the body.

5.7 Animal Models

As noted above, all the findings regarding mitochondrial dysfunction remain inconclusive. This is partly because of technical limitations in clinical studies. To overcome this situation and further study the possible relationship between mtDNA

deletions in the brain and BPD, Kasahara and colleagues generated transgenic mice with neuron-specific expression of mutant POLG1 in which proof-reading activity is removed by a point mutation. The mice accumulated mtDNA deletions in the brain (Kasahara et al. 2006). These mice did not have gross abnormalities in sensorimotor, learning and memory, or emotional functions. The mice had decreased wheel-running activity and altered diurnal activity rhythms such as excessive activity at the beginning of the light phase in 12:12 light and dark condition. Some of transgenic mice showed enhanced activity after treatment with a tricyclic antidepressant. Female transgenic mice also showed periodic alterations in their wheel-running activity, which was improved by lithium treatment. These findings suggested that accumulation of mtDNA deletions in the brain causes behavioral alterations resembling BPD. Electroconvulsive therapy also improved the altered diurnal behavioral rhythms (Kasahara et al. 2008).

As described previously, mitochondria play an important role in calcium regulation and calcium signaling abnormalities have been reported in BPD. To test the possible relationship between mitochondrial dysfunction and calcium signaling abnormalities in BPD, the calcium uptake rate was examined in mitochondria isolated from the brains of the transgenic mice. Contrary to expectations, the calcium uptake rate was enhanced in the transgenic mice. The cytosolic calcium response to G protein-coupled receptor agonist stimulation was diminished in hippocampal slices of the transgenic mice (Kubota et al. 2006).

Gene expression analysis was performed to search for the molecular basis of this finding. Down-regulation of cyclophilin D was observed. Pharmacologic inhibition of cyclophilin D mimicked the finding in the transgenic mice, suggesting that reduced cyclophilin D is a cause of altered calcium signaling in the transgenic mice (Kubota et al. 2006).

As described above, up-regulation of Bcl-2 may be involved in the clinical effects of mood stabilizers. Bcl-2 heterozygous knockout mice showed increased anxiety-related behaviors (Einat et al. 2005), as well as reward seeking and amphetamine sensitization (Lien et al. 2008). The sensitization was attenuated by lithium treatment. Finally, environmental factors might also affect mitochondrial function. For instance, it was reported that chronic mild stress inhibited the mitochondrial respiratory chain (Rezin et al. 2008).

6 Future Directions

Mounting evidence supports the relationship between mitochondria and BPD. However, detailed data are not always concordant. Thus, further studies are needed to ascertain whether mitochondrial dysfunction is involved in the patho
physiology of BPD.

In addition, it should be noted that mitochondrial dysfunction is not at all specific to BPD because mitochondrial dysfunction is commonly implicated in many neurodegenerative disorders (Schapira 2008). In other words, BPD does share a common

pathophysiologic pathway with neurodegenerative disorders, not only with schizophrenia. In the case of Parkinson's disease, substantia nigra neurons are susceptible to cellular insult because synthesis of dopamine causes oxidative stress. In BPD, the characteristic course is well known; the interval between the episodes shortens with progression of the illness. This has been interpreted as reflecting kindling or behavioral sensitization (Post and Weiss 1989). However, based on the mounting data on mitochondrial dysfunction in BPD, it would be reasonable to assume that neurons regulating mood are progressively impaired during the course of BPD. It will be important to clarify which neural systems are impaired by mitochondrial dysfunction in BPD.

The next phase of research on the mitochondrial dysfunction hypothesis in BPD will require more detailed analyses to characterize the mitochondrial dysfunction and to identify the neural systems responsible for BPD.

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Neuroimaging and Neuropathological Findings in Bipolar Disorder

Jonathan Savitz and Wayne C. Drevets

Contents

Abstract Bipolar disorder (BPD) is increasingly recognized as a neuropathological disorder characterized by reductions in grey matter (GM) volume, as measured by magnetic resonance imaging (MRI) and neuronal and postmortem glial cell changes. Here, we use an anatomical framework to discuss the neurobiology of BPD, focusing on individual components of the "visceromotor network" that regulates bodily homeostasis along with neurophysiological and neuroendocrine responses to stress. MRI-defined reductions in GM volume, combined with neuronal changes, are observed in the perigenual anterior cingulate cortex (ACC) of individuals with BPD, while postmortem glial cell loss is also a characteristic of Brodmann's Area 9. Both postmortem neuronal loss and reduced GM volume have

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been reported in the amygdala and hippocampus. These structural changes to components of the visceromotor network are associated with increased regional cerebral blood flow (rCBF) or blood oxygenated level-dependent (BOLD) activity in response to affective or rewarding stimuli, raising the possibility that the BPD-associated structural changes are secondary to a glutamate-driven excitotoxic process.

Keywords Amygdala · Anterior cingulate cortex · Bipolar disorder · Hippocampus · MRI · Neuropathology · Postmortem

1 Introduction

Extant data suggest that bipolar disorder (BPD) results from dysfunction of a "visceromotor network" that consists of portions of the orbital and medial prefrontal cortex (mPFC) and its efferent and afferent connections to structures that regulate bodily homeostasis and, by extension, neurophysiological and neuroendocrine responses to stress. These regions include portions of the orbital frontal cortex (OFC), anterior insula, anterior cingulate cortex (ACC), ventral striatum, mediodorsal and periventricular nuclei of the thalamus, amygdala, hippocampus, hypothalamus, and brain-stem nuclei (Price and Drevets 2010; Savitz and Drevets 2009). In this chapter, we use this anatomical framework (Fig.1) to present the neuropathology and neuroimaging data obtained from studies of BPD.

The phylogenetically old ACC, part of the mPFC, carries out a diverse array of largely integrative functions. It is often heuristically divided into dorsal "cognitive" and ventral "affective" streams. The dorsal ACC (dACC) lies along the superior portion of the cingulate gyrus running dorsal to the corpus callosum (CC), while the regions ventral and/or rostral to the genu of the CC compose the ventral ACC. The dACC forms part of an "executive" attention system that supports response selection, error detection, and performance monitoring, while the ventral ACC regulates emotional and visceromotor responses.

2 The Subgenual ACC

Drevets and colleagues first demonstrated a reduction in grey matter (GM) volume, cerebral blood flow (CBF), and glucose metabolism in the mPFC ventral to the CC genu ("subgenual" ACC) in patients with BPD and major depressive disorder (MDD) (Drevets et al. 1997). The finding of reduced GM has since been replicated by a number of independent groups and appears to apply to both males and females, individuals scanned early in the course of illness, as well as patients with affective psychosis and bipolar spectrum illness (reviewed in Drevets et al. 2008).

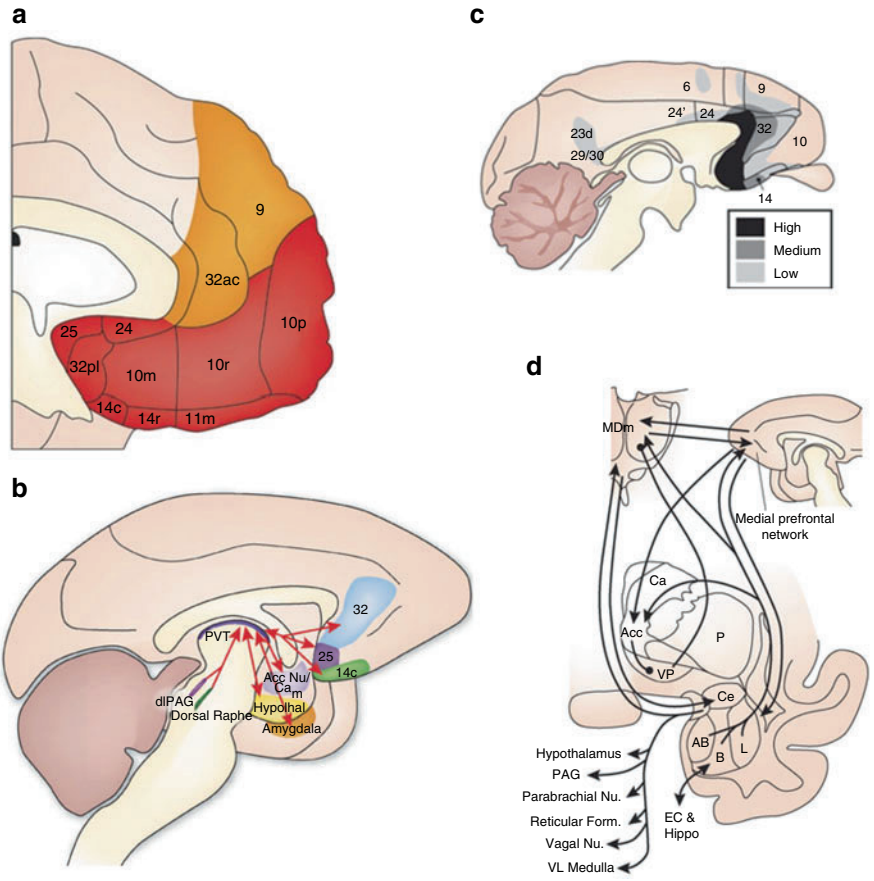

Fig. 1 (**a**) Cytoarchitectonic subdivisions of the human medial prefrontal cortex. The *light gray color* represents medial components, and the *gray color* represents dorsal components of the system. (**b**) Connections between the medial prefrontal cortex, paraventricular nucleus of the thalamus, and other limbic structures making up the visceromotor network. *Acc Nu* nucleus accumbens, *dlPAG* dorsolateral column of the periaqueductal gray, *Hypothal* hypothalamus, *PVT* paraventricular nucleus of the thalamus. (**c**). Sagittal view of medial prefrontal cortex regions that receive projections from the amygdala. The *black color* represents the greatest density of amygdala inputs, and the *light gray* represents the lowest density of amygdala connections. (**d**) View of the amygdala displaying its connections with the medial prefrontal cortex, entorhinal cortex, hippocampus, and brain-stem nuclei. *AB* accessory basal nucleus of the amygdala, *ACC* anterior cingulate cortex, *B* basal amygdaloid nucleus, *Ca* caudate nucleus, *Ce* central amygdaloid nucleus, *EC* entorhinal cortex, *Hippo* hippocampus, *L* lateral amygdaloid nucleus, *MDm* mediodorsal nucleus of the thalamus, *Nu* nucleus, *P* putamen, *PAG* periaqueductal gray, *VL* ventrolateral, *VP* ventral pallidum [adapted from Price and Drevets (2010)]

Furthermore, chronic lithium treatment, which exerts robust neurotrophic effects in animal models (Moore et al. 2000), largely normalizes subgenual ACC (sgACC) volume in treatment responders (Moore et al. 2009). Nevertheless, the data are not

entirely consistent. For example, a recent study that controlled for the effects of individual variation in gyral morphology reported increased cortical thickness (but not volume) in the right sgACC in first episode, male patients with BPD (Fornito et al. 2009).

Consistent with the weight of the volumetric imaging data, a reduction in the number of glial cells together with an increase in neuronal density in the sgACC of patients with familial BPD and MDD was found by Ongur et al. (1998). The reported reduction in glial cells is congruent with a number of diffusion tensor imaging (DTI) studies showing structural abnormalities of white matter (WM) tracts connecting the subcallosal gyrus with limbic nuclei. One study reported a decrease in fractional anisotropy (FA) of the anterior cingulum, which the authors suggested might indicate a loss of structural integrity of the WM in this region (Wang et al. 2008). The same group later reported that a region they described as "perigenual," which excluded the dorsal regions of the ACC, displayed decreased coupling with the amygdala during the processing of sad and happy faces (Wang et al. 2009a,b). Furthermore, the strength of the connectivity between the amygdala and perigenual ACC was found to correlate with the structural integrity of WM fibers as measured by DTI (Wang et al. 2009a,b). These data corroborate findings from two other studies reporting a greater number of reconstructed fibers (Houenou et al. 2007) and increased FA (Versace et al. 2008) in the left uncinate fasciculus, which connects the medial-orbital cortex and sgACC with the lateral amygdala and hippocampus. The latter study also found reduced FA in the right uncinate fasciculus in individuals with BPD, suggesting an imbalance in left versus right hemisphere processing of emotion (Versace et al. 2008). Other studies similarly found reduced FA in the uncinate fasciculus of BPD patients (McIntosh et al. 2008a,b; Sussmann et al. 2009) as well as increased apparent diffusion coefficient (ADC), a measure of water mobility, in both the left and right sgACC in adolescents with BPD (Kafantaris et al. 2009).

In contrast to the findings of Ongur and colleagues described above, Bouras and colleagues reported that autopsied individuals with sporadic BPD displayed significantly reduced cortical thickness and neuronal density (15–20%) in layers III, V, and VI of the left sgACC (Bouras et al. 2001). Methodological limitations prevented the analysis of individual neuron volume or total neuron numbers. Nevertheless, immunocytochemical analysis showed decreased levels of the microtubule-associated proteins MAP1B and MAP2, which may indicate dendritic or axonal atrophy (Bouras et al. 2001). These data are supported by magnetic resonance spectroscopy (MRS) studies which found that higher levels of *N*-acetylaspartate (NAA), a marker of neuronal integrity, in the sgACC are associated with lithium treatment (Moore and Galloway 2002; Forester et al. 2008), potentially consistent with the neurotrophic effects associated with chronic lithium administration in preclinical studies.

After controlling for the effects of GM volume reduction of the sgACC, which leads to erroneous attenuation of neurophysiological activity during PET data analysis (the partial voluming effect resulting from PET's relatively low spatial

resolution), the literature suggests increased neurophysiological activity of the sgACC, which decreases after treatment response (reviewed in Drevets et al. 2008). Similarly, increased hemodynamic activity of the sgACC is induced by a variety of functional imaging paradigms, including artificial stimulation of sadness (George et al. 1995; Mayberg et al. 1999), exposure to traumatic reminders, selecting sad or happy targets in an emotional go/no-go study (Elliott et al. 2000), and extinction learning to previously fear-conditioned stimuli (Phelps et al. 2004).

The sgACC shares cytoarchitectural similarities with the ACC situated anterior to the CC genu (i.e., "pregenual" or rostral ACC), suggesting that distinctions of the cortex at the actual sgACC/pgACC interface are arbitrary. Nevertheless, because the rostral ACC (rACC) and sgACC are often discussed separately in the literature, we will follow this framework here.

3 The Rostral ACC

Fornito and colleagues reported reduced volume of the left paracingulate gyrus in the rACC in individuals with BPD compared with healthy controls (Fornito et al. 2008). Similarly, Matsuo and colleagues found an inverse relationship between volume of the left rACC and a psychometric measure of impulsivity (Matsuo et al. 2009). In another study, adolescents with BPD, who were scanned at baseline and again 2 years later, had greater volume reductions in the left rACC than healthy controls (Kalmar et al. 2009a,b). Consistent with these data, Anand and colleagues detected reduced resting state activity between the rACC and the amygdala and dosomedial thalamus in a sample of patients with BPD (Anand et al. 2009).

The volumetric changes in the rACC may also apply to people at risk for BPD. One study noted that volume reduction in the right "perigenual" ACC region that included both the sgACC and the rACC was associated with increasing genetic risk for BPD (McDonald et al. 2004). Other investigators similarly reported that this region was reduced in volume in a sample of boys with subclinical depression (Boes et al. 2008).

Less functional imaging data are available in the literature. Mah and colleagues found increased resting state metabolism of the right rACC in lithium-treated patients with BPD-II (Mah et al. 2007), and sadness induction was associated in at least one study with increased regional cerebral blood flow (rCBF) to the rACC in patients with BPD (Kruger et al. 2006). In contrast, decreased hemodynamic activity of the rACC in response to emotionally valenced faces has also been found (Blumberg et al. 2005).

With regard to cognitive imaging paradigms, a recent study reported that remitted patients with BPD showed greater activation of the rACC (−10; 38; 12) during a delayed non-match to sample working memory task than the control group

(Robinson et al. 2009). The rACC had previously been shown to be overactivated during decision making in mania (Rubinsztein et al. 2001).

Benes and colleagues performed neuropathological studies on tissue at the level of the rostrum of the ACC between the points at which the gyrus curves above and below the CC. Neuronal terminals immunoreactive to glutamic acid decarboxylase (GAD_{65}) were found to be decreased in the upper cortical layers of the rACC in a BPD sample (Benes et al. 2000). Because GABAergic interneurons have a non-pyramidal shape, this finding is congruent with the reported decrease in neuronal density of non-pyramidal cells in the rACC (Benes et al. 2001a,b).

Follow-up studies by the same group using in situ hybridization confirmed their hypothesis that BPD-associated abnormalities in the rACC appear to be specific to GABAergic cells. Woo and colleagues reported a 35% decrease in neuronal density of GABAergic cells expressing the NR2A subunit of the NMDA receptor in layer 2 of the rACC (Woo et al. 2004), although this was not confirmed in a more recent study (Woo et al. 2008a,b). In an independent sample, the density of GABAergic neurons that express the GluR5 subunit of the kainate receptor was decreased by 40% in layer 2 of the rACC in BPD (Woo et al. 2007). In contrast, a decrease in mRNA expression of GAD_{67} in BA 24 at the level of the genu in patients with schizophrenia, but not BPD, has also been reported (Thompson et al. 2009).

The hypofunction of NMDA and kainate receptors found on GABAergic interneurons may not only disrupt information processing, but the disinhibition of local pyramidal neurons may render regions that receive input from these neurons vulnerable to glutamate-driven excitotoxicity (Olney et al. 1999; Woo et al. 2004, 2007). Consistent with this hypothesis, elevated excitatory amino acid signature in BPD has also been reported, as measured by MRS (Frye et al. 2007). Specifically, increased levels of creatine, glutamate, and GLX (the sum of glutamate and glutamine) were observed in a voxel that included the pgACC, as well as parts of the anterior midcingulate cortex, and mPFC. Nevertheless, the hypofunction may not only be a consequence of neuronal cell loss but also decreased gene expression of NMDA and kainate receptor subunits.

Woo and colleagues raised the possibility that the hypofunction of NMDA and kainate receptors found on GABAergic interneurons was at least partly a compensatory response to the elevated glutamatergic inputs received from the basolateral amygdala rather than neuronal cell loss (Woo et al. 2007). This hypothesis is supported by an evidence for increased BPD-associated DNA fragmentation, suggesting apoptotic damage in *non-GABAergic*, rather than GABAergic cells of layers V and VI of the pgACC (Buttner et al. 2007).

Higher MRS glutamine–glutamate (GLN/GLU) ratio in the rACC of manic patients has also been detected (Ongur et al. 2008). Because glutamate is converted to glutamine in glial cells, and glutamine is converted to glutamate in neurons, the authors interpreted their data to suggest a breakdown in neuronal–glial cell interactions. Thus, glial cell pathology and loss of GABAergic neurons could account for the altered receptor expression observed on GABAergic neurons of the pgACC.

4 The Dorsal ACC

Decreased volume of the left dACC was recorded in one voxel-based morphometry (VBM) MRI study of BPD (Yatham et al. 2007), while reduced hemodynamic activity of the dACC in euthymic BPD patients during the performance of working memory tasks has been reported in a number of studies (Monks et al. 2004; Lagopoulos et al. 2007). However, other investigators have reported that patients with BPD displayed overactivation of the dACC when performing cognitive tasks in the face of an emotional distractor (Wessa et al. 2007; Deckersbach et al. 2008). One hypothesis is that a dysfunction of the dACC impairs the individual's ability to integrate cognitive and emotional stimuli, and that the increased BOLD response to the emotional distractor is compensatory in nature.

The neurophysiological basis of this mal-integrative effect is unclear. Chana and colleagues detected a BPD-associated decrease in neuronal somal size together with an increase in neuronal density in the deeper layers of BA 24 dorsal to the genu (Chana et al. 2003); no changes in glial cells were found. The decrease in neuronal size was interpreted by the authors to reflect a loss of neuropil, particularly of the larger pyramidal neurons (Chana et al. 2003). Eastwood and Harrison reported decreased expression of three synaptic proteins – synaptophysin, growth-associated protein-43 (GAP-43), and complexin 2 – in the dACC (BA24) of individuals with BPD, suggesting reduced synaptic density and plasticity, particularly at excitatory synapses where complexin 2 is differentially expressed (Eastwood and Harrison 2001).

In the same series of brains that had demonstrated glial cell reduction in the sgACC, no significant neuronal cell size, glial cell density, or neuronal density changes were found in BA 24b (Cotter et al. 2001). Nonetheless, a follow-up study showed that the density of calbindin-expressing GABAergic neurons in layer II of the supracallosal gyrus was reduced by 33% in BPD (Cotter et al. 2002). Another study found decreased levels of glial fibrillary acidic protein (GFAP), a cytoskeletal marker of astroglia, in the WM of the supracallosal gyrus (BA 24) of subjects with BPD (Webster et al. 2005). A trend in the same direction was found in the GM, and was most pronounced in layer VI. An earlier study had previously reported reduced GFAP expression in a homogenized frontal lobe sample from subjects with BPD (Johnston-Wilson et al. 2000).

The decreased levels of GFAP could be considered consistent with a DTI analysis that reported decreased FA in the anterior portions of the fronto-occipital fasciculus and superior longitudinal fasciculus extending to the genu of the CC (Chaddock et al. 2009). Furthermore, in this study, genetic liability to BPD among healthy relatives was negatively correlated with FA scores in these deep frontal WM tracts. A recent study found an increase in neurons situated within the WM ventral to the dACC in 25% of a postmortem BPD sample (Connor et al. 2009).

Increased oxidative stress induced by mitochondrial dysfunction is one proposed mechanism for the hypothesized neuronal and glial cell changes in BPD. The degree of oxidative stress measured by the metabolite 4-HNE was found to be

elevated in the supracallosal gyrus in a postmortem sample of patients with BPD (Wang et al. 2009a,b).

5 The Orbital frontal Cortex

The OFC receives inputs from limbic structures such as the ventrolateral amygdala, entorhinal cortex, and the hippocampal subiculum, although the density of such projections within the OFC is highest for the OFC areas that form part of the visceromotor network (Price 1999). The OFC also projects to the amygdala, hypothalamus, and brain stem, modulating limbic-driven behavior (Ongur and Price 2000).

GM volume reductions in the OFC have been reported in adult (Frangou 2005; Haznedar et al. 2005; Lyoo et al. 2006; Nugent et al. 2006) and pediatric BPD samples (Wilke et al. 2004; Najt et al. 2007) together with reduced activity during attentional control paradigms, such as the non-emotional Stroop color-word task (reviewed in Savitz and Drevets 2009).

One study failed to find a BPD-associated change in neuronal density or neuronal size although reductions in size and density were reported in individuals with schizophrenia and MDD samples (Cotter et al. 2000). However, a later study by the same group reported decreased neuronal size (21%) in layer 1 of the caudal OFC in patients with BPD (Cotter et al. 2005). No change in neuronal density or glial cell size or density was detected in this region.

Gos and colleagues provided evidence for increased functional activity of pyramidal neurons of layers V and VI of the medial orbital gyrus in a postmortem sample of individuals with MDD and BPD (Gos et al. 2009). However, another study found no changes in the expression of the NR1 subunit of the NMDA receptor in BA 11 (Toro and Deakin 2005). Thompson and colleagues reported a 30–50% decrease in GAD_{67} mRNA expression in layers II through IV of BA 45 (Thompson et al. 2009). Congruent with these data, another study found reduced NAA and choline concentrations in the OFC of a BPD sample (Cecil et al. 2002).

Using DTI, Beyer and colleagues reported increased ADC values in the WM of the OFC, bilaterally (Beyer et al. 2005). This finding has recently been extended to pediatric samples, where reduced microstructural integrity of the WM of the left OFC has been detected in children with BPD (Frazier et al. 2007); a partial replication was achieved in an adolescent BPD sample that provided evidence for reduced WM integrity of the right OFC (Kafantaris et al. 2009).

6 BA 9 of the Dorsolateral Prefrontal Cortex

The dorsolateral prefrontal cortex (DLPFC) extends across nearly one-fourth of the human cerebral cortex. In this chapter, we have therefore chosen to focus on BA9, an important constituent of the viscero-motor network with projections to the

mPFC regions that form the visceromotor network, the amygdala (Price and Drevets 2010), and the PAG (An et al. 1998) (Fig.1c).

Brain imaging studies tend to focus on the DLPFC as a whole rather than on BA9 in isolation. Some studies have reported GM volume reductions of a large area of the DLPFC (BA 8, 9, 45, and 46) in medicated and remitted BPD-I patients, and partially medicated, "stable" BPD-spectrum individuals, respectively (Frangou 2005; Haznedar et al. 2005). Nevertheless, more circumscribed volume reductions in BA 9 have been reported in a medicated, euthymic pediatric sample (Dickstein et al. 2005). The role of mood state is unclear. In contrast to those studies reporting volume reductions in the DLPFC in euthymic patients (Frangou 2005; Haznedar et al. 2005), a recent VBM analysis showed that depressed but not euthymic subjects with BPD who were unmedicated for at least 2 weeks before scanning had reduced GM in the dorsomedial (BA 9/10, bilaterally) and right DLPFC (BA 9/46) (Brooks et al. 2009a,b). The same group also found that resting metabolic rate as measured by ^{18}F-FDG PET was reduced in the broader DLPFC region (BA 9, 10, and 46) in medicated patients with BPD (Brooks et al. 2009a,b). Moreover, investigators found that during cognitive-emotional processing, individuals with bipolar depression showed a blunted BOLD response in BA 9 of the right hemisphere when matching the emotional expression of one face with another; the authors suggested that this finding may reflect a deficient activation of structures subserving working memory (Altshuler et al. 2008).

Postmortem studies generally indicate a decrease in both neuronal and glial cell density. Rajkowska and colleagues detected a decrease of 20–30% in the density of pyramidal neurons in layers IIIa–c of BA 9 in a postmortem BPD sample (Rajkowska et al. 2001), while the density of GAD_{67} mRNA-containing (GABAergic) neurons in layers II–V of BA 9 was decreased by approximately 25–33% in BPD (Woo et al. 2008a,b). These data are supported by a meta-analysis showing reduced density of calbindin-expressing neurons in layer VI of BA 9 (Kim and Webster 2010). Another study reported a 28% reduction in the density of neurons in layer IV of BA 9 in BPD samples, although this reduction did not appear to be specific to calcium-binding protein expressing neurons (Sakai et al. 2008).

Some studies have reported a BPD-associated decrease in neuronal size rather than density. A decrease in neuronal size might signify a reduction in the neuritic processes supported by that cell. One study reported that neuronal, but not glial, cell size was reduced by 14% and 18% in layers V and VI, respectively, of BA 9 in a postmortem BPD sample (Cotter et al. 2000); a meta-analysis of Stanley Foundation cytoarchitectural data suggested a decrease in the size of pyramidal neurons in layer III of BA 9 (Kim and Webster 2010).

Rajkowska and colleagues found evidence for a decrease in the density (16–22%) of glial cells in layer III of BA 9 in conjunction with glial cell enlargement (Rajkowska et al. 2001). The glial cell density showed a nonsignificant trend toward being reduced in layers II and V. Another study similarly found reduced numbers of oligodendroglia, which can be found in close proximity to neurons, in layer VI of BA 9 (Uranova et al. 2004). A more recent study reported a decrease in neuronal

size in layer IIIc of BA 9 as well as reduced numbers of perineuronal oligodendrocytes in layers IIIa, IIIb, and IIIc of BA 9 (Vostrikov et al. 2007).

A significant number of studies have also reported abnormal increases or decreases in mRNA levels or protein products expressed by various neuronal subtypes. Whether these putative changes are related to the structural changes reported above or whether they result from functional changes in gene expression is, as yet, unclear.

Certainly, the postmortem evidence for glial cell abnormalities is at least consistent with a quantitative PCR analysis of BA 9 tissue that demonstrated significant reductions in mRNA expression of key protein markers of myelination and oligodendrocyte function (Tkachev et al. 2003). Expression of proteolipid protein 1 (PLP1), myelin-associated glycoprotein (MAG), oligodendrocyte-specific protein (CLDN11), myelin oligodendrocyte glycoprotein (MOG), and transferrin (TF) was reduced by approximately two- to fourfold in BPD patients (Tkachev et al. 2003). Furthermore, expression of the OLIG2 and SOX10 genes that code for transcription factors important in oligodendrocyte differentiation and maturation was downregulated by two- to threefold in BPD. Although this decrease in oligodendrocyte-related gene expression could result from cell loss, not all oligodendrocyte-related genes were found to be downregulated (Tkachev et al. 2003), leading the authors to postulate that their results are more consistent with cellular dysfunction than cellular destruction.

Reduced myelination of the deep WM in a region encompassing BA 9 and BA 46 was found in another postmortem BPD sample (Regenold et al. 2007). In addition, the level of the creatine kinase B isoform, which is preferentially expressed in oligodendrocytes and astroglia, was reportedly reduced in BPD (MacDonald et al. 2006). Because creatine kinase generates ATP and creatine from high energy phosphates such as phosphocreatine, these data provide further evidence for glial cell dysfunction and may reflect the aforementioned reduction in oligodendroglia (MacDonald et al. 2006). A BPD-associated decrease in creatine and phosphocreatine was also reported in an MRS study of a voxel that encompassed parts of BA 9 in the left DLPFC (Frey et al. 2007).

Oligodendrocytes are also involved in the turnover of NAA. An MRS study found that males with BPD had reduced NAA concentration in the right DLPFC (BA 8, 9, 10, and 46) compared with healthy controls (Molina et al. 2007). Similar findings had previously been reported in pediatric BPD, with both left and right hemispheres implicated (Chang et al. 2003; Sassi et al. 2005; Olvera et al. 2007).

With regard to neuron-specific gene expression changes, a quantitative polymerase chain reaction (qPCR) analysis of pyramidal cells dissected from the ventral and dorsal banks of the principle sulcus of the DLPFC yielded evidence of increased expression of the AMPA receptor subunit GRIA1 in layer V of samples from subjects with BPD and schizophrenia (O'Connor and Hemby 2007). The authors interpreted their data to suggest hyperexcitability of pyramidal neurons through the increased activity of non-NMDA receptors. On the other hand, Beneyto and Meador-Woodruff reported decreased expression of the GluR2 and GluR4 AMPA receptor subunits in layers II, V, and VI in patients with BPD, although without a

concomitant change in AMPA receptor binding (Beneyto and Meador-Woodruff 2006). Decreased mRNA and protein levels of G-protein subunits, as well as the protein level of G-protein receptor kinase 3 (GRK3), were found in the membrane (but not cytosol) of BA9 in BPD (Rao et al. 2009).

Decreased reelin and GAD_{67} expression in BA 9 was found in a real-time PCR study (Guidotti et al. 2000). Interestingly, these findings only held for the BPD subgroup with psychosis. Because other proteins expressed by GABAergic neurons such as GAD_{65} and DAB1 were not significantly decreased in this BPD sample, the authors hypothesized that the decrease in reelin and GAD_{67} expression was a consequence of changes in gene expression rather than neuronal loss, per se. The decrease in GAD_{67} mRNA-expressing GABAergic neurons in BA 9 was replicated in a BPD sample with a history of psychosis, and may be due to hypermethylation of the GAD gene promoter by DNA methyltransferase 1 (Veldic et al. 2005).

A proteomic analysis of BA 9 from postmortem BPD tissue yielded evidence for altered expression of three proteins (STXBP1, BASP1, and LAMB) involved in synaptic function and neuronal plasticity (Behan et al. 2009). Insulin-like growth factor-binding protein 2 (IGFBP2) was decreased by 34% in unmedicated BPD patients in an anatomical region encompassing BA 9 and BA 42 (Bezchlibnyk et al. 2007a,b). Cytoskeletal and mitochondrial protein expression abnormalities have also been detected in postmortem BPD samples (Beasley et al. 2006). Pennington and colleagues carried out a proteomic analysis of BA 9 tissue from postmortem samples and found 51 proteins that were abnormally expressed in BPD (Pennington et al. 2008). Of these 51 proteins, 25 were involved in energy metabolism or mitochondrial function, and 15 were cytoskeletal or synapse-associated. A number of synaptic proteins such as SNAP-25, DISC1, 14-3-3 gamma, and complexins 1 and 2 have been implicated in NMDA receptor function (Pennington et al. 2008). Apolipoprotein E, which appears to play a diverse role in intracellular and extracellular signaling, has also been reported to be elevated in patients with schizophrenia and BPD with psychosis (Digney et al. 2005), although how this finding translates to pathophysiology remains unknown.

7 The Insula

There is little research investigating insula abnormalities in BPD. Structural MRI studies have reported both increased (Lochhead et al. 2004) and decreased (Haldane et al. 2008; Janssen et al. 2008) GM volume of the insula in patients with BPD, while increased GM volume of the left insula has been suggested to be a marker for genetic predisposition to mood disorders (Kempton et al. 2009). Increased metabolism of the insula has also been reported in depressed BPD samples (Brooks et al. 2009a,b). In addition, some studies have reported an abnormally elevated BOLD signal in the insula during the viewing of negatively valenced pictures, and inhibition of emotionally distracting stimuli, in individuals with BPD (Chang et al. 2004; Wessa et al. 2007).

8 The Thalamus

Both increased (Strakowski et al. 1999; Lochhead et al. 2004; Wilke et al. 2004; Adler et al. 2007) and decreased (McIntosh et al. 2004; Frangou 2005) thalamic GM volume has been reported in BPD. The reduction in volume may also hold for patients with cyclothymia (Haznedar et al. 2005). Nevertheless, most findings are negative (Ng et al. 2009), suggesting that any true structural change is either subtle or specific to particular thalamic nuclei.

Ketter and colleagues first reported increased resting glucose metabolism in the mediodorsal and pulvinar thalamic nuclei of their BPD sample (Ketter et al. 2001). Subsequent fMRI studies provided evidence of abnormally elevated activity of the thalamus in response to both cognitive (Blumberg et al. 2003; Caligiuri et al. 2003; Chang et al. 2004) and emotional (Chang et al. 2004; Malhi et al. 2004) stimuli, although the resolution of these scans did not allow evaluation of individual thalamic nuclei.

Although at least one MRS study reported increased thalamic GLX and lactate in BPD (Dager et al. 2004), no difference in NAA levels were found in this (Dager et al. 2004) and other patient samples (Bertolino et al. 2003; Blasi et al. 2004; Port et al. 2008; Scherk et al. 2008). Consistent with these data, no difference in neuron number in the mediodorsal and anteroventral/anteromedial thalamic nuclei (Young et al. 2004) and in $GAD_{65/67}$ expression in the mediodorsal thalamus was present postmortem (Bielau et al. 2007). Nevertheless, a reduction in gross thalamic volume in BPD patients was also reported (Bielau et al. 2005), as was reduced thalamic mRNA expression of PSD-95 and SAP-102, two proteins that play an important role in postsynaptic NMDA function (Clinton and Meador-Woodruff 2004). On the other hand, Young and colleagues reported that a mixed group of BPD and psychiatric patients homozygous for the short (putative risk) allele of the serotonin transporter insertion/deletion polymorphism displayed a 20% increase in neuron number within the pulvinar nucleus (Young et al. 2007). DTI analyses have provided some evidence for reduced integrity of peri-thalamic WM tracts (Haznedar et al. 2005; Barnea-Goraly et al. 2009; Mahon et al. 2009), but to our knowledge no postmortem studies have described glial cell changes in the thalamus of patients with BPD.

9 The Striatum

Functional imaging studies suggest increased striatal activity during the performance of both reward and non-reward tasks. Interestingly, this effect seems to hold for depressed (Ketter et al. 2001; Bauer et al. 2005; Dunn et al. 2002; Mah et al. 2007; Brooks et al. 2009a,b), euthymic (Wessa et al. 2007; Hassel et al. 2008; McIntosh et al. 2008a,b), and manic, or hypomanic samples (Blumberg et al. 2000; Caligiuri et al. 2003, 2006; Abler et al. 2008). The data thus suggest that a generalized, context-inappropriate activation of the reward system exists in BPD.

Structural MRI studies have reported striatal enlargement in adult (Aylward et al. 1994; Noga et al. 2001; Strakowski et al. 2002) and pediatric (DelBello et al. 2004; Wilke et al. 2004; Ahn et al. 2007; Frazier et al. 2008) BPD samples, although these data may be confounded by the neurotrophic effects of mood stabilizers such as lithium or antipsychotic medications. One discrepant finding was reported by Geller and colleagues, who found that in children with BPD, exposure to a greater number of negative life events was associated with smaller nucleus accumbens volume (Geller et al. 2009).

Consistent with this report, another study found a 32% reduction in the volume of left nucleus accumbens in postmortem BPD (Baumann et al. 1999), and a later study by the same group found reduced gross volume of the putamen (Bielau et al. 2005). The cell types responsible for this putative volume loss are unclear. No significant changes in the expression of striatal NMDA, AMPA, or kainate receptors in BPD subjects were reported in two other studies (Meador-Woodruff et al. 2001; Noga and Wang 2002). However, Kristiansen and Meador-Woodruff discovered reduced mRNA expression of PSD-95 and SAP102, two proteins that interact with the NMDA receptors to facilitate cell signaling (Kristiansen and Meador-Woodruff 2005). There is also preliminary evidence for a disruption to GABAergic signaling in the striatum, with GAD_{67} mRNA levels reportedly reduced in the caudate and nucleus accumbens, but not putamen, of BPD subjects compared with healthy control samples (Thompson et al. 2009). Signs of necrosis or apoptosis-related damage to oligodendrocyte cells in the caudate have also been reported (Uranova et al. 2001).

10 The Hippocampus

Prolonged prenatal and adult stress in primates, rodents, and tree shrews leads to selective hippocampal damage including apoptosis, depressed long-term potentiation (LTP), and neurogenesis, as well as apical dendritic atrophy (Uno et al. 1989; Sapolsky et al. 1990; Watanabe et al. 1992; Magarinos et al. 1996; Czeh et al. 2001). Whether a corresponding stress-induced excitotoxic process occurs in humans with BPD is unclear, but is not inconsistent with the postmortem and neuroimaging data.

A reduction in non-pyramidal neurons of CA2 (but not other hippocampal layers), concomitant with an increase in the density of $GABA_A$ receptors, was reported in a small ($N = 4$) BPD sample (Benes et al. 1998). The same group later reported decreased density of GAD mRNA expressing neurons in CA2/3 and CA4, as well as the dentate gyrus (Heckers et al. 2002). More recently, decreased density of GABAergic neurons in the stratum oriens (SO) of CA2/3 was reported (Benes et al. 2007). Fatemi and colleagues found that the CA4 region of the hippocampus was decreased by 39% in BPD, and after correcting for area, their immunohistochemistry analysis showed decreased density of reelin-expressing neurons in CA4 in the BPD group compared with healthy controls (Fatemi et al. 2000). Reelin is

expressed and released on cortical GABAergic neurons and plays an important role in cell positioning and migration during development. Congruent with these data, a meta-analysis of the Stanley Foundation dataset revealed a reduction in the number and density of parvalbumin-containing neurons (inhibitory interneurons) in CA2 of the hippocampus in BPD (Knable et al. 2004).

The alteration in structure or function of the GABAergic system may extend to other regions of the hippocampus. Pantazopoulos et al. (2007) detected a decrease in both the total number and the density of inhibitory, GABAergic neurons in the superficial layers of the entorhinal cortex of a BPD sample. On the other hand, other studies found no change in immunoreactive GAD cells in the hippocampus (Bielau et al. 2007) and mRNA levels of fibroblast growth factor (a neurotrophin that plays a role in development) (Gaughran et al. 2006).

Reduced mRNA levels of complexins 1 and 2, which are expressed in inhibitory and excitatory hippocampal neurons, respectively, were detected in the subiculum, CA4, and parahippocampal gyrus of the hippocampal formation (Eastwood and Harrison 2000). Because complexins are synaptic proteins, the authors suggested that their data might indicate reduced synaptic terminal density in BPD. On the other hand, hippocampal expression of synaptophysin, a marker of synaptic density, was unchanged in another BPD sample (Vawter et al. 1999). However, in this study, the ratio of two isoforms of neural cell adhesion molecule (N-CAD) was altered in the hippocampus of individuals with BPD compared to controls (Vawter et al. 1999). N-CAD is believed to play an important role in neurodevelopment as well as neuroplasticity in adults, and thus the altered N-CAD ratio in BPD may indicate abnormal synaptic plasticity (Vawter et al. 1999).

Law and Deakin initially reported that mRNA expression of the NR1 NMDA receptor subunit was decreased bilaterally in the dentate gyrus and CA3 (Law and Deakin 2001). The same group later reported that the postsynaptic density protein PSD-95, which plays a role in the coordination of NMDA receptor signaling, was reduced in the molecular layer of the dentate gyrus of postmortem BPD samples (Toro and Deakin 2005). The previously reported decrease in NR1 receptor levels was not, however, replicated (Toro and Deakin 2005). Nevertheless, the BPD-associated decrease in NR1 expression was replicated; in that study, the authors also found decreased expression of NR2A, as well as the NMDA-associated protein SAP102 in CA1–CA4 and the dentate gyrus (McCullumsmith et al. 2007). SAP102 mediates NR2B-containing NMDA receptor trafficking, possibly indicating more widespread changes in the composition of NMDA receptors (McCullumsmith et al. 2007). A more recent study by the same group reported decreased expression of NR1 and NR2B in the perirhinal cortex, but not the entorhinal cortex or the hippocampus of subjects with BPD (Beneyto et al. 2007). The authors did, however, report decreased binding to the NMDA antagonist MK-801 in the hippocampus, raising the possibility that NMDA receptor activity is abnormal in BPD (Beneyto et al. 2007). A decrease in MK-801 binding in CA3 and the subiculum has also been reported in a BPD sample with a history of psychosis (Scarr et al. 2003).

Hippocampal GluR1 and GluR2 receptors are downregulated by chronic treatment with lithium and valproate, thereby decreasing the AMPA/NMDA ratio *in vivo* (Du et al. 2008). The potential pathophysiological role of AMPA receptors in BPD is supported by a study that detected a decrease in GluR1, GluR2, and GluR3 AMPA receptor subunits in the entorhinal and/or perirhinal cortices, but not the hippocampus (Beneyto et al. 2007). Furthermore, BPD subjects showed reduced expression of the kainate receptor subunits GluR5 and GluR6 in the perirhinal and entorhinal cortices, respectively (Beneyto et al. 2007). Congruent with the latter finding, Benes and colleagues reported a reduction in GluR5, GluR6, and GluR7 receptors on the apical dendrites of CA2 pyramidal neurons – but only in neuroleptic-free patients (Benes et al. 2001a,b). The reduction in kainate receptors may represent a compensatory response to increased excitatory activity. Administration of kainate is associated with neuronal cell death in animal models of excitotoxic injury (Benes et al. 2001a,b).

Fewer data indicate hippocampal glial cell abnormalities. Brauch and colleagues reported a reduction in glial cell size in the temporal cortex (region not specified) of postmortem BPD samples (Brauch et al. 2006). Immunoreactivity of myelin basic protein, a surrogate marker of myelination, was decreased in layer I of the hippocampus in female, but not male, subjects with BPD (Chambers and Perrone-Bizzozero 2004).

The postmortem data are supported by structural MRI studies that strongly suggest GM volume loss of the hippocampus once the confounding effects of medications like lithium are controlled for (Savitz and Drevets 2009). The MRS literature also suggests reduced neuronal integrity. Lower levels of NAA were found in the hippocampi of euthymic male patients with familial BPD (Deicken et al. 2003). On the other hand, choline levels appeared normal, arguing against the possibility of myelin breakdown or gliosis (Deicken et al. 2003). These data have been independently replicated in recent studies using metabolite ratios rather than absolute NAA numbers. Bertolino and colleagues found reduced NAA-choline and NAA-creatine ratios in the hippocampi of depressed, manic, and euthymic patients with BPD (Bertolino et al. 2003). Other studies have reported a bilateral hippocampal reduction in NAA-choline and NAA-creatine ratios in first-episode patients with mania (Atmaca et al. 2006), as well as a reduced NAA-creatine ratio in patients with first-episode psychosis (Blasi et al. 2004). Another study similarly detected a reduced NAA-creatine ratio in the left hippocampus (the right hippocampus was not tested) in a euthymic BPD sample (Scherk et al. 2008). The changes in hippocampal chemistry are unlikely to be purely medication-related: decreased NAA-creatine and NAA-choline ratios were found in unmedicated patients with BPD compared to their divalproex or quetiapine-treated counterparts (Atmaca et al. 2007). Negative results have, however, also surfaced in the literature. Two MRS studies found no abnormalities of NAA to creatine ratio in first-episode affective psychosis (Wood et al. 2003) or absolute levels of NAA in euthymic patients with BPD (Senaratne et al. 2009).

11 The Amygdala

The density of glial cells in the amygdala was reportedly unchanged in BPD (Bowley et al. 2002; Hamidi et al. 2004), although a 19% reduction in oligodendrocyte density that reached trend level significance was found in the study by Hamidi and colleagues. Treatment with lithium or valproate is a likely confound; samples from two unmedicated patients with BPD indicated reduced oligodendrocyte density (Bowley et al. 2002). No reduction in glial cell numbers or density was detected in another study, although oligodendrocytes were not analyzed separately from other glial cells (Bezchlibnyk et al. 2007a,b).

Decreased neuronal somal size (30%), suggestive of reduced axo-dendritic arborization, was reported in the lateral amygdaloid (LAN) and accessory basal parvocellular nuclei of patients with BPD (Bezchlibnyk et al. 2007a,b). The reduction in neuronal size was most prominent in the left hemisphere. Similarly, a reduction in the total number (41%) and density (15%) of LAN neurons was observed in another sample (Berretta et al. 2007). In addition, neuronal density was decreased by approximately 20%, and a trend toward a decrease in total neuron number was found in the accessory basal nucleus (ABN) of the BPD samples (Berretta et al. 2007). The LAN is hypothesized to imbue external stimuli with emotional significance and is reciprocally connected with the ABN, which in turn projects to subcortical and cortical regions (Pitkanen and Amaral 1998; Pitkanen et al. 2002).

Loss of GABAergic interneurons in the amygdala could result in both increased excitatory activity and decreased volume. BPD subjects imaged at rest show increased metabolism of the amygdala that correlates positively with the severity of depressive symptoms (Drevets et al. 1992; Ketter et al. 2001). Structural MRI analyses of amygdala volume are somewhat contradictory (reviewed in Savitz and Drevets 2009). We hypothesized that the discrepancy in results across studies was a function of treatment with mood stabilizers. Consistent with our hypothesis, we found that BPD subjects who were treated with lithium or valproate at the time of scanning showed greater amygdala volumes than their matched controls. Conversely, BPD patients who were off medication for at least 2 months before scanning showed significantly smaller amygdala volumes than healthy subjects (Savitz et al. 2010). Another recent study similarly reported that BPD patients treated with lithium, but not untreated patients, had greater right amygdala volumes than healthy controls (Usher et al. 2010). Consistent with these data, a recent study showed that lithium treatment prevents stress-induced dendritic remodeling in the amygdala in rodents (Johnson et al. 2009).

Reduced amygdala volume may indicate functional dysregulation of the amygdala. Kalmar and colleagues found that adolescents with BPD who had the smallest amygdala volumes tended to display the greatest BOLD response to emotional faces (Kalmar et al. 2009a,b). Another study further reported that amygdala volume was positively correlated with immediate and delayed verbal recall in BPD patients but not healthy volunteers (Killgore et al. 2009). An fMRI study of working

memory found that in a working memory task that required active subarticulatory rehearsal, both euthymic patients with BPD and a healthy comparison group showed typical activity in a medial-frontal-parietal-striatal network; however, the BPD patients also displayed a relatively greater BOLD response in the right amygdala (Gruber et al. 2009).

12 Conclusion

A complex array of neuropathology and neuroimaging findings peppers the BPD literature, reflecting the heterogeneity of psychiatric illness and the complexity of neurophysiological systems. One broad theme that emerges from the literature is that of increased physiological activity coupled with reduced GM volume, neurons, or glial cells in the visceromotor or central emotion network. The molecular mechanisms that underpin this inverse relationship between physiological activity and brain volume are not yet understood. Perhaps the most accepted model is that of cellular damage caused by glutamate-mediated excitotoxicity.

Chronic stress may induce excess secretion of glucocorticoids that, in animal models, impair glutamate transporter-mediated glutamate reuptake, upregulate the expression of NMDA receptor subunits, and facilitate the activation of voltage-gated sodium channels, and thus calcium influx (Sapolsky 2000). At sufficiently high concentrations, glutamate acts as an excitotoxin and neuronal death may follow from intracellular calcium-driven cytoskeletal degeneration and free radical production. The excitotoxicity model is also consistent with the postmortem evidence of disrupted glutamate and GABAergic neuron structure or function.

Deeper theoretical questions remain such as the permanence of these putative changes in brain structure and function – an issue we have previously alluded to in the context of cognition (Savitz et al. 2005); the identification of pathological versus compensatory changes; and the integration of neurobiology with current psychiatric nosology.

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Functional Neuroimaging Research in Bipolar Disorder

Benjamin N. Blond and Hilary P. Blumberg

Contents

Abstract Functional neuroimaging techniques have been important research tools in the study of bipolar disorder (BPD). These methods provide measures of regional brain functioning that reflect the mental state at the time of scanning and have helped to elucidate both state and trait features of BPD. This chapter will review converging functional neuroimaging evidence implicating state and trait dysfunction in a ventral prefrontal cortex–amygdala neural system in BPD. Emerging evidence that suggests a developmental progression in dysfunction in this neural system over the course of adolescence will be considered. Finally, new research approaches that have begun to reveal the contribution of specific genetic mechanisms to regional dysfunction in the disorder, potential salutary effects of medications, and structure–function relationships will be discussed.

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Abbreviations

ACC	Anterior cingulate cortex
AdolBPD	Adolescents with BPD
BOLD	Blood oxygen level dependent
BPD	Bipolar disorder
dlPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
fMRI	Functional MRI
MRI	Magnetic resonance imaging
OFC	Orbitofrontal cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
rCBF	Regional cerebral blood flow
vACC	Ventral anterior cingulate cortex
vPFC	Ventral prefrontal cortex

1 Introduction

Functional neuroimaging research has been critical to advances in understanding the neurobiology of bipolar disorder (BPD) at the neural system level. Structural neuroimaging methods reviewed in other chapters of this volume have been important in demonstrating morphological differences in gray and white matter regions in the disorder, which implicate dysfunction in these regions. Functional neuroimaging studies provide measures of regional brain functioning that reflect the mental state at the time of scanning. When performed during manic, depressed, and euthymic states of BPD, functional neuroimaging methods can reveal both mood state- and trait-dependent features of the disorder. The earliest functional neuroimaging studies of BPD used methods to study regional brain activity at rest, including positron emission tomography (PET) measures of resting regional cerebral blood flow (rCBF) and metabolism. Over the past decade, blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) methods have been used to a greater extent, and findings from fMRI studies will comprise the majority of those reviewed in this chapter. An important capability of such functional neuroimaging studies is their ability to reveal abnormalities in the on-line functioning of brain regions during performance of specific behaviors.

Early functional neuroimaging findings revealed frontotemporal dysfunction in adults with BPD. Over the past decade, intensive functional neuroimaging research efforts in BPD have built on the foundation of these early findings. New imaging methods have provided a growing ability to localize regional brain findings. Coupling these methods to increasingly sophisticated behavioral activation paradigms has allowed for the association between regional findings and specific behavioral dysfunction. Some findings are more prominent during acute mood episodes, while others also persist during euthymia implicating them as trait disturbances associated with vulnerability to the disorder.

Although there are some variable findings, overall the functional neuroimaging studies of BPD converge in supporting a central role for abnormalities in a ventral prefrontal cortex (vPFC)–amygdala neural system in the disorder. The vPFC and amygdala are critical in emotional regulation and are highly interconnected. The vPFC provides important top-down regulation of amygdala responses in emotional processing (Rolls 1999). vPFC dysfunction could, therefore, lead not only to abnormalities in vPFC-related behaviors, but could also contribute to the dysregulation of amygdala-associated emotional behaviors. Other regions in this neural system, with substantial connectivity to vPFC and amygdala include dorsolateral prefrontal cortex (dlPFC), hippocampus, striatum, and thalamus. These are associated with additional functions that are disrupted in BPD, including those underlying cognitive and psychomotor symptoms. Thus, dysfunction in this vPFC–amygdala neural system could contribute to the broader range of symptoms characteristic of BPD. Given the central role of the vPFC in regulating this emotional neural system, and the body of evidence supporting its role in BPD, this chapter will commence with reviews of findings in the vPFC. It will then include reviews of evidence regarding dysfunction in mesial temporal regions with a focus on the amygdala, given its central role in emotional processing and in BPD, as well as the hippocampus. These will be followed by a review of findings in the additional associated brain regions.

BPD often emerges during adolescence and young adulthood. These are developmental epochs when the vPFC–amygdala neural system is still dynamically maturing. During adolescence, the frontal components of the neural system undergo structural and functional maturation that contributes to an increased frontal regulation of the neural system that in turn subserves the development of more refined and adaptive behavioral responses. The timing of the development of maturation of the vPFC–amygdala neural system coincides with a peak in the emergence of BPD symptoms (Lewinsohn et al. 1995; Lish et al. 1994; Loranger and Levine 1978). This suggests that disruption in vPFC–amygdala neural system development in adolescence could contribute to the emergence of the emotional dysregulation associated with BPD. This is supported by findings of abnormalities in components of this neural system in adolescents with BPD (AdolBPD), and by preliminary reports of a possible progressive divergence in vPFC structure and function over adolescence in individuals with and without BPD. In this chapter, studies of adults will be presented first. These sections will be followed by a section discussing studies of AdolBPD.

Most recently, functional neuroimaging methods have been integrated with other imaging research methods, such as structural imaging techniques. This has created opportunities to investigate structure–function relationships that provide evidence for structural abnormalities that underlie neural system dysfunction in the disorder. Moreover, the integration of neuroimaging and genetics research methods is suggesting specific molecular mechanisms that may underlie particular aspects of neural system dysfunction in BPD. Identification of these could be key to the development of new detection and treatment methods. Preliminary findings also suggest that treatments may have the potential to reverse neural system abnormalities in BPD. These new research directions will be discussed in the final section of this chapter.

2 Ventral Prefrontal Cortex

Functional neuroimaging studies of the vPFC in BPD have included different methodologies that have yielded vPFC findings that have varied across studies, both in the localization to specific vPFC subregions and in the direction of the findings. Nevertheless, the overall data demonstrate a strong convergence in supporting vPFC dysfunction in BPD and potentially a central role for vPFC dysfunction in trait vulnerability to the disorder. As studies differ in the vPFC subregions studied and often cross subregions, the term vPFC will be used in this chapter to include a broad range of ventral frontal regions including orbitofrontal cortex (OFC), inferior and rostral frontal cortices, and the ventral and perigenual components of the anterior cingulate cortex (ACC).

2.1 Studies of Research Participants at Rest

Early functional neuroimaging studies of BPD included studies of individuals with BPD at rest during scanning. rCBF or metabolism, measured by methods including PET, provided an index of regional brain activity. An advantage of these methods over fMRI methods is that they are not as vulnerable to artifacts in the ventral-most regions of the frontal cortex. These imaging methods revealed abnormalities in the vPFC in the resting state in adults with BPD, which appear to differ in the direction (increases or decreases) of findings depending on mood state. The earliest studies of BPD demonstrated relative frontal decreases encompassing more ventral frontal regions during mania as compared to depression (Rubin et al. 1995). An $H_2{}^{15}0$ PET study demonstrated decreased resting state activity in the OFC in individuals with BPD experiencing manic episodes at the time of scanning, as compared to both individuals with BPD who were euthymic at scanning and healthy comparison subjects (Blumberg et al. 1999). A study by this group also demonstrated relative increases in dorsal ACC in mania in BPD (Blumberg et al. 2000). An increase in

dorsal ACC rCBF was also detected by Kruger et al. (2003) in remitted BPD subjects, suggesting that this might be related to trait vulnerability to mania.

In contrast to studies of mania, PET studies of regional glucose metabolism in the depressed phase of BPD have shown increases in vPFC resting metabolism (Mah et al. 2007). These increases have been shown to be associated with depressive symptoms. For example, the magnitude of right subgenual ACC (BA 32, 25, 24) hypermetabolism showed a correlation with psychomotor-anhedonia symptoms (Dunn et al. 2002). Taken together with the findings in mania described above, these studies suggest that acute mood states of BPD are associated with frontal dysfunction, and that the relative ventral–dorsal distribution of mood-state-related deficits in activity at rest may contribute to the valence of the mood state, such that decreased ventral relative to dorsal vPFC activity is characteristic of mania, whereas increased ventral relative to dorsal vPFC activity is characteristic of depression. The finding during remission also suggested that abnormalities in the ventral–dorsal frontal balance may contribute to trait vulnerability to the disorder.

2.2 Studies of Research Participants During Task Performance

Functional neuroimaging studies performed while research participants engage in specific behavioral tasks during scanning also demonstrate vPFC dysfunction in adults with BPD. In these studies, regional brain responses to specific activation tasks, designed to probe specific behaviors and their associated neural circuitry, are measured. These tasks probe abnormalities in the functioning of brain regions that subserve the performance of emotional and cognitive functioning disrupted in BPD. Similar to the findings in the resting studies above, these activation studies implicate mood state-related, as well as trait-related, vPFC functional abnormalities in BPD.

2.2.1 Processing of Emotional Stimuli

The vPFC plays a central role in emotional processing and regulation of emotional behavior (Devinsky et al. 1995; Rolls 1999) and is therefore implicated in the emotional dysregulation characteristic of BPD. Consistent with this, abnormalities in vPFC response have been demonstrated in functional neuroimaging studies in which participants with BPD process emotional stimuli. These include a variety of emotional stimulus types including faces, emotionally valenced words, and autobiographical scripts.

Abnormalities in vPFC response to face stimuli in BPD have been reported by numerous research groups. These have included face stimuli of varying emotional valence and tasks with differing response requirements. Although these studies demonstrate a striking consistency in eliciting dysregulated vPFC responses, the

studies do vary in the vPFC subregions in which differences have been detected and in the direction of the differences.

During passive viewing of faces of positive and negative emotional valence, perigenual ACC response was diminished in adults with BPD (Blumberg et al. 2005). Dysregulated vPFC responses have also been observed in BPD in studies in which subjects performed implicit emotional face processing during performance of tasks orthogonal to the processing of facial emotions, such as determining the sex of the face. These have included findings in bipolar depression of abnormalities in vPFC responses to faces depicting fearful, sad, and happy expressions (Chen et al. 2006; Lawrence et al. 2004). Overall, these findings suggest that BPD may be characterized by abnormalities in vPFC functioning during the implicit processing of faces of both positive and negative emotional valence.

Mood state- and potentially BPD-trait abnormalities in the vPFC have also been reported in tasks requiring explicit processing of emotion. Dysregulated vPFC responses during the explicit processing of emotional faces, such as during the labeling of facial emotions and the intensity of the emotion depicted, have been reported in individuals with BPD during both manic and depressed states, though studies differ as to direction of findings, reporting decreases or increases (Foland et al. 2008; Altshuler et al. 2005a, 2008; Chen et al. 2006). There is some suggestion of relationships between mood state and the emotional valence of the face stimuli with features of the vPFC differences in BPD. When explicitly processing facial emotion, individuals with BPD demonstrate possible evidence of mood-congruent responses in the vPFC. For example, in manic states, attenuated subjective rating of the intensity of sad facial expressions and associated attenuation of activation in the ventral anterior cingulate cortex (vACC) have been observed (Lennox et al. 2004; Chen et al. 2006).

Dysregulated responses in the vPFC have now been observed in euthymic individuals with BPD across tasks involving the processing of emotional faces and words, as well as during sad mood induction (Malhi et al. 2005, 2007a; Kruger et al. 2003; Jogia et al. 2008; Shah et al. 2009). This supports the presence of trait abnormalities in the vPFC during emotional processing in BPD. Moreover, Kruger et al. (2006) noted vPFC abnormalities in the healthy siblings of individuals with BPD, supporting the presence of vPFC dysfunction in vulnerability to BPD.

2.2.2 Performance of Cognitive Tasks

Scanning tasks requiring the inhibition of appropriate responses in order to provide correct responses, such as in the inhibition of prepotent response tendencies and in decision-making, have consistently demonstrated vPFC activity abnormalities in BPD. An early PET study of mania demonstrated decreased right OFC response during performance of a word generation task (Blumberg et al. 1999). Later studies also reported consistent right OFC and inferior prefrontal cortex (PFC) deficits in activation in individuals with BPD in manic states while they performed tasks that required the inhibition of prepotent responses in order to provide correct responses,

such as go/no-go, color-naming Stroop, and probability-based decision tasks (Altshuler et al. 2005b; Blumberg et al. 2003a; Rubinsztein et al. 2001; Mazzola-Pomietto et al. 2009).

vPFC findings in association with acute mood states have tended to be on the right in mania and on the left in depression (Blumberg et al. 2003a). These findings are consistent with a longstanding theory of right–left hemispheric lateralization of processing of stimuli of negative and positive emotional valence. This posits that processing of negative emotions is concentrated in the right hemisphere, whereas the processing of positive emotions is concentrated in the left (Davidson and Irwin 1999). Consistent with this theory, in secondary mood symptoms such as those associated with trauma, cerebrovascular lesions, and seizure foci, mania is associated with right hemisphere abnormalities and depression with left-hemisphere abnormalities (FlorHenry 1969; Wexler 1980; Sackeim et al. 1982; Starkstein et al. 1988, 1991).

Blumberg et al. (2003a) noted deficits in vPFC response during euthymia in BPD during performance of a Stroop task, implicating vPFC dysfunction as a trait feature of BPD. Other research groups subsequently reported similar findings in the study of currently euthymic individuals with BPD during performance of Stroop as well as go/no-go and gambling tasks (Kaladjian et al. 2009; Kronhaus et al. 2006; Frangou et al. 2008). Decreases in vPFC response have also been reported in individuals with BPD during euthymia, and in their unaffected relatives, on tests of working memory such as the N-back task (Monks et al. 2004; Thermenos et al. 2009). These data support BPD-trait deficits in vPFC recruitment during goal-directed behavior. However, there are also functional neuroimaging studies using cognitive tasks in studying individuals with BPD in euthymic periods and their unaffected family members that show elevated vPFC responses (Adler et al. 2004; Strakowski et al. 2004; Lagopoulos et al. 2007; Drapier et al. 2008; Thermenos et al. 2009; Robinson et al. 2009). Tasks employed include those testing attention and working memory, such as delayed non-match to sample, continuous performance, N-back, and Sternberg tasks. Reasons for the elevations are not clear. Strakowski et al. (2004) suggest that while the participants with BPD were performing putatively nonemotional tasks, they may have displayed trait vulnerability in attaching a heightened emotional valence to the task. Overall, these findings in BPD during euthymia further support the presence of vPFC dysregulation as a trait feature of BPD in adults.

Given the role of the vPFC in regulating adaptive responses in the setting of changing reinforcement contingencies, and clinical observations that individuals with BPD have difficulty adaptively regulating behavior in hedonically valenced situations, researchers have also attempted to implement tasks in the study of BPD in which adaptive response inhibition is required in the context of processing emotionally valenced stimuli. For example, studies by Elliott et al. (2004) and Wessa et al. (2007) implemented go/no-go tasks with word or face stimuli of positive or negative valence. They found that the "emotional" go/no-go task was better at revealing vPFC differences than a go/no-go task without emotional stimuli. Notably, similar to the findings with emotional stimuli described above, these studies also revealed

dysregulated vPFC responses to emotional stimuli of both positive and negative valence. This was in contrast to findings in unipolar depression in which sad faces particularly elicited differences (Elliott et al. 2002). These findings are consistent with the view that emotional stimuli of positive emotional valence may be especially helpful in eliciting pathological vPFC responses in BPD. It has been suggested that this may reflect a relatively unique vulnerability to BPD, as excursions to positive mood states of the acute manic episode are the hallmark of the disorder. Therefore, it is possible that response to positive emotional stimuli may help to distinguish BPD from other disorders (Blumberg et al. 2005).

Thus, differences across studies could relate to the mood state of the subject and the design of the task. Differing levels of task difficulty and demands on executive functioning can also influence findings. In order to better assess the relationship between task demands, performance, and circuitry differences, studies are increasingly incorporating parametric designs. In one study that used a reversal learning task, which is dependent on vPFC function, increased difficulty as modeled parametrically was associated with increased differences in activation in the vPFC between a group with BPD and a healthy comparison group (McIntosh et al. 2008).

The prominent vPFC differences across the majority of studies of BPD are believed to provide an important distinction from schizophrenia. Note that in some of the studies above, more dorsal PFC findings were also present; however, overall vPFC findings emerge as prominent. It has been theorized that, although more pervasive PFC findings can be seen, abnormalities in dlPFC are more prominent in schizophrenia, whereas abnormalities in vPFC are more prominent in BPD. For example, in the study by McIntosh et al. (2008) above, dlPFC differences were more prominent in the schizophrenia group, whereas vPFC differences were relatively specific to the BPD group.

3 Amygdala

In the vPFC–amygdala neural system model of BPD, disruptions in vPFC top-down regulation of the neural system, and especially of the amygdala, could lead to the loss of affective homeostasis. However, it is possible that excesses in amygdala activity themselves could also contribute to the emotional behaviors seen in BPD. There has been a striking convergence of findings of excessive resting activity and response of the amygdala during task performance in BPD.

PET studies demonstrate amygdala hypermetabolism in the resting state in individuals with BPD, who were depressed at scanning (Drevets et al. 2002; Mah et al. 2007). The magnitude of the increases correlated positively with depressive severity and cortisol levels (Drevets et al. 2002). Studies of the amygdala in BPD during task performance are more numerous; many consistently report heightened amygdala response during subject performance of various activation tasks.

Many of these functional neuroimaging studies were designed to assess abnormalities in emotional processing, given the amygdala's crucial role in this function in

normal health. Most numerous are face emotion processing tasks, which have consistently shown excessive amygdala responses in individuals with BPD in both manic and depressed mood states and during both implicit and explicit processing of faces of both positive and negative valence (Yurgelun-Todd et al. 2000, Altshuler et al. 2005a; Chen et al. 2006; Lawrence et al. 2004; Malhi et al. 2004a; Blumberg et al. 2005). The persistence of an elevated amygdala response into euthymia in BPD (Lawrence et al. 2004; Blumberg et al. 2005) suggests that this abnormality may be a trait feature of the disorder. As in the vPFC, it has been suggested that positive emotional faces may be especially salient stimuli for eliciting abnormalities in amygdala response in BPD (Blumberg et al. 2005). Differences in amygdala response in individuals with BPD, compared to healthy individuals, have also been documented during performance of putatively "nonemotional" cognitive tasks such as continuous performance tasks and go/no-go tasks (Ketter et al. 2001; Strakowski et al. 2004; Kaladjian et al. 2009).

4 Hippocampus

Episodic memory deficits are among the most consistent cognitive deficts reported in BPD, implicating the hippocampus in the disorder. Although both structural and functional differences in the hippocampus have been reported in BPD, overall, these have not been as consistent and robust as the findings in the vPFC and amygdala. While vPFC and amygdala dfferences in BPD have shown themselves across studies using a wide variety of activation tasks, hippocampal differences have not been reported as frequently. However, there are few functional imaging studies in which the study design specifically targeted the hippocampus.

Differences in hippocampus response in BPD across depressed, manic, and euthymic states, compared to healthy comparison groups, have been reported during emotional processing of negatively valenced emotional stimuli (Lawrence et al. 2004; Chen et al. 2006; Malhi et al. 2007b; Lagopoulos and Malhi 2007). In one study of emotional prosody, activation abnormalities correlated with depression severity (Mitchell et al. 2004). Hippocampus dysfunction has also been reported across the mood states in individuals with BPD while they performed cognitive tasks including a go/no-go task (Altshuler et al. 2005b), an auditory discrimination continous performance task (Ketter et al. 2001), and a semantic clustering task (Deckersbach et al. 2006).

5 Basal Ganglia and Thalamus

An important component of frontal neural systems is processing through striatal-thalamic circuits (Alexander et al. 1986). The ventral striatum, and its associated thalamic projection regions, are especially implicated in BPD, as the ventral

striatum has a key role in hedonically driven, motivated behaviors suggesting its role in the impulsive responses to rewarding stimuli in mania and the anhedonia of depression (Womer et al. 2009).

Resting PET scans of individuals with BPD have shown state-dependent striatal-thalamic effects with rCBF increases in the caudate in mania (Blumberg et al. 2000) and increases in caudate, putamen, and thalamus in depression (Mah et al. 2007). Increases have also been reported in mania and depression in BPD during emotional processing task performance, including implicit processing of emotionally valenced faces and emotional induction tasks, as well as go/no-go and working memory tasks using emotional stimuli (Lawrence et al. 2004; Wessa et al. 2007; Malhi et al. 2004a, b). This includes a finding specifically in the ventral striatum (Lawrence et al. 2004).

Reflecting their role in motor and cognitive functioning, more dorsal striatal and associated thalamic differences have also been demonstrated in BPD during performance of motor and cognitive tasks. Increases in caudate and putamen have been demonstrated in mania, depression, and euthymia in BPD in individuals performing motor tasks (Caligiuri et al. 2003, 2006; Marchand et al. 2007), perhaps reflecting the psychomotor disturbances that can be seen in the disorder. In performance of cognitive tasks, though increases have been reported such as on a working memory task (Adler et al. 2004), basal ganglia and thalamic activation findings in BPD euthymia have primarily been of decreases on tasks including delayed non-match to sample tasks and Stroop and stop signal tasks (Robinson et al. 2009; Strakowski et al. 2005, 2008) potentially reflecting deficits in mnemonic functioning and in the inhibition of maladaptive prepotent responses in the disorder.

Two studies using cognitive tasks have elicited ventral striatal activation increases. In one, an auditory continuous performance task was used (Ketter et al. 2001). In the second, described in the vPFC section above, a parametric analysis of a reversal learning task was performed showing increased activity in right ventral striatum that was also associated with errors in BPD, compared to healthy control participants (McIntosh et al. 2008).

6 Neuroimaging Studies in Adolescents with BPD

Functional neuroimaging studies of AdolBPD are primarily fMRI studies, as PET studies have not been performed owing to concerns regarding exposure to the radiotracers required. The fMRI studies have revealed some similarities to the findings in adults, suggesting that some neural characteristics of the adult phenotype within the vPFC–amygdala neural system may emerge at least as early as adolescence. Others appear to progress over the course of adolescence.

In one of the first fMRI investigations of AdolBPD, Blumberg et al. (2003b) studied AdolBPD while they performed a color-naming Stroop task. Consistent with studies conducted in adults, they found subcortical differences in striatum and thalamus. Ventral striatal differences were associated with the severity of depressive

symptoms. However, vPFC differences were not detected. This may have been due, at least in part, to statistical power owing to the small sample and/or characteristics of the study design. However, this research group also noted that AdolBPD did not display the age-related increases in signal in rostroventral PFC that were present among healthy comparison subjects. The pattern in healthy adolescents was consistent with the view that the vPFC increasingly comes online with age in the service of providing adaptive inhibition of prepotent response tendencies. Blumberg and colleagues suggested that the failure of AdolBPD to show this age-related pattern might reflect abnormalities in the maturation of vPFC function during adolescence in BPD that could result in the vPFC trait findings in adults with the disorder (described above).

Since then, neuroimaging studies of AdolBPD have shown functional differences in subcortical structures across several types of tasks. The most consistent findings have been of increases in amygdala response to emotional stimuli. For example, compared to healthy adolescents, AdolBPD perceived neutral facial expressions as more threatening and had associated increases in amygdala activation during direct processing of the facial emotions (Rich et al. 2006). Amygdala hyperactivity has also been demonstrated in unmedicated euthymic AdolBPD during processing of both positive and negative emotional stimuli (Pavuluri et al. 2007, 2008, 2009).

One of the most consistent findings in BPD neuroimaging research is of decreases in amygdala volume in AdolBPD (Blumberg et al. 2003c; Chang et al. 2005; Chen et al. 2004; DelBello et al. 2004; Dickstein et al. 2005; Wilke et al. 2004). Independent reports of elevated response in amygdala and of decreased volume in AdolBPD raised the interesting question of whether the two were associated. In order to address this, a recent study by Kalmar et al. (2009b) performed both structural and functional MRI scanning in the same research subjects in order to investigate structure–function relationships. They demonstrated an inverse relationship between amygdala volume and amygdala response to emotional stimuli, such that the AdolBPD with the smallest volume showed the most exaggerated amygdala response. Possible pathophysiological etiologies that could underlie this combination include decreases in the inhibitory neurons in amygdala or excessive glutamatergic inputs that could be neurotoxic in the amygdala. The former is supported by a recent preliminary postmortem study showing decreased neurons in the amygdala (Berretta et al. 2007). As with the findings in adults, Kalmar et al. (2009b) and the other studies in AdolBPD described above detected differences in association with faces of both positive and negative valence with more prominent findings in association with happy faces. This again suggests the salience of positive emotional face stimuli in eliciting pathological responses in BPD and further suggests that this is an early feature of the disorder.

In addition to the findings in the amygdala, increases in striatal and thalamic activation have been reported in AdolBPD during the processing of emotional faces (Chang et al. 2004; Dickstein et al. 2007). Additional subcortical deficits have also been observed in AdolBPD during performance of tests of memory and motor inhibition. For example, AdolBPD showed increased activation of the left

putamen and thalamus in a visuospatial memory task (Chang et al. 2004). While performing a motor inhibition task, AdolBPD had greater activity in striatum than controls when comparing stopping correctly to stopping incorrectly (Leibenluft et al. 2007).

Although the early response inhibition study of AdolBPD did not show vPFC differences, multiple studies that have used emotional processing tasks have detected differences in the vPFC in AdolBPD although the directions of findings across studies differ. In a series of studies of emotional processing in adolescents by Pavuluri and colleagues, in implicit and explicit emotion processing tasks, and integrated emotion and cognition tasks, BPD was associated with dysregulated vPFC responses. These findings included differing localizations within the vPFC and increases and decreases depending on task requirements (Pavuluri et al. 2007, 2008, 2009). In other studies of AdolBPD using implicit and explicit emotional processing tasks, Chang et al. (2004), Dickstein et al. (2007), and Rich et al. (2006) also found dysreglulated vPFC responses in processing faces depicting negative affect, although the localization and magnitude of findings varied across studies, with some effects of stimulus type.

The variable findings highlight the complex interactions that may occur with specific features of the paradigms used during scanning. This may be especially important to consider in the study of pediatric samples, for which developmental stage needs to be considered when implementing tasks. vPFC functional abnormalities have been demonstrated less consistently in AdolBPD on performance of cognitive tasks. There was a report of a vPFC difference in AdolBPD on a visuospatial working memory task (Chang et al. 2004). With regard to examining task feature and performance, Leibenluft et al. (2007) used a stop signal task and found a difference in the direction of vPFC findings in AdolBPD that depended on performance on the task. Elevated right vPFC and ventral striatum activation was revealed in AdolBPD compared to healthy adolescents when comparing stopping correctly to stopping incorrectly, but activation was decreased when comparing stopping incorrectly to the "go" condition (Leibenluft et al. 2007).

Taken together, the above findings support the presence of vPFC–amygdala neural system dysfunction at least as early as adolescence in BPD. Subcortical dysfunction, especially in the amygdala, appears to be a prominent feature. Emerging evidence suggests that vPFC differences are also present in AdolBPD. These have been detected primarily in the context of emotional face processing task performance that may be particularly robust in eliciting BPD pathology. Differences in vPFC functioning in AdolBPD, especially with regard to adaptive behavioral inhibition, may still be progressing as compared to healthy adolescents over the teenage years. More definitive study of the differences in developmental trajectories will require longitudinal analyses. Few such studies exist. In one neuroimaging report of brain structure, vPFC volume differences showed a progressive divergence between adolescents with and without BPD (Kalmar et al. 2009a). This suggests there may be a similar progressive divergence in functional development in AdolBPD, but more conclusive determination awaits future studies.

7 Functional Connectivity

In addition to accumulating evidence implicating the various brain regions individually, emerging variations of fMRI methodology now allow for studies investigating the functioning between brain regions within the neural system. These "functional connectivity" methods can provide a measure of how well coordinated responses in different brain regions are. They use methods to assess the temporal relationships between the activity of brain structures within a neural system. Tighter coupling of responses in time is considered to be a measure of higher functional connectivity.

These methods have provided evidence for abnormalities in the top-down regulation of the amygdala by the vPFC and decreased functional connectivity within the vPFC–amygdala neural system. Foland et al. (2008) demonstrated decreased vPFC modulation of the amygdala during a task requiring labeling of emotion among individuals with BPD in the manic phase. These decreases showed association with the degree of manic symptoms, as well as course features such as number of prior manic episodes and illness duration (Foland et al. 2008). Resting state functional connectivity analyses suggest that functional connectivity may be particularly disrupted between the perigenual ACC and amygdala in BPD. Unmedicated BPD subjects displayed decreased functional connectivity, at rest, between pregenual ACC and amygdala (Anand et al. 2009). Preliminary results suggest that this deficient connectivity remains across mood states.

Using a new approach for combining fMRI with diffusion tensor imaging (DTI) to examine structure–function relationships in BPD, a recent study reported perigenual ACC–amygdala functional connectivity findings in BPD that were also demonstrated to be associated with structural differences in white matter. fMRI functional connectivity methods demonstrated decreased functional connectivity between perigenual ACC and amygdala in adults with BPD while they processed either happy or fearful faces (Wang et al. 2009). The subjects in this study also underwent DTI scanning. Combining DTI analyses with the fMRI analyses demonstrated a significant association between the abnormalities in perigenual ACC–amygdala functional connectivity and decreases in the structural integrity of white matter structures that provide connections between the perigenual ACC and amygdala (Wang et al. 2009). This suggests that white matter abnormalities might contribute to the dysfunction in the vPFC–amygdala neural system in BPD.

Preliminary evidence suggests that similar abnormalities may be present in AdolBPD. For example, DTI studies of AdolBPD indicate abnormalities in the integrity of white matter (Adler et al. 2006). A functional connectivity study of AdolBPD demonstrated abnormalities in amygdala functional connectivity, although it demonstrated differences in the connectivity to posterior association regions (Rich et al. 2008). This suggests that connectivity, especially in the posterior part of the neural system, may already be established by adolescence.

8 Functional Neuroimaging, Genes, and Treatment

Functional neuroimaging studies can help to localize findings in BPD and suggest possible mechanisms that may contribute to them. In order to determine these mechanisms, researchers are finding new ways to pair functional neuroimaging methods with other research methods. As noted above, combining imaging modalities may help to elucidate structure–function relationships. Postmortem studies can suggest the cell types that may be involved.

A research strategy to investigate the molecular mechanisms that underlie these differences is to perform studies integrating genetic and neuroimaging methods. One study using this approach in BPD examined the influence of variation in a serotonin transporter promoter polymorphism (5-HTTLR, locus *SLC6A4*) on vPFC–amygdala response in BPD. This study found decreased vACC activation in response to emotional face stimuli in carriers of the short "s" allele, compared to individuals homozygous for the long "l" allele. Individuals with BPD who were also "s" carriers exhibited the greatest magnitude of vACC dysfunction (Shah et al. 2009). This suggested the possibility of a subtype within BPD related to this genetic variation. This could have implications for detection and treatment of individuals with this subtype.

Functional neuroimaging studies have provided preliminary evidence that treatment can reverse functional abnormalities in the vPFC–amygdala neural system in BPD. For example, several research groups have noted that individuals with BPD taking mood-stabilizing medications at scanning, including lithium and valproate, do not show the magnitude of amygdala response excesses to emotional stimuli seen in individuals unmedicated at the time of scanning (Blumberg et al. 2005; Jogia et al. 2008). Perigenual ACC and inferior PFC deficits in responses during emotional face processing and cognitive tasks have also been suggested to be reversed by mood-stabilizing treatment, including lithium and lamotrigine (Blumberg et al. 2005; Jogia et al. 2008; Haldane et al. 2008).

9 Conclusion

Over the past decade, there has been an accumulation of evidence in functional neuroimaging research implicating the salience of dysfunction in a vPFC–amygdala neural system to BPD. Amygdala hyperactivity and vPFC dysfunction both appear to contribute to dysregulation of a neural system that may chiefly be implicated in emotional function. Dysfunction in connected brain regions, such as the hippocampus, ventral striatum, basal ganglia, and thalamus may explain the variety of symptoms associated with BPD. Research has demonstrated both state and trait features of BPD in a variety of behavioral and activation tasks, although some of the data remain unclear. Much work remains to be done in order to clarify current findings. The varying results of different studies suggest that even subtle

differences in methodology may be influencing the results of functional neuroimaging. The localization of findings also needs to be refined. Particularly in the vPFC, future work that distinguishes specific subregions may prove important. As this work continues, more sophisticated research techniques are beginning to integrate information from diverse approaches in order to form a more complete picture of BPD. Functional neuroimaging research is now providing exciting new data and hypotheses at multiple levels, from functional connectivity analyses demonstrating the connections within a neural system to genetics suggesting possible molecular bases for the disorder. Analysis of structure–function relationships will help to synthesize information from previously separate techniques in order to form a more complete picture of abnormality in BPD. This exciting pace of discovery will shed new light on the causes of this debilitating psychiatric condition and will hopefully provide new insights on designing improved treatment.

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Sleep and Circadian Rhythm Abnormalities in the Pathophysiology of Bipolar Disorder

Jessica Levenson and Ellen Frank

Contents

Abstract Among other factors, bipolar disorder is characterized by disturbances in sleep and biological rhythms that typically cycle over a 24-h, or circadian period. Indeed, almost all of the functions that constitute symptoms of depression and mania (changes in mood, energy, sleep, interest, appetite, capacity for concentration, etc.) show relatively regular variation over the circadian period. Thus, it would appear logical to search for clues to the pathophysiology of bipolar disorder in the

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function of the circadian timing system (Wirz-Justice in Int Clin Psychopharmacol 21:S11–S15, 2006). In this chapter, we review the known sleep and biological rhythm abnormalities associated with bipolar disorder. We describe the nature of these circadian rhythm abnormalities and review the evidence supporting their role in bipolar episodes. Last, we discuss a number of pharmacologic and psychosocial treatments for bipolar disorder that target sleep and biological rhythm abnormalities, and we examine their effect on bipolar episodes and symptoms.

Keywords Chronobiology · Pharmacology · Psychotherapy · Rhythmicity · Social Rhythms

Abbreviations

CBT	Cognitive behavior therapy
CC	Collaborative care
CSM	Composite scale of morningness
CT	Cognitive therapy
DT	Dark therapy
FFT	Family-focused therapy
HPA	Hypothalamic-pituitary-adrenocortical
IPT	Interpersonal psychotherapy
IPSRT	Interpersonal and social rhythm therapy
LT	Light therapy
M/E	Morningness/eveningness continuum
MTBD	Maintenance therapies in bipolar disorder
SD	Sleep deprivation
SRM	Social rhythm metric
STEP-BD	Systematic treatment enhancement program in bipolar disorder
SZ	Schizophrenia
SZA	Schizoaffective disorder
TAU	Treatment as usual

1 Introduction

One of the most prominent clinical features of bipolar disorder is its rhythmicity (Goodwin and Jamison 2007). Among other factors, the disorder is characterized by disturbances in sleep and biological rhythms that typically cycle over a 24-h, or circadian period. The human circadian timing system regulates rhythms of physiological variables such as body temperature, hormone secretion, sleep–wake cycles, and mood (Linkowski 2003). Indeed, almost all of the symptoms of depression and

mania show relatively regular circadian variation. Thus, it would appear logical to search for clues to the pathophysiology of bipolar disorder in the function of the circadian timing system (Wirz-Justice 2006).

Over the last several decades, considerable interest in sleep and circadian rhythm disturbances has fostered theories directly relating these parameters to affective illness. The literature on biological rhythms in bipolar disorder is consistent in pointing to significant abnormalities, some of which appear to be trait-like characteristics of those who suffer from this illness and may leave them vulnerable to subsyndromal mood instability and recurrence of mania and depression. Social rhythm disturbances, though not biological per se, are also of interest based on their ability to affect and to be affected by sleep and other circadian rhythms. Taking sleep or social rhythm irregularities as proxies for circadian rhythm disturbance, one can tentatively conclude that there are associations between circadian rhythm disturbance and clinical state in bipolar depression and mania (Wehr and Goodwin 1981; Wirz-Justice 2006).

In this chapter, we review some of the rhythm abnormalities with known relevance to bipolar disorder, including sleep/wake, rest/activity, body temperature, cortisol, melatonin, social rhythm, and chronotype. We describe these abnormalities and review recent evidence supporting their role in precipitating bipolar episodes, and as markers of the disorder. Preliminary evidence has also suggested that interventions targeting sleep–wake rhythms, light–dark cycles and social rhythms may improve outcomes in bipolar disorder (e.g., Benedetti et al. 2005b; Frank et al. 2005; Miklowitz et al. 2007b). Thus, we examine the efficacy of treatments that target these rhythm abnormalities.

2 Rhythm Abnormalities in Bipolar Disorder

2.1 Sleep/Wake Rhythms

Sleep disturbances are key characteristics of bipolar episodes. Empirical evidence suggests that the nature of the sleep disturbance in bipolar disorder varies according to the phase of the illness. As summarized in a recent review (Harvey 2008), the majority (69–99%) of patients experience reduced need for sleep during manic episodes, while depressive episodes are characterized by either hypersomnia (23–78% of patients) or insomnia (up to 100% of patients). Sleep disturbance akin to insomnia also remains present during euthymic periods (Harvey et al. 2005).

Sleep duration, a parameter partially under circadian regulation, appears to be particularly important to the manifestation of bipolar disorder. Although earlier studies had implicated shorter sleep duration in mood instability (Barbini et al. 1996; Leibenluft et al. 1996; Perlman et al. 2006), a recent analysis from the Systematic Treatment Enhancement Program in Bipolar Disorder study (STEP-BD; Sachs et al. 2003) found that both short and long sleep durations were associated

with poorer function and quality of life relative to normal sleep duration, with short sleep duration additionally associated with more severe symptomatology (Gruber et al. 2009). Prospective studies have also demonstrated that *changes* in sleep duration predict imminent large changes in mood (Bauer 2008; Bauer et al. 2006).

In episodes of bipolar disorder, sleep may be disturbed in a number of ways. In bipolar depression, sleep disturbances manifest as greater early morning awakenings and greater total REM density (Plante and Winkelman 2008). Hypersomnia has been observed in bipolar depression, but this may better reflect anergia and fatigue than true sleepiness (Plante and Winkelman 2008). Sleep abnormalities in mania have been characterized as reduced delta-sleep (Hetta et al. 1985), shortened total sleep time, increased time awake in bed, and shortened REM latency (Plante and Winkelman 2008). Decreased total reporting period, increased time awake in the last 2 h of recording, and increased REM density (Hudson et al. 1988) are also characteristic of sleep in mania.

These findings emphasize sleep disturbances in the pathophysiology of bipolar disorder and have clear relevance to interventions that attempt to increase the regularity of sleep–wake schedules.

2.2 Rest/Activity Rhythms

Rest/activity measures of circadian functioning are related to sleep, but are actually distinct. This construct measures an individual's level of movement and activity during sleep and wake times, and may be measured using actigraphy, an objective measure of body movement that corresponds to measures of sleep and wakefulness (Buysse 2005). As expected, given the known rhythm disturbances in bipolar disorder, recent actigraphy studies demonstrate that patients with mood disorders have greater variability in objectively measured sleep duration, sleep timing, and activity patterns than controls (Jones et al. 2005; Millar et al. 2004). Among participants in the STEP-BD study, Gruber and colleagues (Gruber et al. 2009) found an average variability in sleep time comparable to the jet lag associated with moving from the east to west coast of the United States each week. While this study did not use actigraphy to measure sleep time variability, future work may find similar results using actigraphy to test this effect. Although a previous actigraphy study found no phase differences in sleep–wake rhythms between those with bipolar I disorder and controls (Jones et al. 2005), Salvatore and colleagues (Salvatore et al. 2008) recently reported that sleep–wake rhythms may be phase-advanced in patients with bipolar I disorder, especially during manic episodes.

2.3 Chronotype

The notion of dividing the world into chronotype, i.e., the extent to which someone is morning-active versus evening-active, is a familiar one. Tools measuring

chronotype (also known as the morningness/eveningness continuum, or M/E) predict the timing of sleep onset and offset, as well as periods of high versus low energy and acuity. Chronotype is typically measured by the Composite Scale of Morningness (CSM), a 13-item questionnaire developed by Smith and colleagues (Smith et al. 1989). Our own data suggest that a marked tendency to eveningness may characterize a subset of individuals with bipolar disorder. We used the CSM to evaluate chronotype among patients with bipolar I disorder, unscreened controls, and patients with schizophrenia or schizoaffective disorder. Patients with bipolar I disorder were significantly more likely to be "evening" types than controls or patients with schizophrenia/schizoaffective disorder when age was considered (Mansour et al. 2005). In a separate study, a sample of adults with bipolar disorder was compared with controls drawn randomly from the same residential areas. Individuals with bipolar disorder again were more likely to be "evening" type, after accounting for potentially confounding variables (Wood et al. 2009). Our analyses also support a relationship between chronotype and mood fluctuation as mood symptoms were positively correlated with chronotype scores. A recent study in Korea on chronotype distribution in bipolar I disorder and schizophrenia also confirms the preference for eveningness in the bipolar I population (Ahn et al. 2008).

2.4 Social Rhythms

Both theoretical (Ehlers et al. 1988, 1993) and empirical work (Frank et al. 2005; Malkoff-Schwartz et al. 1998) have emphasized the relationship between life events and changes in biological rhythms. These events typically involve changes in daily routines that may be benign from a psychological standpoint, but can place considerable stress on the body's attempt to maintain synchronized sleep–wake, appetite, energy, and alertness rhythms. Disruptions in sleep–wake and circadian rhythms are influenced by the regularity of one's social rhythms, and they may be a critical pathway to both mood symptoms and fully syndromal episodes of mania and depression. It is this link that makes social rhythms a critical part of understanding the pathophysiology of bipolar disorder. Social rhythm disruptions are often measured with the Social Rhythm Metric (SRM; Monk et al. 1990, 2002), a self-report diary of social routines.

We define *social zeitgebers* as "persons, social demands, or tasks that serve to entrain biological rhythms" (Ehlers et al. 1988, p 948). In healthy individuals, the disruption or loss of social zeitgebers may manifest as a change in energy, interest, sleep, and mood, typically followed by re-entrainment to a new routine and sleep–wake pattern. According to the *social zeitgeber* hypothesis, when life events associated with disruption or loss of social zeitgebers lead to a destabilization of social rhythms and sleep–wake/rest–activity patterns, the risk of episode onset may be particularly high in individuals who are vulnerable to mood disorder. Perhaps because of trait disturbances in behavioral and circadian rhythms, individuals with

bipolar disorder may be unable to re-equilibrate after these challenges and may remain in an episode of depression or mania.

Recent work has shown that individuals with bipolar disorder are, indeed, more vulnerable to the effects of social rhythm disturbance. Those at risk for the disorder and those with bipolar spectrum conditions have less regular routines and greater sleep duration variability than controls without specific risk for bipolar disorder (Meyer and Maier 2006; Shen et al. 2008). In a prospective follow-up study of several years' duration, Shen and colleagues (Shen et al. 2008) showed that low social rhythm regularity significantly predicted first prospective onset of major depression, mania, and hypomania. However, reducing variability and consolidating social rhythms appears to constitute a protective factor against recurrence in this population (Frank et al. 2005; Miklowitz et al. 2007b).

2.5 Biological Rhythms

Other biological rhythm abnormalities have been identified in bipolar disorder as well, including disturbances in melatonin, cortisol, and body temperature rhythms. In humans, these rhythms follow characteristic periodicity based on external cues and an endogenous circadian pacemaker (see Goodwin and Jamison 2007 for a description of circadian rhythms in humans). Wakefulness is typically characterized by an absence of melatonin secretion, falling cortisol levels, and increasing body temperature; the opposite is typically found during sleep, with a temperature minimum just before dawn (Goodwin and Jamison 2007). However, these rhythms may be dysregulated in bipolar disorder.

Melatonin is secreted by the pineal gland, typically during the night, and is suppressed by light (Lewy and Sack 1993). Some evidence suggests nocturnal melatonin increase during mania (Lewy et al. 1979; Wirz-Justice and Arendt 1980, both as cited in Healy and Williams 1989), especially as compared to depression, although the rhythm of this hormone is maintained (Kennedy et al. 1989). However, other evidence suggests that melatonin is decreased during all bipolar mood states compared to controls (Kennedy et al. 1996). Melatonin dysregulation is also evidenced by the hypersensitivity of patients with the disorder to the melatonin suppressing effects of light, and melatonin peak may be phase-delayed in response to light (Hallam et al. 2005; Lewy et al. 1985 as cited in Pacchierotti et al. 2001; Nurnberger et al. 2000), although some work refutes this idea (Lam et al. 1990). Despite the mixed nature of findings in this area, some authors use these data to suggest that hypersensitivity of melatonin suppression to light may be a trait marker for bipolar disorder (Kennedy et al. 1996; Pacchierotti et al. 2001).

Twenty-four hour cortisol is one of the most widely used markers of the human circadian clock (Linkowski 2003). Cortisol hypersecretion is often reported in depressed patients (Gallagher et al. 2006; Kennedy et al. 1989; Linkowski et al. 1985, as cited in Linkowski 2003), and individuals who are manic or mixed are also thought to have abnormal cortisol profiles (Linkowski 2003; Linkowski et al. 1994;

Swann et al. 1992). Some work also suggests that the phase of the cortisol rhythm may be altered (Linkowski et al. 1985, as cited in Linkowski 2003; Linkowski et al. 1994), although other work refutes this idea (Cervantes et al. 2001; Kennedy et al. 1989; Linkowski et al. 1994).

Body temperature is also thought to be dysregulated in bipolar disorder. Some patients with bipolar depression exhibited reduced body temperature during wakefulness, especially during the early morning hours, with elevated nocturnal body temperatures and a diminished 24-h rhythm in a few patients (Nikitopoulou and Crammer 1976; Souetre et al. 1988). With recovery these effects reversed, suggesting impaired thermoregulation in depression. In their review, Goodwin and Jamison (2007) suggest that the temperature rhythms of patients with bipolar depression are likely to be phase advanced, although this may not be the case for patients with mania (Nikitopoulou and Crammer 1976).

Although the direction of effects observed is not entirely consistent, these findings implicate melatonin secretion abnormalities, dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) function (e.g., Linkowski et al. 1994), and impaired thermoregulation in the pathophysiology of bipolar disorder. Irregularities in other parameters may also be present, such as growth hormone, prolactin, and thyroid stimulating hormone (TSH) rhythms (Linkowski 2003; Linkowski et al. 1994; Souetre et al. 1988).

3 Treatments for Bipolar Disorder Targeting Rhythm Abnormalities

3.1 Interpersonal and Social Rhythm Therapy

Interpersonal and social rhythm therapy (IPSRT; Frank 2005), an adaptation of interpersonal psychotherapy (IPT; see Klerman et al. 1984; Weissman et al. 2000, 2007), focuses on the amelioration of symptoms via the establishment of highly regular social and sleep/wake routines and the resolution of interpersonal difficulties. IPSRT maintains the structure, format, and interpersonal focus of IPT; however, the initial phase of the treatment typically puts the majority of emphasis on social rhythm regulation with the use of the SRM (Monk et al. 2002) as an initial means of symptom reduction. Patients also learn to prepare for and/or manage events that disrupt daily routines. The treatment is typically 16–20 sessions in duration and encourages the use of adjunctive pharmacologic treatments where appropriate. Patients receiving IPSRT select one of five interpersonal problems (grief, grief for the lost healthy self, role disputes, role transitions, and interpersonal deficits) to focus on during treatment, based on the interpersonal challenge associated with the onset of the episode.

IPSRT was first tested in the Maintenance Therapies in Bipolar Disorder study (MTBD). This study was a long-term randomized clinical trial in which IPSRT was compared with an intensive clinical management control condition as both an acute

and maintenance treatment for patients with bipolar I disorder (Frank et al. 2005). After accounting for significant covariates of outcome, we found that receiving IPSRT in the acute treatment phase was associated with significantly longer time to recurrence during the maintenance phase. At the end of the acute treatment phase of the trial, patients assigned to IPSRT demonstrated significantly higher social rhythm regularity than those in the control condition. Also, the length of the illness-free period during the maintenance phase was significantly related to the extent to which patients increased the regularity of their social rhythms during the acute phase, indicating that increased social rhythm regularity mediated longer survival without a new episode.

3.2 Family-Focused Treatment

Family-Focused Treatment (FFT; Miklowitz 2008; Miklowitz and Goldstein 1997) integrates the family into treatment by teaching the family about the disorder, the effects of the family environment on the patient, and the effects of the disorder on the family. FFT encourages the use of adjunct pharmacological treatment where appropriate (Miklowitz 2008; Miklowitz and Goldstein 1997). FFT's other objectives include identifying and coping with episode triggers, accepting the patient's vulnerability to future episodes, distinguishing between the patient's personality and the disorder, integrating experiences associated with bipolar episodes, and reestablishing relationships after an episode. FFT is conducted over 21 sessions in three phases: psychoeducation, communication enhancement training, and problem-solving (Miklowitz 2008; Miklowitz and Goldstein 1997). FFT integrates rhythm disruption in its conceptualization of bipolar disorder based on the vulnerability–stress model. During the family psychoeducation portion of the treatment the importance of standardizing daily rhythms and maintaining good sleep hygiene are emphasized, and tracking sleep and daily routines with the SRM is also encouraged (Miklowitz 2008; Miklowitz and Goldstein 1997).

In a review of the efficacy of FFT for bipolar disorder, Morris and colleagues (Morris et al. 2007) noted that patients receiving FFT in treatment trials showed better symptomatic outcomes, lower rates of recurrence, longer times to recurrence, and less severe symptoms in the follow-up period than patients in a control condition (Miklowitz et al. 2000, 2003, both as cited in Morris et al. 2007). As compared to patients receiving a treatment of equal frequency and intensity as FFT, those receiving FFT were less likely to relapse or to be hospitalized (Rea et al. 2003, as cited in Morris et al. 2007).

3.3 Cognitive-Behavioral Therapy

Several adaptations of Cognitive-Behavioral Therapy (CBT) have also been used as a short-term treatment for bipolar disorder (Basco and Rush 2005; Lam 1999;

Otto et al. 2003; Scott 1995, 2001), which typically focus on identifying and improving maladaptive thoughts and behaviors. The adaptation by Otto and colleagues targets five treatment parameters: (1) medication adherence, (2) early detection and intervention, (3) stress and lifestyle management, (4) treatment of comorbid conditions, and (5) treatment of bipolar depression. This treatment also emphasizes psychoeducation, problem-solving, and communication training. Rhythm disruption is a focus of treatment within stress and lifestyle management, in which the patient learns to monitor sleep/wake cycles and activity levels, and to determine an optimal regular bedtime based on a regular daily schedule (Otto et al. 2003). The patient learns that disrupting life events may impact the sleep/wake cycle, which may lead to increases in bipolar symptoms.

The other CBT adaptations also include a focus on rhythm disruption to varying degrees. This includes the use of mood and activity schedules to monitor daily routines (especially sleep and eating) and to identify realistic routine targets (Lam 1999), managing behavioral symptoms by providing the patient with educational material on improving sleep in mania and depression (Basco and Rush 2005), and establishing regular activity and sleep patterns, and regular daily routines (Scott 1995, 2001).

Jones (2004) reviews some of the studies that have been conducted in this area, which generally recognize CBT for bipolar disorder as effective in reducing relapse and improving mood and social functioning. Two earlier studies also showed that CBT, as compared to a control condition, resulted in better medication adherence, fewer hospitalizations, and a reduction of the number of new bipolar episodes (Cochran 1984, Hirshfeld et al. 1998, both as cited in Otto et al. 2003). More recently, Lam's group showed that those receiving cognitive therapy (CT) experienced fewer bipolar episodes, and improved bipolar symptoms, medication compliance, and social functioning than patients receiving treatment as usual (TAU) (Lam et al. 2000). Later, this group showed that patients receiving CT experienced a decrease in the frequency of episode relapses, the number of days in an episode, and the degree of mood fluctuation, as well as a greater improvement in mood symptoms than those receiving minimal psychiatric care (Lam et al. 2003).

Similarly, Scott and colleagues (Scott et al. 2001) showed greater reduction in some symptoms, and greater improvements in functioning for patients receiving CT than patients in a wait-list condition, although some of these improvements were not fully maintained at 6 months (Scott et al. 2001). A later study did not support an added benefit of CT to TAU for patients with severe bipolar disorder, although CT had some added benefit for study participants who had 12 or fewer bipolar episodes (Scott et al. 2006).

Most recently, IPSRT, FFT, and CBT were studied as the intensive psychosocial treatments in the STEP-BD (Sachs et al. 2003). All study participants with bipolar I or II depression received pharmacotherapy; half were randomly assigned to one of the three intensive treatments, while the remainder were assigned to a briefer psychoeducational control condition called Collaborative Care (CC) (Miklowitz et al. 2007b). Participants in the intensive treatments demonstrated better times to recovery and rates of recovery than those in CC, although there were no significant

differences among the intensive treatments with regard to time to recovery (Miklowitz et al. 2007b). Patients who received an intensive treatment also reported better relationship functioning and life satisfaction after 9 months of treatment than those receiving CC (Miklowitz et al. 2007a).

3.4 *Light Therapy, Dark Therapy, Sleep Deprivation*

The efficacy of behavioral chronobiologic treatments also supports a role for circadian processes in the pathophysiology of bipolar disorder. These include: (1) light therapy (LT), or exposure of the eyes to bright light at appropriate intensity, duration, and timing during the day (e.g., Terman and Terman 2005); (2) dark therapy (DT), or dark bedrest for up to 14 h at night (e.g., Wehr et al. 1998); and (3) sleep deprivation (SD), or partial or total sleep restriction during the night (e.g., Kasper and Wehr 1992).

Experimental work in this area has aimed to show the antimanic effect of sleep and the antidepressant effect of wakefulness. Total SD, particularly in conjunction with LT, provides a rapid antidepressant response in up to 60% of depressed bipolar patients (Benedetti et al. 2005a; Colombo et al. 2000), and is associated with a phase advance in the rest–activity rhythm (Benedetti et al. 2007). The effect of SD may be strong enough to cause a switch into mania or hypomania, at a rate comparable to that of selective serotonin reuptake inhibitors (SSRIs) (Colombo et al. 1999). Generally, LT and phase advance help sustain the antidepressant effect of SD.

In a parallel fashion, a pilot study of DT for mania showed that the addition of DT to TAU was associated with a faster reduction of manic symptoms than with TAU alone during the first two weeks of an episode (Barbini et al. 2005). Prior to that, DT was used to resynchronize the sleep–wake cycle of an individual with rapid cycling bipolar disorder with the day–night cycle (Wehr et al. 1998). The patient's sleep and mood stabilized following this treatment. Still, it is unclear whether these improvements are the result of increased sleep or increased time in the dark.

3.5 *Pharmacologic Treatments for Bipolar Disorder*

Uncovering the rhythm abnormalities that underlie bipolar disorder may be complicated by pharmacotherapy, as many of the treatments in current use may affect the patient's chronobiology. However, understanding the mechanisms of these treatments may provide some insight into the pathophysiology of the disorder, especially relating to rhythm disturbances. Here, we review evidence that drug treatments for bipolar disorder affect sleep and circadian systems.

Lithium may reduce REM activity and increase NREM Stage 3–4 sleep. It has also been observed to increase circadian period length (e.g., Abe et al. 2000), an effect that may be related to its therapeutic action (Ikonomov and Manji 1999; Manji and Lenox

2000). The anticonvulsant divalproex appears to affect regulation of sleep–wake activity via its facilitation of GABAergic neural inhibition. Divalproex may also have circadian effects (Bowden and Singh 2005) and is thought to lengthen the circadian period across species, including humans (e.g., Dokucu et al. 2005; Johnsson et al. 1983). Quetiapine, an atypical antipsychotic, may have an impact on sleep via its sedating effect (Todder et al. 2006; Yoon et al. 2006). Agomelatine, a potent agonist of the melatonin (MT1, MT2) receptors, is perhaps the most intriguing pharmacotherapy for mood disorders from a circadian perspective. Agomelatine produces phase shifts in body temperature, cortisol, and TSH (Leproult et al. 2005), is a potent antidepressant in animal models of depression (e.g., Zupancic and Guillerminault 2006), and appears to be an effective adjunctive treatment in bipolar disorder (Calabrese et al. 2007). The capacity of these drugs to affect sleep and/or to alter circadian phase while improving mood state further supports the role of sleep and circadian rhythm in the pathophysiology of the disorder.

4 Conclusions

Sleep and biological rhythm abnormalities are present in bipolar disorder, although their effects may be episode-specific. The evidence reviewed here suggests the presence of one or more rhythm disturbances as a core feature of the disorder. Measures of the sleep/wake cycle are clearly disturbed in most bipolar episodes, and are linked with social rhythm dysregulation. Individuals with bipolar disorder also tend to be "evening" types and are likely to demonstrate greater variability in rest/activity rhythms. The biological rhythm disturbances reviewed here suggest a role for melatonin dysregulation, thermoregulatory impairment, and abnormality in HPA functioning, although evidence has been mixed as to the specific direction of these effects. A number of psychosocial treatments have been developed that target these rhythms and have been used as adjuncts to pharmacotherapy, generally with some success. A number of the most frequently used pharmacotherapies for bipolar disorder also have clear effects on rhythms. Future work is needed to understand how the various forms of rhythm abnormality work together in precipitating and maintaining bipolar symptomatology. Further development and refinement of chronobiological treatments also appears warranted.

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Pharmacological Treatments for Bipolar Disorder: Present Recommendations and Future Prospects

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Contents

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Abstract In selecting and adapting medications to treat the specific clinical features of a patient with bipolar disorder (BPD) over time, a foundation strategy is to have good working knowledge of up-to-date practice guidelines. The World Federation of Societies of Biological Psychiatry Guidelines has the reasoned advantage of weighing safety/tolerability as high as efficacy. Most successful treatments for BPD start to separate from placebo within 1 week; most differences between regimens occur within the first 4 weeks. This observation extrapolates to a strategy of discontinuing or adding a second drug for symptoms unimproved within 1 month of treatment initiation. The weight of evidence argues against starting treatment with combination regimens, despite evidence that over time most patients do receive combination drug regimens and appear to tolerate them well. The current design paradigm for adjunctive trials generally strongly weights trials in favor of the sponsor drug.

Well managed, BPD is often compatible with fully good health, both symptomatically and functionally. Consequently, for whatever regimens are found to accomplish excellent symptom control, it is important to achieve regimens that are well tolerated by all bodily systems. This chapter emphasizes the tactics needed to accomplish this specific to individual medications. The chapter also addresses the serious, broad failure of pharmaceutical companies to develop new drugs with novel mechanisms for BPD therapy and proposes a series of steps that might reenergize drug development to the benefit of psychiatrists and patients alike.

Keywords Bipolar · Depression · Guidelines · Mania · Treatment

1 Introduction

Psychopharmacological treatment of bipolar disorder (BPD) has evolved substantially over the past decade. This chapter discusses the key changes and the evidence behind them. However, the changes principally involve treatment strategies, greater incorporation of adverse effect profiles, and more combined treatment strategies; in contrast, there has been relatively minimal change in the drugs available. Impediments to new drug development and recommendations to shift developmental paradigms to yield more effective regimens are also presented in the chapter. BPD is inherently complex, displaying in its symptoms and in patient cognition the underlying pathophysiological disturbances that translational research has partially characterized. BPD incorporates symptoms characteristic of other psychiatric disorders; as a result, in many circumstances patients present first with symptoms not specific to BPD, resulting in initial diagnosis and consequent treatment that, over time, is insufficient. This chapter also considers strategies for developing personalized treatment regimens that yield sustained highly satisfactory outcomes.

2 Early, Accurate Diagnosis of BPD

Because depressive episodes are generally more frequent than hypomanic episodes in BPD, more likely to prompt a patient to consult a physician, and more easily diagnosed by the physician, it is likely that patients with hypomanic or subthreshold features of BPD may be unrecognized and/or misdiagnosed as having major depressive disorder (MDD) (Bowden 2009a). Studies have indicated that bipolar characteristics can be detected in at least one-fourth of patients diagnosed with MDD (Goodwin et al. 2008; Hirschfeld et al. 2003). Using the knowledge that a subset of manic symptoms (distractibility, racing thoughts, affective instability, increased activity, pressured speech, and reduced need for sleep) are common in bipolar depressive states can aid in recognizing fundamental BPD in persons presenting with a major depressive episode (Goldberg et al. 2009; Vieta et al. 2010). Depressed bipolar patients treated with standard antidepressants without mood stabilizers are much more likely to experience affective instability, switches into hypomanic states, and not respond to adequate medication trials (O'Donovan et al. 2008; Tondo et al. 2009).

3 Assessing Published Studies in BPD

The common identifiable problems in clinical trials in BPD involve the degree of illness severity in a sample, dosing equivalence, clinical state (currently depressed, manic, mixed, subsyndromal, or in remission), enrichment to favor one arm of a study, and analytic techniques that are not optimal for the questions of interest. Consistent with other disorders, patients need to have evidence of at least moderate severity of illness, as indicated by proportion of time ill, number of syndromal episodes, and indicators of severity (e.g., hospitalization, suicide attempt, and a recent full episode). Without at least some of these indices, results are both suspect in validity and weakly generalizable to clinical settings. If a maintenance treatment regimen is to be interpreted as effective for all persons with BPD, patients with current depressive and current manic/hypomanic clinical states need to be enrolled (Bowden 2009a). For instance, a study that limits enrollment to patients experiencing manic episodes can only be assessed as relevant to continuation care for manic patients (Goodwin et al. 2008). A recent maintenance study enrolled subjects with an entering median GAF score of 80. Although this does not bias the study, it limits generalizability to a miniscule portion of the BPD population who are, in general, free of symptomatic and functional impairment (Geddes et al. 2010).

Occult difficulties include selection bias, which can be difficult to sort out. Perhaps, the indices easiest to identify are the proportion of patients enrolled who met the criteria for randomization and the proportion of patients randomized who completed the study. For both measures, a rate below 50% raises the likelihood of significant selection bias. One of the largest maintenance studies completed to date

in BPD randomized 31.9% of the subjects enrolled, and ended with only 9% of the enrolled subjects completing the 104-week randomized phase, despite a design that included drugs known to be effective in both treatment arms (Suppes et al. 2009).

Most adjunctive treatment maintenance studies require that patients considered for enrollment have failed a standard treatment trial with either lithium or valproate. In addition, once in an open acute phase, the only patients eligible for randomization are those patients both benefiting from the combination regimen of the experimental drug and the continued lithium or valproate, and who are also adequately tolerating the experimental drug. While this practice is consistent with some clinical situations, it also results in a higher effect size advantage for the regimen including the experimental drug in either an acute or maintenance study. Only one maintenance study allowed treating psychiatrists to choose use of either of the two drugs (valproate, lithium) that were to be the active treatments in the randomized, blinded phase, thereby avoiding bias in the critical maintenance phase (Bowden et al. 2000).

Regulatory agencies have not seen fit to find fault with maintenance studies that explicitly favor a sponsoring company's drug. This bias is called time-to-treatment bias in other areas of medicine (Greenhouse 1992). One approach that would yield equipoise across randomized treatment groups would be to randomize at the point of study enrollment; however, this practice has not been used to date.

Medication procedures during randomization can also introduce subtle biases. If relatively high and persisting use of medications for sleep, anxiety, or irritability is allowed, differences between randomized blinded regimens can be muted consequent to reduced symptomatology from the rescue medication and from greater use of the rescue medication in the group receiving the less efficacious regimen (Thase et al. 2008). In addition, the use of time to event analyses, which have obvious appeal because they yield a firm outcome and generally result in withdrawal of the subject from the trial, is increasingly recognized as problematic (Lavori 1992). Some patients will never have the defined endpoint in the period of the trial; also, early events are weighted more strongly than later ones in Kaplan–Meier analyses. The construct of terminating at first indication of relapse/recurrence is also at variance with clinical practice, which is to increase the dose of a partially effective and adequately tolerated regimen and/or to add an adjunctive medication that has either a different profile of symptom benefits or a differing mechanism of action (or both).

Evidence further indicates that analyses that use last observation carry-forward (LOCF) analyses tend to inflate the drug–placebo difference in maintenance trials (Barnes et al. 2008). The definition of endpoints in maintenance trials can be problematic. For instance, a major change in regimen (e.g., discontinuation, addition of another mood stabilizer, and hospitalization) has at least face validity for clinical importance. A recent randomized open study in BPD included simply increasing the dose of the randomized treatment in the face of worsening symptomatology as a criterion for treatment failure (Geddes et al. 2010). This criterion is at variance with most guidelines and clinical practice, in which increasing the dose of an adequately tolerated drug is generally the first step in addressing care of a still

symptomatic patient. Also, in an open trial, use of such an endpoint is subject to investigator and patient biases regarding the effectiveness of the regimen to which the patient was randomized.

Studies using design features that are intended to retain as high a proportion of randomized subjects as possible by continuing patients beyond a first defined endpoint, and that reduce early terminations from all causes, are much less prone to distorting the results. The practicability of this strategy is strongly supported by the success of such methods in the recent LiTMUS study, which compared lithium plus optimized treatment to optimized treatment without lithium in a 6-month trial, and retained 85% of patients to study completion (Thase et al. 2010).

4 Practice Guidelines

Over the past decade, treatment guidelines for major medical disorders have become routinely available. These can simplify the efforts of clinicians to remain current and deal most effectively with complex decisions required in the course of treating individual patients. The symptomatic and functional complexity of BPD, coupled with the chronic expression of the illness over much of a lifetime, serves to make guidelines particularly useful in BPD. Most guidelines are the products of professional organizations, although some guidelines have been developed by individual countries or by health delivery systems. The latter can have advantages in tailoring treatment strategies to medications and cost considerations specific to a country, or to a specific health care system. However, in general, psychiatrists will find greater utility in guidelines that are regularly revised based on new information. For instance, the Texas Implementation of Medical Algorithms (TIMA) guidelines were developed with national inputs, an expert staff, and several unique perspectives [involvement of patients and advocacy groups in the process, field testing of the practicability of the guidelines and of their impact on clinical outcomes in public sector psychiatric settings (Suppes et al. 2005)]. The particular circumstances that provided the leadership and funding for the initiative appear unlikely to recur. Therefore, although TIMA guidelines remain useful for many purposes, new knowledge and new treatments developed since 2005 limit their utility as a primary resource.

The guidelines of the American Psychiatric Association, the Canadian-based CANMET guidelines, and those of the World Federation of Societies of Biological Psychiatry (WFSBP) have particularly broad relevance, adequately resourced staff support for review efforts, and expert advisory groups covering all facets of treatment. However, emphases and development strategies differ among these (Grunze et al. 2009, 2010; Yatham et al. 2009). Only the WFSBP guidelines systematically raise safety, tolerability, and potentially undesirable interactions to an equal level with efficacy versus placebo in determining recommendations (Grunze et al. 2009). These recommendation grades (RG), which combine assessments of efficacy and safety/tolerability, can be viewed as steps: Step 1 would be prescription of

a medication with a RG of 1, indicating the highest rating on both dimensions. Were this treatment to fail, all other Grade 1 options would generally be tried first before shifting to a treatment with an RG of 2, then 3, 4, or 5. In some cases, and depending on the evidence from controlled studies, the combination of an RG 1 and an RG 2 option could preferentially be tried instead of combining two RG 1 options. Full evidence for efficacy from controlled studies is based on two or more double-blind, parallel-group, randomized controlled studies showing superiority to placebo.

Fifty-three members of the WFSBP Task Force on Treatment Guidelines for Bipolar Disorders provided critical reviews and addition of remarks about specific treatment considerations in their respective countries. A second draft, revised according to the considered recommendations, was then distributed for final approval. These guidelines were established without any financial support from pharmaceutical companies. Both the mania and separately published depression guidelines recommend that treatment generally be initiated with a medication fulfilling the criteria for category of evidence for efficacy (CE) of "A" and a RG of "1."

Evidence regarding how long clinicians should wait before changing or amending a medication is generally lacking. However, in controlled studies, most successful investigational drugs start to separate from placebo within 1 week, and most differences between regimens occur within the first 4 weeks of adequate exposure. The WFSBP task force recommends that clinicians usually commence treatment with carefully chosen monotherapy before adding a second drug to minimize side effects and medical risks.

5 Tactics in Selecting and Implementing Therapies

The WFSBP guidelines review fundamental strategic therapeutic goals and specific tactics to accomplish them. These include the importance of continuing engagement of significant others in the treatment plan and visits. When choices exist for a recommended medication, treatment should be started with the form most likely to be tolerated, which will generally be a sustained release preparation over an acute, shorter than 24-h half-life formulation. New drugs and new formulations should be incorporated into practice decisions as they become available. When endeavoring to simplify a regimen, the WFSBP guidelines recommend discontinuing medications with the greatest side effect burden first. Discontinuation of any medication should be gradual unless medical necessity requires otherwise. When adding a new medication, use an "overlap and taper" strategy. Previous experience with a drug, patient preference, and evidence for efficacy in maintenance treatment should all be taken into account. The presence of other medical disorders or specific adverse effect profiles frequently experienced with prior medications (e.g., cognitive dulling or sedation) should be considered in drug selection. Although some guidelines recommend stronger consideration of an antipsychotic if manic symptoms are severe, there is negligible information to support this strategy. The one direct

comparison of an antipsychotic and a traditional mood stabilizer (haloperidol vs. valproate) for hospitalized patients with psychotic mania found equivalent outcomes with the two drugs (McElroy et al. 1996).

Substantial differences exist across guidelines, both in format and in ranking recommendations. For instance, the WFSBP guidelines for depression in BPD ranked the efficacy information for lamotrigine at E (not recommended at all) on the basis of five consistently negative registration trials versus placebo (Grunze et al. 2010). However, given a small significant effect size benefit in a meta-analysis as well as other small positive studies (including one as adjunctive to failed lithium), the task force decided on a final category for efficacy recommendation of "B" and an overall recommendation grade of "3" on the 1–5 scale (Grunze et al. 2010). In contrast, other recent guidelines recommended lamotrigine as a first line selection for depressive episodes (Yatham et al. 2009). Some guidelines emphasize algorithms in recommendations; however, beyond the first or second decision levels, almost no systematic open, much less blinded, randomized data exist (Suppes et al. 2005). The WFSBP guidelines are exceptional in providing practical details on the magnitude of difference, or effect size advantage of efficacious treatments, and also on study characteristics that might influence the reader to have more or less confidence in using a particular treatment in an individual patient. As an example, some studies have cross-over designs, possible sponsor bias, or included both patients with BPD and MDD, each of which reduces confidence in guidance for BPD interventions. The WFSBP guidelines also modify criteria for efficacy relevant to psychotherapy studies, requiring evidence for superiority to a "psychological placebo" in a study conducted with adequate blinding.

Registration trials generally use relatively high doses of a drug for the good reason that it is better to achieve benefit over that seen with placebo even at the cost of some increased adverse effects rather than fail to show benefit. For the few drugs for which serum levels can be used as a guide, the most extensive data come from studies in hospitalized manic patients. In those studies, the serum levels indicated for valproate and lithium were not established as necessary for maintenance efficacy. One study of valproate indicated that a range of 75–99 μg/ml yielded better outcomes than higher or lower ranges; another report clearly indicated increased adverse effects at serum levels over 100 (Bowden et al. 2000; Keck et al. 2005). Although serum levels are not generally useful for other commonly used drugs for BPD, in the few maintenance studies that have compared two dosages, few or no significantly greater benefits accrued with the higher dosages, yet adverse effects were generally higher. Therefore, cautious efforts to reduce the dose of medications begun during full episodes are a sound policy, even for drugs without explicit data on the point [monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), norepinephrine and serotonin reuptake inhibitors (NSRIs), and gabapentin]. Lamotrigine dosed at 400 mg did not appear as effective as 200 mg/day in maintenance for depression, although the sample size was too small to provide definitive results (Calabrese et al. 2003).

6 Specific Components of Treatment

6.1 Mania

The WFSBP mania guidelines list four medications in the top level (1 on the 5 point scale) with strong evidence of both efficacy and safety/tolerability: aripiprazole, risperidone, valproate, and ziprasidone. Four antipsychotic drugs – asenapine, haloperidol, olanzapine, and quetiapine – as well as lithium and carbamazepine were rated as level 2 consequent to safety, risks in combination with other organ system pathology, or drug interaction problems. For example, factors contributing to the ranking for lithium included slower onset of action, need for frequent plasma levels, thyroid and kidney monitoring, and unsuitability for use in persons with thyroid or renal disorders. However, the guidelines also note that if there are reasons to select it for maintenance treatment (e.g., prior benefits and tolerability), it would qualify for level 1.

Treatment with tamoxifen also appeared to be beneficial in a small, single-site study (Zarate et al. 2007). The lack of multiple sites, adequate sample size, and any confirmatory studies regarding proof-of-concept precludes making strong recommendations for this agent; however, with appropriate caution and explication to the patient about limited evidence, this drug might be tried if the regimens summarized above were inadequate.

6.1.1 Combination Regimens for Mania

Most of the medications approved for monotherapy treatment of mania have also been studied in adjunctive or combination regimens. In adjunctive designs, patients taking lithium or valproate for mania for at least 2 weeks at adequate dosage/serum levels who continue to experience at least moderately severe manic symptoms have had an antipsychotic drug started at the point of randomization, with lithium or valproate continued in open fashion along with placebo. The design therefore selects only patients who have failed, or partially failed, to benefit with one of the two mood stabilizers. The monotherapy arm of the studies is thereby weighted toward lithium/valproate nonresponders, thus favoring the adjunctive treatment regimen. Two studies that included patients who were not taking lithium or valproate at the time of enrollment but had one or the other started at the same time that the combination antipsychotic drug (risperidone in one, quetiapine in the other) was started did not report superiority for the true combination regimen (Sachs et al. 2002; Yatham et al. 2004).

Taken in aggregate, these results argue against commencing antimanic treatment with combination therapy (commencing treatment with two drugs), based on reduced likelihood of efficacy, and independent concerns about safety, drug interactions, or increased costs. In addition, two adjunctive trials were conducted by including patients who remained manic while receiving carbamazepine. In each

trial, risperidone or olanzapine failed to show superiority to carbamazepine alone, consequent to clinically significant reductions in plasma concentrations of the two antipsychotic drugs mediated by carbamazepine's induction of the 3A4 isoform of hepatic oxidative enzymes (Tohen et al. 2008; Yatham et al. 2003). Adjunctive valproate added blindly to haloperidol in hospitalized manic patients both significantly improved manic symptomatology compared to haloperidol plus placebo and, importantly, resulted in significantly lower haloperidol dose in the adjunctively treated group (Muller-Oerlinghausen et al. 2000). One of the two combination studies for quetiapine and the single adjunctive study for ziprasidone in acute mania did not result in superiority for the antipsychotic plus mood stabilizer compared to mood stabilizer alone (Weisler et al. 2004; Yatham et al. 2004).

An additional line of evidence suggesting that adjunctive treatment regimens generally do not warrant initial use comes from comparing the rates of completion of blinded acute mania studies versus rates of completing open acute mania phases that were preludes to randomization for mania trials. Whereas completion rates for olanzapine as monotherapy were over 60% in both trials, in the adjunctive trial only 29% completed the open phase (Tohen et al. 2002). Similarly, whereas over 50% of quetiapine-treated patients completed monotherapy trials, the rate was 31% completing the open phase before randomization for a maintenance trial. These results indicate that actual persistence and tolerability rates are substantially lower than reported in the monotherapy studies (Suppes et al. 2009).

6.1.2 Mixed Manic States

Recommendations for mixed mania are tentative in part because of inadequate definitions of the state. DSM-IV-TR requires that patients meet full criteria for manic and depressive episodes concurrently; however, many authorities recommend variants on this criterion (Swann et al. 1997). Descriptive studies indicate that patients who qualify for mixed states have full depressive symptoms but somewhat less severe manic symptomatology than observed in acute mania (Swann et al. 2001). Furthermore, the few treatment studies of mixed states base inclusion on severity of manic rating scale scores, but do not require threshold severity for depression. Also, most reports are not limited to mixed mania, but include secondary analyses of patients meeting either manic or mixed mania criteria. Although several studies of acute mania indicate less benefit with lithium treatment than with valproate, and second-generation studies report equivalent outcomes in mixed and manic subjects, the lack of samples selected strictly for mixed mania limits conclusions applicable to practice settings. The major study of treatment outcomes in maintenance care noted that patients with mixed states had less overall benefit with regard to efficacy and tolerability than did manic patients, regardless of whether they were treated with lithium or valproate (Bowden et al. 2005). Examination of these results suggests that mixed states are principally more difficult to treat because their overall severity of illness is higher that strictly depressed or manic patients, and that they are associated with poor tolerability of regimens.

6.1.3 Psychotherapy

No studies have been published indicating superiority of a psychological intervention for mania versus placebo (Grunze et al. 2009).

6.2 Depression

The firmest observations regarding treatment in the WFSBP bipolar depression guidelines are that the risk of treatment-emergent affective switches during relatively short-term treatment is low to negligible, as long as the antidepressant is added to an adequately dosed mood stabilizing drug. Among all mood stabilizers and antidepressants, the only one for which the recommendation was at the top level for acute treatment was quetiapine; however, due to its tolerability issues, quetiapine does not qualify for a recommendation grade higher than 3 for extended use. Valproate, lamotrigine, olanzapine–fluoxetine combination, fluoxetine, olanzapine, and modafanil were rated as 3. No other treatment, including lithium, SSRIs, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagal nerve stimulation (VNS), was rated above grade 4. The guidelines conclude that "... it is virtually impossible to give a recommendation for antidepressants as a group given the diversity of agents, their dosing, observed outcomes and trial quality" (p. 93). The recommendation in the guideline is therefore essential to apply the steps described earlier in *Tactics* (Sect. 5).

I will briefly review data for individual drugs. Quetiapine has two strongly positive acute depression monotherapy studies in BPD-I and BPD-II depression. However, the possibility exists that blinding was inadequate consequent to quetiapine's side effects, and that nonspecific effects on weight gain, sleepiness, and appetite contributed to superiority versus placebo; in addition, the presence of serious adverse effects associated with the drug temper the overall grade of recommendation (Grunze et al. 2010; McElroy et al. 2008; Thase et al. 2006). Similarly, adverse effects associated with both olanzapine and fluoxetine, plus the modest benefit of olanzapine alone in acute bipolar depression, have tempered evidence-based support and use of each intervention (Grunze et al. 2010). Four small single-site studies, plus a meta-analysis of these, indicate a significant effect size benefit of 0.35 for valproate in bipolar depression, plus relatively strong evidence of the maintenance benefits of valproate over both placebo and lithium (Bowden et al. 2000; Smith et al. 2010).

Despite consistently negative monotherapy studies of lamotrigine, in a single study, lamotrigine added to lithium or valproate that had not alleviated bipolar depression was superior to continued lithium or valproate alone. However, the study had an enriched design favoring adjunctive lamotrigine (van der Loos et al. 2009). Two lamotrigine maintenance studies – one enrolling recently depressed, the other recently manic patients – found good evidence for prophylaxis against new depressive episodes, but lamotrigine was inferior to lithium in prophylaxis of manic

episodes. Another recent, randomized, blinded maintenance study of lamotrigine alone versus lamotrigine plus valproate for patients who had responded to combined lamotrigine and valproate while acutely depressed found consistent advantages for this combination regimen over lamotrigine alone on depressive symptoms and relapse over an 8-month period (Singh et al. 2009). Thus, although a role for lamotrigine in maintenance treatment is consistently supported, its use acutely or as maintenance monotherapy is not warranted based on current evidence. Negative trials in bipolar depression have been reported for both aripiprazole and ziprasidone (Sachs et al. 2009; Thase et al. 2008).

Several additional drugs appear beneficial in small, single-site studies. The lack of multiple sites, adequate sample sizes, and any confirmatory studies regarding proof-of-concept preclude making strong recommendations for this diverse group, but with appropriate caution and explication to the patient about limited evidence, any of these drugs might be tried if the regimens summarized above were inadequate. The drugs include the dopamine agonist pramipexole (Zarate et al. 2004) and stimulants (Shelton and Reddy 2008). Finally, although no recent studies have been published, current evidence suggests that MAOIs have a much more benign tolerability profile (Stahl and Felker 2008).

6.3 Maintenance Therapy

The evidence for lamotrigine's prophylactic benefits on depression and that for valproate are summarized above, but for other treatments very limited adequate evidence of benefit on depression is available. This is partly due to study designs that enrolled manic or recently manic patients but not depressed patients. Quetiapine maintenance enrolled both manic and depressed patients in the open phases of maintenance studies and demonstrated benefits on time to depressive episodes, but used designs that favored quetiapine tolerability and efficacy. No significant benefit on depressive symptomatology was noted during maintenance treatment with aripiprazole or ziprasidone. A 2007 systematic review of all maintenance studies published at the time compared diverse treatments with placebo; results indicated that divalproex reduced the risk of withdrawal for depression by 60%, lamotrigine reduced the risk by 35%, lithium reduced the risk by 27%, and olanzapine reduced the risk by 22%. The reductions produced by divalproex and lamotrigine were significant, but those produced by lithium and olanzapine were not (Smith et al. 2007).

7 Tactics for Adverse Effects

Lamotrigine generally has the most benign profile of drugs used to treat BPD, with headache, dizziness, and, among patients with initial obesity, a usually desirable loss in weight over 1 year of treatment as the only consistent side effects (Bowden

et al. 2006a). The severe risk of Stevens Johnson-type immune system response is generally avoidable by slow titration of dosage as recommended, including starting valproate in patients stabilized on lamotrigine by reducing lamotrigine dose by half.

Valproate's teratogenic risk is limited to the first trimester of pregnancy. Hepatic impairment is limited to youth with immature hepatic function, generally under 2 years of age. Alopecia can be avoided or minimized by supplemental selenium or zinc taken as a multivitamin, separated by several hours to avoid chelation in the gastrointestinal tract. Valproate reduces cholesterol levels, with some evidence indicating that this is principally in patients with initially elevated levels (Bowden et al. 2006b). Valproate is consistently better tolerated than lithium or carbamazepine (Smith et al. 2007).

The 3A4 oxidative enzyme effect of carbamazepine broadly reduces levels of many drugs, both psychotropic and general medical. For example, concurrent carbamazepine reduced risperidone and olanzapine levels so that the usual benefits of these drugs in mania were quenched (Tohen et al. 2008; Yatham et al. 2003).

Most serum level relationships for valproate and lithium are based on acute mania studies (Bowden 1996, 2000; Bowden et al. 1996). For both drugs, evidence-based information suggests that many patients will sustain benefits at lower serum levels than ordinarily used in mania. For valproate, there is evidence of a lower level of benefit around 45 μg/ml; increased adverse effects, particularly sedation, increased appetite, and platelet count reduction, are seen at doses above 100 μg/ml (Allen et al. 2006; Bowden et al. 2000).

7.1 Insulin Resistance, Diabetes, and Obesity

The mainstream use of olanzapine and quetiapine has shown that these two antipsychotics routinely cause worsening laboratory parameters for lipids and glucose and for physical status (e.g., weight gain). Although both first- and second-generation antipsychotics can have such effects, the frequency and magnitude of these problems are strongly associated with the molecular structure of all of the "pine"-suffix drugs: clozapine, olanzapine, and quetiapine. Structures identified as "dones or zoles" have little or no such impact: aripiprazole, haloperidol, risperidone, ziprasidone, and lurasidone. The single drug that is inconsistent with this division is asenapine, which appears to have low risks for these problems. Use of drugs with this propensity is generally not of major consequence in treatment of acute manic episodes, but continued use of medications with these risks is highly likely to be associated with metabolic syndrome. If drugs with such effects are deemed suitable for continuation care, it is incumbent to frequently assess weight, abdominal girth, hemoglobin A1C, glucose, and LDL levels (Grunze et al. 2009; Yatham et al. 2009).

Carbamazepine and lithium have been associated with increased LDL in multiple studies, with lithium also moderately increasing weight (Tohen et al. 2002, 2008). Valproate causes weight gain but does not contribute to other aspects of

metabolic syndrome. In both acute and maintenance use, it has consistently been associated with reduced lipid levels, particularly in patients with elevated cholesterol levels (Bowden et al. 2000, 2006b). Lamotrigine appears to be neutral with regard to laboratory indices of metabolic syndrome and, for patients with elevated BMI scores, likely to contribute to weight loss in maintenance treatment (Bowden et al. 2006a). The use of antipsychotic drugs with these propensities in youth with BPD is particularly risky, with studies reporting major increases in weight within a month of exposure (DelBello et al. 2006). The FDA black box warning regarding this increased risk has recently been updated to stress these risks. Obesity at an early age lengthens the duration of risk impact of such adverse effects on overall health status.

7.2 Thyroid Function

Although lithium is the only drug used to treat BPD that adversely affects thyroid function, psychiatrists need to evaluate thyroid function as part of a comprehensive assessment in all patients, since diverse types of studies indicate increased risks for depression associated with suboptimal thyroid function. Although evidence is largely inferential, it appears that high levels within the standard range labeled as normal are actually associated with increased risks for depression. The large sample of lithium-treated patients in lamotrigine maintenance registration trials provided an excellent test of this phenomenon. Patients treated with lithium whose thyroid-stimulating hormone (TSH) levels increased over the course of the 18-month study were significantly more likely to develop depressive episodes than those who had no increase in TSH. No increases in TSH or similar increases in depressive episodes were observed with lamotrigine or placebo (Frye et al. 2006). The data suggest that if lithium has benefited a patient and is to be continued in prophylaxis, regular assessment of thyroid function is required; concomitantly, thyroid supplementation should be vigorously maintained, with targeted TSH levels in the range of 1.5–2.

7.3 Renal Function

Similar to lipid and glucose metabolism, renal function poses the additional conundrum that it is generally symptomatically silent to the patient and physician. Patients receiving lithium should be regularly assessed and even small elevations over time in creatinine noted as sufficient reason to discontinue lithium to forestall severe renal impairment. Patients need to be informed of the serious additive risk of using NSAID-type analgesic medications during lithium therapy.

7.4 Cognitive Adverse Effects

Almost any drug that enters the brain poses some risk for obtundation, psychomotor slowing, sedation, and slowed reaction time in some individuals. The risks of such side effects are generally dose-dependent and highly variable on both a drug class basis and from one person to another. Given the fundamental objective of attaining healthy functional status for most patients with BPD, cognitive dysfunction in any form should be viewed as unacceptable, and efforts undertaken to reduce dosage, timing of dosage, or discontinue use of the causal drug. This group of side effects is much less often associated with valproate, particularly in extended release forms, lamotrigine, and those antipsychotics with less or negligible directly sedative properties (e.g., aripiprazole and ziprasidone). Benzodiazepines and similar mechanism drugs, e.g., zolpidem, pose particular challenges. Patients obtain prompt desired effects (sleepiness, reduction in acute anxiety, or physical manifestations thereof), but are at substantial risk for overall impairments in reaction time, speed of associations, and both verbal and working memory. Additionally, indirect evidence from animal studies suggests that benzodiazepine effects in reducing cortisol production may interfere with consolidation of learning, thereby adversely impacting adaptive efforts to overcome excessive fear responses to perceived threats, a common problem in anxiety-prone BPD (Garfinkel et al. 2009).

7.5 Agitation/Tremor/Akathisia

Many drugs effective in treating BPD have admixtures of these adverse effects. Understanding the differences in mechanisms of these adverse effects can aid in assessment. Akathisia and agitation, although distinct from classical Parkinsonian-like side effects, still may have some physical examination evidence of cog-wheeling, worsening with intentional motor activity, micrographia, and similar lack of efficient integrated movements of flexor and extensor muscles. These characteristics implicate antipsychotic drugs, even if they are toward the end of the spectrum with low extrapyramidal risks (e.g., quetiapine and olanzapine). Resting tremor is consistently more common with lithium than with antipsychotic drugs or valproate. Movement abnormalities from serotonergic drugs generally cause jerking movements of large muscle groups. Rarely, but significantly, MAOIs may result in dyskinetic movements fully analogous to those consequent to antipsychotic drugs.

7.6 Stevens–Johnson Syndrome

Two drugs useful in treating BPD – lamotrigine and carbamazepine – cause this immune system-mediated reaction, so psychiatrists need to be fully aware of risk factors for developing the severe skin, mucous membrane, and internal organ

manifestations of this inflammatory, small vessel disrupting syndrome. Because there appears to be cross-reactivity of the large number of drugs that can cause this syndrome and its variants, initiation of either drug in any person who has a history of likely serious rash is inadvisable. Second, other limitations exist in terms of evidence-based efficacy and, for carbamazepine, pharmacokinetic disturbances that markedly limit the circumstances in which it is suitable; thus, neither drug should be used in such conditions. Obviously, the two drugs should not be used together. In this author's experience, one should not assume that other physicians, physician's assistants, or nurse practitioners will know about the risks of severe, painful, life-threatening rash from these drugs, nor know how to differentiate a serious from a nonserious rash. Therefore, when either drug is started, in addition to describing early warning signs, provide a plan for the patient's prompt assessment by a knowledgeable clinician. With these straightforward steps, plus appropriate incremental dosing, including adding lamotrigine to valproate or the reverse addition, most patients will reach stable dosing schedules beyond which risks for severe rash are extremely low unless dosage is interrupted for a sustained period; in this case, retitration is essential.

For all drugs and ECT, the simple tolerability objective in implementing the therapies is to use them in such a manner that persistently annoying or function-limiting adverse effects – e.g., impaired concentration, alertness, or motor speed or accuracy – do not occur. Similarly, drugs that can cause physical changes noticeable to others, e.g., tremor, sleepiness, significant weight gain, or other organ system health risks (e.g., metabolic syndrome), should either not be used or the dose should be adjusted to eliminate the side effect. This tactic, also driven by the particular profiles of benefits provided by individual drugs, will more often than not result in combination regimens for which substantial evidence exists of both acute and maintenance control of manic symptoms. Examples include adding second-generation antipsychotics to lithium or valproate, adding valproate to antipsychotics, and combining treatment with lithium and valproate. Recent evidence regarding control of depression also supports the addition of lamotrigine to lithium and valproate to lamotrigine (Singh et al. 2009; van der Loos et al. 2009).

8 Circadian Rhythm Pattern

A high proportion of individuals with BPD have sleep disturbances, but these differ from those observed in other medical conditions. Patients with BPD tend to increase their activity and interests in the evening, which contributes to their staying awake well into the early morning hours, resulting in fewer hours asleep and in turn likely contributing to impaired cognition, alertness, and memory consolidation (Mansour et al. 2010; Stickgold 2005). This propensity to maintain an idiosyncratic pattern of activity often interferes with job requirements. Some individuals with BPD recognize this disturbed pattern, but many view it simply as the way they approach a day. For the latter group, a sustained effort in treatment

is needed to first help the patient recognize the adverse consequences of the pattern and, second, develop ways to modify it. Although not systematically studied, many psychiatrists use small doses of olanzapine or quetiapine (rather than drugs that act on benzodiazepine receptors). Such practice is indirectly supported by human and animal studies indicating that sleep loss results in excessive activation of dopaminergic systems in the brain (Oganesyam et al. 2010; Volkow et al. 2008).

9 Vocational Initiatives

BPD presents a unique challenge to mental health professionals in regard to patients' desires to remain employed, to seek temporary or permanent disability status, and, most commonly, to return to work after a period of inability to work. The evidence for work loss associated with BPD is consistent and compelling (Bowden 2009b). Functional impairment contributing to greater vocational impairment from BPD than from MDD is also consistently observed. A key point in workforce issues with patients usually stems from inconsistencies in their apparent capabilities, which can appear higher than the person's current or recent work experience. Here, evidence-based facts help us, but ultimately this requires that patients apply judgment and flexibility for both their work setting and in revising work goals. These judgments require that individual patients weigh the advantages and disadvantages associated with work. Some of this counseling and goal setting will need to be a part of a brief psychiatric appointment, but often concurrent counseling on a more frequent basis will yield better long-term outcomes in this area. Recent studies indicate that patients with BPD have subtle but sustained impairments in some aspects of cognitive function, particularly working memory (Goldberg and Burdick 2008). These deficits are generally much less severe than the ones seen in schizophrenia, but can still contribute to workplace and educational difficulties.

10 Moving Toward and Managing Health

Achieving adequate sleep and effective social relationships, improving structured thinking, and helping the patient to develop a structured, healthy lifestyle all serve to move the patient over time on a trajectory to health both symptomatically and functionally. It is critical that all of these factors and experiences generally associated with health, not illness, be addressed in routine medical visits. As with any habit-related issue, such goals are not achieved through one-time learning, but gradually become integrated, yielding durable benefits that complement other parts of an overall treatment effort. These efforts are also particularly important because they gradually place the patient in charge of this multifaceted illness, thus allowing some patients an opportunity at effective self-correction outside of the

doctor's office, and increasing their confidence in managing stressors. If these salutary outcomes occur, it is essential that the psychiatrist or other mental health professional shift from a principally illness-oriented attitude (e.g., "you are fundamentally sick") to an attitude focused on maintaining health. For example, this can mean focusing on the balance between work and recreational activity, dealing with important family issues, and refining major life goals; all are issues difficult to deal with while severely impaired. Such issues may not seem to be the substrate of BPD as a disease, but to avoid shifting to this health-focused level is to fail our professional responsibilities. Such a shift is not fundamentally different from the shift an internist would make with a patient who gets hypertension or an immune system disorder under control and is in remission.

Large prospective studies consistently report that a substantial proportion of broadly representative patients with BPD-I and BPD-II achieve sustained excellent symptomatic and functional status (Weiss et al. 2005). These patients take prescribed medications faithfully, often engage in counseling even over several continuous years, have come to develop effective habits regarding sleep and activity, and recognize subtle indices of BPD.

11 Toward a Fresh Mindset on Drug Development, Early Phase Testing, and Design of Registration Studies for BPD

Over the past 2 years, many major pharmaceutical companies have terminated thousands of employees working on neuropsychopharmacology units, largely consequent to failure to develop genuinely novel compounds despite expenditure of ever-larger sums toward such goals. Over 50 years after the introduction of lithium, antidepressants, and antipsychotics, approaches to drug discovery and clinical testing remain for the most part embedded in the same paradigms. Yet, less than 50% of patients with BPD receive adequate mood stabilization regimens. Psychosocial treatments with demonstrated efficacy in randomized trials are infrequently adopted in community settings, jeopardizing long-term outcome (Bowden 2008). Current clinical trial methodologies contribute barriers to fundamental advances founded in translational research studies. Furthermore, design features used for registration studies of new drugs for BPD have inherent limitations that limit their external validity and generalizability, particularly in community settings (Bowden 2008).

The procedures applied by industry for developing new molecules continue largely to use basic science paradigms that were developed for drugs targeting major neurotransmitter receptors. These animal model systems (e.g., forced swim test) and rating instruments [e.g., Hamilton scales, Young Mania Rating Scale (YMRS), Montgomery Asberg Depression Rating Scale (MADRS)] developed over 50 years ago still hold sway, despite important, mode-shifting new knowledge in areas such as neuroplasticity, signal transduction in neurons, and overlap of

certain disturbed behaviors across several syndromes. Other barriers include the consequences of market driven preferences for emphasizing efficacy, even if short term, and deemphasizing tolerability. Such practices adversely impact adherence and sustainability of benefits of a regimen and reduce opportunities to discover early, via animal and clinical testing, what constitutes the full profile of beneficial targets of a molecule. Other factors include a shift away from basic laboratory development of new molecules, even among some of the largest pharmaceutical firms, and business policies that place clinical testing of a drug subsequent to first authorized sale of the drug in a sales unit, not a clinical research group. An unintended consequence of this latter policy is that it reduces the likelihood of testing additional symptomatic or other syndromal disorders that might be targets of a drug's actions.

Such policies serve to retard drug development. Other current policies – for instance, separating efficacy results from tolerability and sustainability results – have in some instances delayed recognition of and attention to adverse consequences of a treatment. For this health policy and public health issue, the most appropriate level to initiate changes is not at the disease level nor within the pharmaceutical industry, but in the national regulatory agency that sets policies for what is required, what is optional, and what is not allowed in planning and execution of studies intended for approval for clinical use.

Changes in two other areas of federal policy could substantially strengthen the clinical development of novel compounds. Unlike areas such as intellectual property, in which the artist and his or her heirs retain certain financial interests in profits and control of use for over half a century, in the USA, with small variations across other countries, the patent life clock starts ticking when a drug patent is first filed with the FDA. This results in an understandable plan to front-load both high unit pricing and sales volume through large-scale advertising so as to recoup developmental costs and yield a profit before patent protection is lost. This author is neither a patent attorney nor law professor, but believes that an appropriate body convened to study these issues could propose plans that incentivize longer-term scientific product development that would still be consistent with national statutes. Companies would then have greater incentive (as opposed to present actual disincentives) to take a longer-term approach toward product development, toward testing for alternative uses to that of the first approved disorder, and toward amortization of developmental cost projections. Although I understand the reasonable desire of the public and political leaders to see drug costs realistically low, such objectives could be met by changes such as these, which would serve the public health interests of patients and payers.

Experts in all walks of neuroscience have proposed approaches that can contribute to breaking the logjam of very low success rates in drug development and providing cost-effective applications for both simple and novel interventions for BPD. As a final example, I refer back to the section on sleep and circadian dysfunction in BPD. Were changes along the lines suggested here in place, firms and clinical investigators would actually study treatments for sleep disturbance in BPD, which is totally lacking under present laws. They would actually develop

scales and outcome criteria dealing with fundamental domains of illness such as circadian status, supporting a componential rather than the current syndromal first, last, and only approach. Doctors, patients, and the health of the nation would all benefit, as would the climate for private enterprise in pharmaceutical drug development and sales.

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Nonpharmacotherapeutic Somatic Treatments for Bipolar Disorder (ECT, DBS, rTMS)

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Contents

Abstract Nonpharmacotherapeutic, somatic treatments play an essential role in the management of bipolar disorder (BPD). Studies indicate that electroconvulsive therapy (ECT) is an effective treatment for acute mania, bipolar depression, and

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mixed affective states. Furthermore, it is an important second-line treatment option, as most pharmacotherapy-resistant patients respond to ECT. Specific challenges for patients with BPD receiving ECT include the risk of mood switching, and the need to evaluate and manage concurrent treatment with lithium and anticonvulsant mood stabilizers. Although the current evidence for alternative and newer physical treatments (e.g., transcranial magnetic stimulation, vagus nerve stimulation, stereotactic ablation, and deep brain stimulation) is preliminary, all of these novel methods show promising potential and merit further research.

Keywords Anticonvulsants · Bipolar disorder · Deep brain stimulation · Depression · Electroconvulsive therapy · Lithium · Mania · Stereotactic ablation · Transcranial magnetic stimulation · Vagus nerve stimulation

1 Electroconvulsive Therapy

Considerable evidence exists for the efficacy of electroconvulsive therapy (ECT) in treating episodes of mania, depression, and mixed affective states in patients with bipolar disorder (BPD).

1.1 Treatment of Acute Mania

A review of retrospective and prospective studies up to 1994 found that about 80% of acutely manic patients respond to ECT treatment (Mukherjee et al. 1994). In the only sham-controlled trial of ECT in mania, Sikdar et al. (1994) compared outcomes after eight active or sham bitemporal ECT in a randomized trial involving 30 manic patients. All patients also received concurrent treatment with chlorpromazine starting at a dose of 600 mg. Outcomes were highly significantly different and clearly superior in the active ECT group, with more patients recovered (12/15 vs 1/15), and a faster rate of improvement.

1.1.1 Efficacy Relative to Other Treatments

Only two randomized controlled trials have tested the efficacy of ECT relative to other treatments in acute mania. Small et al. (1988) randomized patients to receive ECT or lithium treatment over 8 weeks. Patients were also on concomitant antipsychotic medications, and evaluations of outcome were not completely blinded due to the study design (no sham ECT or placebo medications). Overall efficacy outcomes did not significantly differ between the two groups, though a slight advantage for

ECT was found in global assessment ratings (Clinical Global Impression and Global Assessment scales); these were evident only at weeks 6–8. Efficacy in the ECT group may have been compromised in that the first six ECT patients received unilateral ECT with no improvement before going on to receive a mean of only 5.2 bitemporal ECT treatments. The form of unilateral ECT used was almost certainly suboptimal, with the closer Lancaster (rather than d'Elia) spacing of electrodes and dosing that was probably not sufficiently suprathreshold (exact details not given).

Mukherjee et al. (1988, 1994) randomized manic patients who had failed to respond to treatment with either lithium or antipsychotic medications to treatment with ECT ($N = 22$, right unilateral, left unilateral, or bitemporal) or a combination of lithium and haloperidol ($N = 5$). Thirteen of the 22 patients receiving ECT met strict criteria for remission lasting at least a week after the completion of ECT, while none of the pharmacotherapy group responded. One other earlier randomized controlled trial that compared ECT with chlorpromazine in patients with mania and schizophrenia found no difference in outcomes (Langsley et al. 1959). However, as results were not reported separately for patients with mania and schizophrenia, it is difficult to draw any conclusions from this.

The likely superiority of ECT to pharmacotherapy is supported overall by a number of retrospective comparisons. In a case-matched review, McCabe et al. (1976) found ECT superior to chlorpromazine, with all ECT patients responding compared to 18 of 28 in the chlorpromazine group. The ten medication nonresponders then responded to ECT. Thomas and Reddy (1982) found no significant differences between treatment with ECT, chlorpromazine, or lithium, though all ten patients in the ECT group responded. Black et al. (1987) ($N = 37$) found that significantly more patients improved with ECT (78%) than with lithium given at adequate dosage (62%) and at inadequate dosage (56%). Pharmacotherapy nonresponders then received ECT, with a 69% response rate. Alexander et al. (1988) ($N = 18$) and Stromgren (1988) ($N = 17$) both reported ECT response rates of 56% and 59% in patients who had previously failed to respond to pharmacotherapy.

1.1.2 Efficacy in Mania Compared with Other Affective States

In a retrospective review, Black et al. (1986) found similar rates of marked improvement in patients receiving ECT for unipolar depression ($N = 368$, 70% improved), bipolar depression ($N = 55$, 69% improved), and mania ($N = 37$, 78% improved), suggesting that ECT is a highly effective treatment for all these conditions.

1.1.3 The Optimal Form of ECT in Treating Mania

In unipolar depression, the relative efficacy and side effects of right unilateral and bilateral ECT at a range of suprathreshold doses have been studied in several well-designed, randomized controlled trials. However, there is insufficient evidence

regarding the relative benefits of different forms of ECT in treating acute mania. Although some earlier studies suggested that (right) unilateral ECT may be less effective than bilateral ECT in treating mania (Small et al. 1988), unilateral ECT was suboptimally given in these studies, as discussed above. Others have suggested that left unilateral ECT should be particularly effective in treating mania, based on the lateralized hypothesis of mood control (Sackeim et al. 1982). In a small prospective evaluation ($N = 20$), Mukherjee et al. (1988) found no clear difference in response to various ECT treatment approaches – right unilateral (five of eight responded), left unilateral (two of five responded), and bitemporal ECT (four of seven responded) – though the numbers involved are clearly too small to draw firm conclusions.

Two recent, double-blind, randomized controlled trials compared bitemporal and bifrontal ECT in manic patients. Barekatain et al. (2008) ($N = 28$) found bitemporal ECT (at a dose just exceeding seizure threshold) and bifrontal ECT (given at a higher relative dose, at 1.5 times seizure threshold) to be similarly effective, with 8 of 14 and 10 of 14 patients responding, respectively. There was a significant cognitive advantage for bifrontal ECT, with lesser decline in mini-mental state examination (MMSE) scores. Hiremani et al. (2008) ($N = 36$) compared both forms of ECT at a dose of 1.5 times seizure threshold and found significantly faster improvement (though there was no difference in the number of treatments required) in the bifrontal group. Overall response rates were high and similar between groups: bifrontal 87.5%, bitemporal 72.2%. Surprisingly, cognitive outcomes, examined with a range of tests, were not significantly different between groups, though this is probably due to the small sample tested ($N = 25$) and the comparison being made only after five ECT treatments, rather than at the end of the treatment course. The findings of these two studies are consistent with results for bifrontal ECT in treating depression, where most studies have found that similar efficacy, but fewer cognitive side effects, is associated with bifrontal ECT (reviewed in Loo et al. 2006).

Thus, the literature comparing different forms of ECT in mania is preliminary and lacks adequate comparisons involving high-dose unilateral ECT. Studies so far support the efficacy of bitemporal and bifrontal ECT, and unilateral ECT may be equally effective if given at adequately suprathreshold doses.

1.2 Treatment of Bipolar Depression

There is a robust evidence for the efficacy of ECT in treating depression (The UK ECT Review Group 2003), but most patients in these studies had unipolar depression. However, although specific reviews of the outcome of ECT treatment in bipolar depressed patients draw on relatively small samples, they support a similar efficacy in bipolar depression; half to three quarters of patients with bipolar depression in those studies met criteria for treatment response (Devanand et al.

2000; Ciapparelli et al. 2001; Medda et al. 2009a). Most of these patients had failed therapy with antidepressant medications.

1.2.1 Efficacy of ECT Relative to Antidepressant Medications

Furthermore, comparisons of the relative efficacy of ECT with other somatic treatments suggest that ECT is at least as effective as, and probably more effective than, antidepressant medications (Zornberg and Pope 1993). Most early studies comparing ECT with tricyclic antidepressant medications and monoamine oxidase inhibitors (MAOIs) found that more patients were rated as having a "marked improvement" with ECT (Greenblatt et al. 1964: 78% vs 59%; Bratfos and Haug 1965: 61% vs 25%; Avery and Winokur 1977; Avery and Lubrano 1979: 100% vs 47%; Homan et al. 1982: 23% vs 12.5%; Black et al. 1987: 69% vs 47%), though these differences only reached significance in some studies. Both shorter (Bratfos and Haug 1965) and longer (Homan et al. 1982) hospitalizations after treatment with ECT compared with antidepressant medications were reported. Most studies did not report long-term outcome after the acute treatment course. Bratfos and Haug (1965) found similar rates of relapse 3 months after discharge from the hospital (38% ECT, 34% antidepressants), though it is unclear whether these patients were receiving maintenance pharmacotherapy during the follow-up period.

1.2.2 Comparative Efficacy in Bipolar and Unipolar Depression

The literature is inconsistent in terms of the relative responsivity of unipolar and bipolar depression to ECT. Most studies have not found different response rates to ECT in the two types of depression (Greenblatt et al. 1964; Black et al. 1986; Andrade et al. 1988b; Sobin et al. 1996; Grunhaus et al. 2002), though some have suggested slightly lower rates of improvement or response in patients with BPD [Homan et al. 1982: 23% vs 43%; Medda et al. 2009a: 70% (BPD-I) and 73% (BPD-II) vs 88% (unipolar)]. On the other hand, there is the suggestion that response may be more rapid in bipolar depression, with fewer treatments required (Daly et al. 2001; Sienaert et al. 2009); the opposite (Perris and d'Elia 1966), as well as no difference (Black et al. 1986), has also been reported. The latter discrepancy may possibly reflect more effective ECT treatment techniques (e.g., adequate suprathreshold dosing for unilateral ECT) in later studies.

1.2.3 Risk of Switching to Mania

The risk of inducing hypomania or mania with antidepressant medications has been described in multiple studies (for a summary, see Goldberg and Truman 2003). The risk appears to be greater for patients with BPD (as opposed to unipolar depression), or a family history of BPD (Angst et al. 1992; Goldberg and Truman 2003), and

may be greater for BPD-I than BPD-II (Hirschfeld et al. 2002; Altshuler et al. 2006). An overview of several studies estimated that the risk of switching associated with antidepressant medications in patients with BPD is 20–40% (Goldberg and Truman 2003). From careful life chart reviews, Altshuler et al. (1995) also estimated that cycle acceleration may occur in one-fourth of patients with BPD treated with heterocyclic antidepressants and MAOIs. Some investigators have questioned whether the risk exceeds that found in the natural course of BPD. In a retrospective chart review, Lewis and Winokur (1982) reported switch rates of 41% with no treatment, 28% with a tricyclic antidepressant, 22% with ECT, and 25% with a MAOI. However, the results of most studies support an increased rate of switching with treatment.

Relatively few studies have reported on switching after ECT. In two small case series of patients, Lewis and Nasrallah (1986) and Andrade et al. (1988a) reported switch rates of 6.4% (6 of 94 patients) and 12.5% (4 of 32 patients), respectively. The largest body of evidence comes from Angst et al. (1992) who retrospectively reviewed 1,057 hospital admissions for depression between 1920 and 1981, comparing switch rates from periods when there were no somatic treatments for depression, to treatment with ECT ($N = 139$) and later, treatment with antidepressants. They found that ECT treatment increased switch rates in unipolar depression [3.3% with no treatment, 8.6% with ECT ($p < 0.05$ compared with no treatment group), and 2.9% with antidepressants]; however, differences were smaller and not significantly different in bipolar depression, probably due to the higher base rate of switching (28.6% with no treatment, 37.5% with ECT, and 29.5% with antidepressants). Furthermore, switch rates may have been overestimated in this study, as a switch was defined as the development of manic or hypomanic symptoms within the same episode of illness and attributed to treatment even if the switch occurred weeks after the period of treatment. In a prospective 6-week study of 44 bipolar depressed patients, switch rates of 4 of 11 (36%) for ECT and 8 of 33 (24%) for selective serotonin reuptake inhibitors (SSRI) antidepressants were reported (Henry et al. 2001).

While several studies have found that switch rates vary with type of antidepressant medication [SSRIs are associated with a lower switch rate than tricyclic antidepressants (Goldberg and Truman 2003)], there are insufficient data to conclude whether switch rates vary with different types of ECT (e.g., unilateral versus bilateral electrode placement, stimulus parameters, and frequency and number of treatments).

There is no consensus on the management of ECT-induced mania. Preliminary evidence exists that concurrent treatment with lithium may reduce the risk of switching. In the study by Henry et al. (2001) reported above, treatment with lithium was found to significantly reduce switch rates (4 of 26 patients on lithium vs 8 of 18 patients not on lithium), while anticonvulsant mood stabilizers did not reduce switch rates (3 of 7 on anticonvulsants vs 5 of 11 on no mood stabilizers). In two case reports, the addition of lithium during the course of ECT was effective in managing the emergence of recurrent manic symptoms (Andrade et al. 1990) and rapid cycling (Zavorotnyy et al. 2009), allowing these bipolar

depressed patients to be successfully treated with ECT. Because ECT is also an effective treatment for mania, another approach is to continue treatment with ECT in the event of a manic switch. The efficacy of this approach has not been systematically studied.

1.3 Treatment of Mixed Affective States

Naturalistic reports suggest that ECT is also an effective treatment, with over 50% of patients responding, and response rates at least equivalent to those of ECT in bipolar depression. Tundo et al. (1991) reported good response in 19 of 26 patients. Gruber et al. (2000) found that seven patients who had not improved after treatment with lithium in combination with carbamazepine or valproate and in some cases also an antipsychotic medication nevertheless responded to bitemporal ECT. They noted that more ECT treatments (number not stated) were needed than in a typical course of ECT. In a retrospective review of 38 patients with bipolar depression, ten patients with mixed states, and five manic patients treated with unilateral or bitemporal ECT concurrently with a range of medications, Devanand et al. (2000) reported response rates of 76%, 80%, and 100%, respectively. They also noted that slightly more ECT treatments were required in the mixed group than in the depressed group (mean 9.3 vs 7.1 treatments).

Ciapparelli et al. (2001) evaluated outcomes of twice-weekly bitemporal ECT treatment in a naturalistic study of patients with BPD-I: 41 with mixed affective state, 23 with bipolar depression. Patients had failed to respond to at least 16 weeks of combined pharmacotherapy (mood stabilizers, antipsychotics, and antidepressants) and continued on these medications during the ECT course. Response rates were higher in the mixed group, 56% vs 26% (Clinical Global Impressions scale, CGI) and 78% vs 52% (MADRS). The response rates for the bipolar depressed group were slightly lower than those of most other studies. It is possible that the efficacy of ECT was compromised in this study by the concurrent administration of anticonvulsant medications in all patients (see below). There was no indication that more ECT treatments than usual were required, as both groups received approximately 7.2 treatments. The authors also noted that ECT was highly effective in reducing suicidal ideation (MADRS item 10), general psychopathology, and activation (Brief Psychiatric Rating scale, BPRS), particularly in the mixed group, but that residual (BPRS) activation scores at the end of treatment were still higher in the mixed group.

In a similar approach, Medda et al. (2009b) evaluated outcomes prospectively in 96 BPD-I patients with medication-resistant mixed state ($N = 50$) or depression ($N = 46$). Patients were also treated with twice-weekly, bitemporal ECT (average 7.4 treatments, both groups) and continued on failed medications with the exception of anticonvulsants. Response rates were robust in both groups: 76% vs 67% (CGI), 66% vs 70% (Hamilton Depression Scale, HAM-D), respectively, and higher than in the Ciaparelli study, possibly reflecting the absence of concurrent anticonvulsant

treatment. The mixed group had higher BPRS (total and psychotic cluster) and Young Mania Rating scale (YMRS) scores before ECT. Substantial improvement across all symptom domains (assessed by HAM-D, CGI, YMRS, and BPRS) was found in the mixed group, but with residual BPRS (psychotic cluster) and YMRS scores that were still slightly higher after ECT treatment than in the depressed group.

In summary, there are no randomized controlled trials evaluating the efficacy of ECT relative to other treatments in mixed affective states. However, the above reports provide evidence for the safe and effective use of ECT, including in patients refractory to pharmacotherapy, suggesting a superior and clinically useful efficacy. In addition, response to ECT usually occurred within 3–4 weeks in patients who had previously failed many weeks of pharmacotherapy. Thus, ECT should be considered the treatment of choice in patients with mixed affective states not responding to medications, though clinicians should be vigilant for residual symptoms requiring further management.

1.4 Maintenance ECT in BPD

Maintenance ECT, i.e., ECT treatments usually given at fortnightly to monthly intervals, has been demonstrated to be useful in preventing relapse and recurrence of depression, either alone or in conjunction with medications. No randomized, controlled trials of maintenance ECT specifically in BPD exist, but some studies of maintenance ECT included patients with BPD (see Vaidya et al. 2003 for a summary). These naturalistic observations comparing patients receiving maintenance ECT with patients not receiving maintenance ECT, or periods of maintenance ECT treatment with periods of other treatment in the same patient, suggest that maintenance ECT may be useful in reducing the frequency of mood episodes in BPD. Maintenance ECT was found to be useful in patients with BPD initially treated with an index course of ECT for mania, depression, or mixed state, including rapid cyclers ($N = 4$, Vanelle et al. 1994) and patients who had previously relapsed with maintenance pharmacotherapy (Vaidya et al. 2003). However, there are no data on the relative efficacy of maintenance ECT in preventing the different types of episodes associated with BPD: mania, depression, or mixed states. Thus, the limited evidence available suggests that maintenance ECT may be a useful prophylactic treatment in patients with BPD, particularly for those who tend to have frequent episodes of mood disturbance despite pharmacotherapy.

1.5 Concurrent Medications

As noted above, patients with BPD are often on lithium or anticonvulsant mood stabilizers when the need for treatment with ECT arises. The decision to continue or cease these medications before, or during ECT, has been the subject of some clinical debate.

1.5.1 Lithium

The safety of concurrent administration of lithium during ECT remains controversial. There have been reports of its safe use in many patients as well as reports of increased neurological complications, e.g., confusion, disorientation, spontaneous, or prolonged seizure activity (El-Mallakh 1988; Mukherjee 1993). Although serum lithium levels were high in some of these cases (>0.8 mmol/L), in others levels were moderate (≤0.6 mmol/L). The use of sine wave ECT probably increased the likelihood of neurotoxic effects in some older case reports. A retrospective study of 31 patients who received ECT with lithium compared with age- and gender-matched controls who received ECT without lithium found no difference in rates of delirium, confusion, or other adverse effects (Jha et al. 1996). However, another retrospective review of 25 patients who received concurrent ECT and lithium suggested a higher incidence of memory loss and atypical neurological symptoms, compared to patients who received ECT without lithium (Small et al. 1980). The issue has not been definitively resolved, as there have been no prospective, randomized studies examining this question. However, several case reports of patients who experienced complications while receiving ECT with lithium, but who had no complications when ECT was given alone, earlier or later in the same course of treatment, are highly suggestive of a problematic interaction between ECT and lithium.

With ongoing use of lithium combined with modern ECT technique in recent decades, case reports of both toxicity and safe usage continue to emerge (Sartorius et al. 2005; Dolenc and Rasmussen 2005), and it is likely that some patients are susceptible to adverse effects from the combination. Thus, it is safest to cease lithium before ECT unless there is good clinical reason for its continued use. Patients treated with lithium and ECT concurrently should be closely monitored for adverse neurological and cognitive outcomes, and lithium should be ceased if the patient develops substantial cognitive impairment while on the combination of lithium and ECT. If lithium is given concurrently during ECT (e.g., to prevent mood switching or introduced toward the end of the ECT course for prophylaxis), serum levels should be checked and high levels avoided. It may be useful to omit lithium doses the night before ECT. On the other hand, care should be taken in ceasing lithium in patients prone to mood switching or rapid cycling during ECT. Two case reports found lithium to be highly effective in managing and preventing the emergence of mania and rapid cycling during ECT (Andrade et al. 1990; Zavorotnyy et al. 2009).

1.5.2 Anticonvulsants

The effects of concurrent anticonvulsants on ictal EEG quality, cognitive and efficacy outcomes have not been systematically studied. The literature lacks randomized, controlled trial data and consists mainly of case reports (see Sienaert and Peuskens 2007 for review). Impressions from these reports suggest the following

effects of concurrent anticonvulsant use: a higher electrical dosage is often needed to induce satisfactory seizures; where adequate seizures can be produced, ECT may have good therapeutic efficacy; efficacy may be compromised where seizure induction is compromised, e.g., resulting in poor quality seizures, and in these cases reduction in the anticonvulsant dose is usually helpful; there is a greater risk of subconvulsive stimuli, which increase the risk of post-ECT confusion. Thus the American Psychiatric Association (2001) recommends that anticonvulsant medications that are prescribed for psychiatric indications should be tapered off before the commencement of ECT. It is uncertain whether the withholding of anticonvulsant doses the night before ECT is an adequate alternative to this practice. It is also unclear whether some anticonvulsant medications may have lesser effects on impeding ECT-induced seizures than others, with one retrospective study finding that lamotrigine did not shorten seizures (Sienaert et al. 2006). Thus, the above recommendations should apply to all anticonvulsants used as mood stabilizers in patients with BPD.

2 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) has emerged in the last three decades as a noninvasive means of brain stimulation, using high intensity, rapidly fluctuating magnetic fields. Unlike electrical stimulation, the skull offers no impedance to magnetic fields and thus the stimulation is relatively focal. However, with conventional TMS, only the outer centimeter of neural tissue is effectively depolarized, though technology for deeper stimulation (deep TMS) is under development.

Therapeutic applications of TMS have generally used repetitive TMS (rTMS), i.e., stimuli given repeatedly to a cortical site within a stimulation session, with multiple sessions usually conducted on consecutive weekdays. Important variations in stimulation parameters include frequency (Hz, number of pulses per second) and intensity (usually quoted as a percentage relative to the subject's motor threshold, i.e., the intensity of stimulation required to activate the motor cortex, to produce responses in peripheral muscles). There is some evidence from neurophysiological and neuroimaging studies that high frequency rTMS (e.g., $\geq$5 Hz) increases cortical excitability, whereas low frequency rTMS depresses cortical excitability (Pascual-Leone et al. 1994; Chen et al. 1997; Speer et al. 2009; Loo et al. 2003).

Given the hypothesis that the right and left hemispheres have opposing effects in mood control (Sackeim et al. 1982), therapeutic applications of rTMS have generally followed the paradigm of using high frequency rTMS to activate the left prefrontal cortex (or conversely low frequency rTMS to suppress the right prefrontal cortex) in depression or the right prefrontal cortex in mania.

2.1 rTMS in the Treatment of Acute Mania

In all studies of rTMS as a treatment for mania, patients were treated concurrently with a range of medications, usually lithium, anticonvulsants used as mood stabilizers, and antipsychotic medications, often in combination, no doubt for safety and ethical reasons. This has made it difficult to evaluate the effects of rTMS alone on mania, and probably reduced the ability of controlled trials to find a difference between rTMS and comparator groups.

An initial, parallel design, controlled study of left vs right high frequency rTMS (20 Hz, 80% motor threshold, ten consecutive weekdays) in 16 patients with acute mania yielded promising results (Grisaru et al. 1998). Response to right prefrontal rTMS was superior, with a 71% decline in mean YMRS scores, compared to left prefrontal rTMS (29% change). However, a sham-controlled, follow-up study by the same group in 25 manic patients found no difference between active and sham treatment, despite using the same treatment approach (Kaptsan et al. 2003). In both studies, most patients were on concurrent medications (lithium, anticonvulsants, and/or antipsychotic medications). Considering the results of the two studies together, the authors hypothesized that left prefrontal rTMS may have exacerbated mania, thus leading to a significant difference with the right prefrontal comparator group in their first study; i.e., that improvements seen were largely the result of treatment with concurrent medications rather than rTMS.

Two small open pilot studies (Michael and Erfurth 2004; Saba et al. 2004) reported good results with right prefrontal rTMS as an add-on treatment to concurrent medications (mood stabilizers, antipsychotic medications). Mania scores improved by 50% or more in eight of nine and six of eight subjects in these studies. The Michael and Erfurth study was also the only one to treat subjects for more than 2 weeks (ten consecutive weekdays), continuing rTMS at a reduced frequency of three times per week for a further 2 weeks, and reporting sustained improvement at 2-week follow-up. This is in keeping with the literature on rTMS in treating depression, which suggests that rTMS should be given for at least 4 weeks for optimal outcomes (Loo and Mitchell 2005).

A recent sham-controlled study in a larger sample ($N = 41$) that used rTMS at a higher stimulus intensity (which may be more effective; Loo and Mitchell 2005) (110% motor threshold) found active treatment superior to sham, despite all patients receiving concurrent pharmacotherapy (Praharaj et al. 2009).

Thus, the literature on the use of rTMS to treat mania is preliminary and confounded by the presence of concurrent medications, but is promising. All studies so far have tested right prefrontal, high frequency rTMS, and results to date support the laterality hypothesis of mood described above. However, definitive evidence for the efficacy of rTMS in treating mania, either as a sole therapy or add-on to medications, is not yet available. The optimal form of rTMS (stimulation site, parameters) for the treatment of mania also remains to be clarified.

2.2 rTMS in the Treatment of Bipolar Depression

The vast majority of clinical trials of rTMS in psychiatry have focused on the treatment of depression, with a recent large, placebo-controlled trial and meta-analysis of randomized controlled trials to date confirming the antidepressant effects of rTMS given as high frequency stimulation to the left prefrontal cortex in most studies (O'Reardon et al. 2007; Schutter 2009). However, relatively few trials have examined bipolar depression per se. Bipolar depressed patients were included in some of the above studies, but results for these patients were mostly not presented separately, apart from reports of mood switching (see below).

Thus, useful data on the efficacy of rTMS in bipolar depression are drawn mainly from four trials. An initial randomized trial comparing ten sessions of rTMS (type of rTMS not specified) with placebo stimulation found more improvement in mood after real stimulation, though the degree of improvement was not clinically impressive (Dolberg et al. 2002).

In a placebo-controlled study in 21 depressed patients with BPD-I or BPD-II, or mixed state ($N = 2$), Nahas et al. (2003) failed to find an effect for 2 weeks of high frequency, left prefrontal rTMS. Patients had been withdrawn from concurrent medications which were likely to have an antidepressant effect. Seven patients in the active group were on anticonvulsant medications, and it has been suggested by other investigators that these may impede the effects of rTMS (Hoffman et al. 2000).

In keeping with the other main treatment approach used in rTMS depression trials, two other small studies investigated low frequency (1 Hz) rTMS to the right prefrontal cortex. Tamas et al. (2007) treated four subjects with active rTMS and one subject with sham rTMS with concurrent mood stabilizers. In this study, only 100 stimuli were given in each rTMS session, and sessions were spaced twice per week over 4 weeks. The authors reported more improvement after active treatment, but the difference was only evident 2 weeks after the end of rTMS. In Dell'Osso et al. (2009), 6 of 11 patients responded to 3 weeks of rTMS, given on consecutive weekdays. All were on concurrent antidepressant medications and valproate.

Maintenance rTMS (i.e., sessions of rTMS given at a lesser frequency to prevent relapse) is now being examined in depressed patients. There are case reports of eight patients with bipolar depression who responded to an acute course of rTMS receiving maintenance rTMS concurrently with pharmacotherapy. Li et al. (2004) reported that three of seven patients receiving rTMS once per week did not relapse over a 1-year period. Dell'Osso and Altamura (2008) similarly reported lack of relapse over 6 months in one patient receiving two sessions of rTMS (on consecutive days) given per fortnight.

Overall, the above trials provide weak preliminary evidence that rTMS may be effective in the acute treatment of bipolar depression, but this needs to be tested in further, larger trials, with rTMS given at more optimal parameters.

2.3 *rTMS: Switching into Mania and Other Adverse Effects*

rTMS-induced switch into mania or hypomania has been reported in 13 unipolar or BPD patients receiving treatment for depression, two subjects receiving rTMS for the treatment of post traumatic stress disorder (Xia et al. 2008), and three healthy volunteers in experimental studies Loo et al. (2008a). In reviewing randomized controlled trials of rTMS in depression, Xia et al. (2008) estimated switch rates of 0.84% and 0.73% after active and sham rTMS, respectively, though these rates were based on only four subjects who developed mania.

It is worth noting that most of the 13 depressed subjects who became manic during rTMS treatment were on concurrent medications with antimanic properties (anticonvulsant mood stabilizers, antipsychotic medications, or benzodiazepines). The rate of switching was estimated as 3.1% for patients with BPD, as opposed to 0.34% for unipolar depressed patients. Mania was also induced by a variety of rTMS stimulation approaches: high frequency (5–20 Hz) left prefrontal rTMS, low (1 Hz) and high (10 Hz) frequency right prefrontal rTMS. Thus, patients receiving rTMS treatment should be cautioned about the risk of developing mania or hypomania, regardless of the presence of prior episodes of mood elevation, and should be monitored closely for this complication.

Clinicians administering rTMS should also be aware of other possible adverse effects, the most serious of which are induced seizures (see review in Loo et al. 2008a, b). Of concern, a generalized tonic-clonic seizure was induced in a hypomanic patient after only several single pulses of TMS. While other factors may have contributed to a lowered seizure threshold in this case, it is unknown whether manic patients may be more susceptible to induced seizures.

3 Vagus Nerve Stimulation, Stereotactic Ablation, and Deep Brain Stimulation

These surgical interventions range from the least focal vagus nerve stimulation (VNS), to the most focal deep brain stimulation (DBS), with stereotactic lesions procedures in between. Differences in their apparent speed of therapeutic action, effectiveness, and adverse effect profiles are of potential mechanistic as well as clinical significance. Data are very limited in all these domains. The long-term perspective is crucial for outcomes assessment for any surgical procedure, and especially here, given the expected naturalistic course of BPD.

Vagus Nerve Stimulation. In a retrospective analysis using a subset of 25 patients with BPD-I or BPD-II from a larger trial, the effects of short- and long-term (up to 2 years) VNS on bipolar and unipolar depression were found to be similar. Expanding the definition of response to include lack of manic symptoms did not increase the response rate (Nierenberg et al. 2008). A pilot, prospective, open-label study of nine rapid-cycling patients with BPD (excluded from larger trials) found evidence of benefit over 12 months (Marangell et al. 2008).

Stereotactic Ablation. Patients undergoing lesion procedures are drawn from the extreme end of the treatment-refractory spectrum. This is important to consider when comparing outcomes across treatments, since achieving and maintaining therapeutic gains are expected to be inherently more difficult in the patient subgroups undergoing ablation. Here again, the data are sparse. A recent prospective study followed 16 patients with otherwise intractable BPD who underwent limbic leukotomy (subcaudate tractotomy and cingulotomy). At 7-year follow-up, mean HDRS depression severity declined over 50%, while BDI self-ratings declined 41%. Measures of anxiety and negative symptoms also declined. Two-thirds of the patients had a robust response on global measures. In contrast, mean YMRS scores were unchanged. Adverse effects were described as transient (Cho et al. 2008). The possibility that depressive and manic symptoms respond differentially to ablation of fronto-basal-thalamic pathways is important both clinically and mechanistically.

Deep Brain Stimulation. Patients with BPD have generally been excluded from DBS trials in psychiatric patients. Focal stimulation can induce hypomanic or manic symptoms across neuropsychiatric populations and stimulation targets, and the risk of such events is presumed to be greater in patients with BPD. Hypomania or mania was observed during DBS of the subthalamic nucleus (STN) or globus pallidus (GP) in Parkinson's disease (Funkiewiez et al. 2004; Miyawaki et al. 2000). The same phenomena can occur during ventral capsule/ventral striatum (VC/VS) stimulation for obsessive-compulsive disorder (OCD) (Greenberg et al. 2010a) or unipolar depression (Malone et al. 2009), or for OCD patients receiving DBS at the STN (Mallet et al. 2008). Given the burden of refractoriness in patients with bipolar depression, very cautious attempts to use DBS safely in this group might be considered. Clinical observations from a single BPD-I case suggest that a combination of low-intensity DBS and multiple mood stabilizers might reduce induction of manic symptoms by DBS when treating bipolar depression (B. Greenberg, unpublished observations).

4 Concluding Remarks

Current evidence supports the use of ECT in treating bipolar depression, mania, and mixed states. There is also emerging evidence that rTMS may be a useful treatment for these mood states, but more research is needed to clarify efficacy, safety, and optimal approach to stimulation.

Several new developments are under way in somatic treatments for depression and it is likely that these will also be therapeutically relevant for the treatment of both bipolar depression and acute mania. The practice of ECT may be revolutionized by recent reports of vastly reduced cognitive side effects when the stimulus pulsewidth is reduced to the ultrabrief range (Sackeim et al. 2008; Loo et al. 2008a, b). Transcranial direct current stimulation, the use of very small, polarizing currents to nonconvulsively stimulate the brain, is now being evaluated as a treatment for depression (Arul-Anandam and Loo 2009) and may emerge as another therapeutic

option in BPD. Data from VNS, modern ablative procedures, and DBS are all highly preliminary in bipolar depression, but each method might hold some promise for highly selected patients, and each holds some potential for careful translational research (see Greenberg et al. 2010b as an example) into the neurocircuitry underlying treatment response in an illness that can remain challenging to treat.

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Potential Novel Therapeutics for Bipolar Disorders

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Abstract Existing pharmacological treatments for bipolar disorder (BPD), a severe recurrent mood disorder, are in general insufficient for many patients. Despite adequate doses and treatment duration, many individuals with this disease continue to experience mood episode relapses, residual symptoms, and functional impairment. This chapter reviews a number of targets/compounds that could result in putative novel treatments for BPD, including the dynorphin opioid neuropeptide system, the glutamatergic system, the purinergic system, the cholinergic system (muscarinic and nicotinic systems), the oxidative stress system, and the melatonergic system. The arachidonic acid cascade and intracellular signaling cascades (including glycogen synthase kinase 3 and protein kinase C) are also reviewed, as are agents that affect multiple targets (e.g., modafinil, Uridine RG2417). Further study of these and similar agents may improve our understanding of relevant drug targets and their clinical utility as potential therapeutics for this devastating disorder.

Keywords Bipolar disorder · Depression · Mania · Targets · Treatment

1 Introduction

Bipolar disorder (BPD) is a severe, chronic, and multifaceted mood disorder associated with high rates of subsyndromal symptoms, relapses, functional impairment, and psychosocial disability. Current therapeutic approaches for patients with BPD experiencing major depressive episodes, rapid cycling, or mixed episodes remain far from ideal for many patients; similarly, these treatments are often ineffective at preventing relapse. While current treatments for the manic episodes associated with BPD are generally more effective, issues of safety and tolerability remain (Gitlin 2006; Judd et al. 2002). It is important to emphasize that, to date, no agent has been specifically developed to treat BPD. Problems such as high dropout rates, placebo effects, and difficulty in recruiting patients have limited the faster discovery and development of novel treatments. However, this lack of improved therapeutics is predominantly due to our continued lack of understanding of the key underpinnings of this disease or relevant therapeutic targets. Thus, the search to identify novel therapeutic targets (receptors) in BPD research is ongoing.

Here, we review the most significant studies in this area with a particular emphasis on the potential value of these systems with regards to future drug development and proof-of-concept clinical research. These new therapeutics for BPD show initial positive findings for the treatment of both mania and depression and are predominantly based on initial proof-of-concept clinical studies or preclinical data. They include the dynorphin opioid neuropeptide system, the glutamatergic system, the purinergic system, the cholinergic system (muscarinic and nicotinic systems), and the melatonergic system, as well as agents that affect multiple targets (e.g., modafinil, Uridine RG2417), oxidative stress and bioenergetics, the arachidonic acid (AA) cascade, and intracellular signaling cascades (glycogen synthase kinase 3 (GSK-3) and protein kinase C (PKC)).

The criteria used to define these targets included: (a) studies showing antimanic effects in humans or beneficial effects on irritability, hyperactivity, or mood; (b) antidepressant properties in bipolar depression; and (c) antidepressant-like properties in animal models and either "antimanic-like" properties in animal models or antipsychotic-like properties in either humans or animal models of psychosis (e.g., prepulse inhibition). Agents that have been extensively reviewed elsewhere or that were found to be ineffective in large, randomized, controlled studies are not reviewed here.

2 The Opioid Neuropeptide System

The neuropeptide system includes members of the opioid peptide family and is involved in the regulation of mood, cognition, motor, and endocrine functions. The three types of opioid receptors – delta, mu, and kappa – are coupled to different intracellular effector systems. Dynorphins are a class of opioid peptides that arise from the precursor protein prodynorphin; they predominantly bind to kappa opioid receptors and induce nonopioid effects predominantly via their direct effects on *N*-methyl-D-aspartate (NMDA) receptors.

Opioid peptides and their receptors are potential candidates for the development of novel mood disorder treatments. These endogenous peptides are coexpressed in brain areas critically implicated in mood regulation and the action of antidepressants (Schwarzer 2009). Interestingly, stress increases dynorphin levels in limbic brain areas, and this effect is blocked by antidepressant treatment (Chartoff et al. 2009; Shirayama et al. 2004), suggesting a role for this system in stress-related major depressive disorder (MDD). In patients with BPD, a significant decrease (37–38%) in prodynorphin mRNA expression was found in the amygdalo-hippocampal area and in the parvicellular division of the accessory basal area (Hurd 2002).

Standard monoaminergic antidepressants, commonly used to treat both MDD and BPD, activate the opioid system and have analgesic effects in neuropathic and inflammatory pain. Interestingly, these mood effects were blocked by the opioid antagonist naloxone. For instance, naloxone blocked the antidepressant-like

effects of clomipramine, desipramine, and venlafaxine in the forced swim model of depression (Berrocoso et al. 2004; Devoize et al. 1984). Activation of the opioid system was also shown to enhance the analgesic effects of traditional antidepressants (Gray et al. 1998). Preclinical studies also suggest other therapeutic roles for the opiate system, including the mediation of anticonvulsant effects by kappa agonists (reviewed in Schwarzer (2009)). The latter finding raises the possibility that these agents may play a therapeutic role in BPD, given that anticonvulsants have to date played a prominent role in the treatment of this disorder. Diverse preclinical models similarly suggest that these agents may have relevant anxiolytic effects (Wittmann et al. 2009).

2.1 Kappa Opioid Receptors

Kappa opiate receptor activation has been shown to induce depressive symptoms in both humans and animals (Barber and Gottschlich 1997; Carlezon et al. 2006). As a result, it has been hypothesized that kappa opiate agonists might exert antimanic effects. One caveat, however, is that activation of these receptors may also induce psychotomimetic and dysphoric effects (Rimoy et al. 1994; Walsh et al. 2001), as well as increase risk for addictive behavior. In preclinical models, the highly selective full kappa opioid receptor agonist salvinorin-A (*Salvia divinorum*) induced depressive-like behaviors that were associated with reduced extracellular concentrations of dopamine (but not serotonin) in the nucleus accumbens (Carlezon et al. 2006). Further support for the relevance of kappa opioid receptors in mood disorders comes from evidence that the kappa opioid antagonist MCL-144B exerted antidepressant-like effects in the forced swim test (Mague et al. 2003; Reindl et al. 2008).

In humans, the partial kappa agonist pentazocine (Talwin) was tested adjunctively in ten individuals with BPD during a manic episode. In this uncontrolled study, patients received two 50-mg doses of pentazocine 2 h apart. Manic symptoms were reduced within 1 h after each dose (44% after the first dose and 41% after the second dose). The results suggest that this agent improved manic symptoms without inducing depression (Cohen and Murphy 2008). No significant adverse events were observed. To date, no selective kappa agonists have been clinically evaluated as monotherapy for mood disorders. However, activation of this system has been shown to induce depressive symptoms in healthy volunteers, suggesting that future controlled proof-of-concept studies are needed to clarify the relevance of kappa opioid receptors in the pathophysiology and therapeutics of BPD.

Mu receptors appear to be involved in response to stressors, and several mu-receptor agonists have shown antidepressant-like effects in preclinical studies (Besson et al. 1996; Rojas-Corrales et al. 2002; Tejedor-Real et al. 1995). For instance, central administration of the mu opioid selective peptides endomorphin-1 and endomorphin-2 decreased immobility time in the forced swim and tail suspension

tests, and these effects were blocked by the nonselective opioid antagonist naloxone and the mu receptor-selective antagonist β-funaltrexamine (Fichna et al. 2007).

The synthetic opioid tramadol binds weakly to mu receptors and has antidepressant-like effects in preclinical studies (Rojas-Corrales et al. 1998, 2004; Yalcin et al. 2007). Case reports also suggest that tramadol has antidepressant effects both as monotherapy or when used adjunctively in individuals with treatment-resistant MDD; it also appears to have potential rapid antidepressant and antisuicidal effects (Fanelli and Montgomery 1996; Shapira et al. 2001; Spencer 2000).

Delta receptors have a high-affinity for the endogenous opioid peptide proenkephalin; for instance, proenkephalin-knockout mice show increased risk for anxiety and depressive-like symptoms. Several delta receptors agonists appear to exert antidepressant-like effects in preclinical studies (Jutkiewicz 2006; Ragnauth et al. 2001). Nevertheless, clinical studies are needed to confirm these preliminary data; a clinical trial using a delta-opioid agonist (AZD2327) for the treatment of depressive symptoms and anxiety is ongoing in our clinical research center.

3 The Glutamatergic System

Glutamate is the main excitatory neurotransmitter in the brain and modulates several important physiological functions such as synaptic plasticity, learning, and memory (Bannerman et al. 1995; Collingridge 1994; Collingridge and Bliss 1995; Watkins and Collingridge 1994). Increased levels of glutamate and altered glutamatergic turnover have been associated with the dysregulation of brain neuroplasticity and cellular resilience hypothesized to occur in BPD. Diverse glutamatergic modulators have been developed to better modulate these presumptive dysfunctional effects found in critical targets of key brain circuits that mediate mood, behavior, thoughts, and actions. In this context, glutamatergic compounds have been tested in proof-of-concept studies, targeting either the glutamate receptors directly (mostly through NMDA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), and metabotropic receptors) or glutamate before it is released into the extracellular space. In addition, diverse preclinical studies have identified new compounds capable of selectively targeting key regions within this system with potential antimanic and antidepressant effects. The three subgroups of glutamatergic ion channels identified as putative targets for mood therapeutics are classified based on their pharmacological ability to bind synthetic ligands, and include NMDA, AMPA, and kainate receptors (Machado-Vieira et al. 2009).

3.1 NMDA Antagonists

NMDA receptor antagonists have been shown to have antidepressant-like effects in various preclinical models of depression (reviewed in Zarate et al. (2002,

2003)). In animal studies, the NMDA antagonists dizocilpine (MK-801) and CGP 37849 have consistently shown antidepressant-like effects either alone or in combination with standard antidepressants (Meloni et al. 1993; Padovan and Guimaraes 2004; Papp and Moryl 1993; Skolnick et al. 1992; Trullas and Skolnick 1990).

Ketamine is a high-affinity NMDA receptor antagonist with a specific type of channel closure (called "trapping block"). Ketamine induces significant presynaptic release of glutamate by enhancing the firing of glutamatergic neurons (Moghaddam et al. 1997). In preclinical models, ketamine induced anxiolytic and antidepressant effects (Aguado et al. 1994; Garcia et al. 2008; Maeng et al. 2008; Mickley et al. 1998; Silvestre et al. 1997). Further studies found that blocking AMPA activation prevented ketamine's antidepressant effects, suggesting that these antidepressant properties take place by increasing AMPA throughput (Maeng et al. 2008).

In humans, an initial study showed improvement in patients with treatment-resistant MDD 72 h after ketamine infusion (Berman et al. 2000). A subsequent double-blind, placebo-controlled, crossover study evaluating patients with treatment-resistant MDD found that ketamine infusion (single-dose, 0.5 mg/kg for 40 min) resulted in a fast (within 2 h), significant, and relatively sustained antidepressant effect (lasting 1–2 weeks) (Zarate et al. 2006). In that study, more than 70% of patients met criteria for response (50% improvement) at 24 h after infusion whereas 36% showed a sustained response after 1 week. Research is currently being conducted at the NIMH to examine the efficacy of ketamine in treatment-resistant bipolar depression.

The selective NMDA antagonist memantine (at a dose of 20 mg/day) was also studied in a double-blind, placebo-controlled, 8-week trial of 32 subjects with MDD, but showed no antidepressant efficacy. However, Teng and Demetrio (2006) described two cases where memantine significantly improved cognitive function and exerted mood stabilizing effects in individuals with treatment-resistant bipolar depression (Teng and Demetrio 2006). A recent case report similarly described significant antimanic efficacy with memantine in a subject with treatment-resistant BPD comorbid with idiopathic bilateral frontotemporal atrophy (Agarwal and Tripathi 2009). The potential antimanic efficacy and tolerability of memantine (20–50 mg/d) was also evaluated in an open-label study of 35 subjects with BPD-I. Individuals were assigned to 21 days of treatment, and all responded by Day 21 (response was defined as an at least 50% reduction in Young mania rating scale (YMRS) scores from baseline); the greatest improvement was observed in patients who received doses ranging from 20 to 30 mg/day. Adverse events were observed in 54.3% of patients; constipation, nausea, and headache were the most frequent. Taken together, the results suggest that further study of NMDA antagonists in the treatment of mood disorders is warranted. In addition, trials testing more selective subtype NMDA antagonists are in progress; such trials would help clarify whether rapid antidepressant effects can be achieved without the psychotomimetic effects associated with ketamine.

3.2 AMPA Potentiators

AMPA receptor potentiators limit receptor desensitization and/or deactivation rates in the presence of an agonist (Bleakman and Lodge 1998). Preclinical studies suggest that they have significant antidepressant effects (Black 2005; Du et al. 2007; Miu et al. 2001). For instance, Ampalex induced antidepressant-like effects in rats during the first week of treatment (Knapp et al. 2002). AMPA receptor trafficking (including receptor insertion, internalization, and delivery to synaptic sites) is believed to be involved in the antidepressant effects of AMPA receptor potentiators; trafficking plays a critical role in regulating activity-dependent regulation of synaptic strength, as well as various forms of neural and behavioral plasticity (Sanacora et al. 2008). Specifically, lamotrigine and riluzole, which show predominantly antidepressant effects in BPD, increased surface expression of hippocampal glutamate receptor type 1 (GluR1) and glutamate receptor type 2 (GluR2) and the phosphorylation of GluR1 at the PKA (cAMP-dependent protein kinase) site (S845), while valproate significantly reduced surface expression of GluR1 and GluR2 and phosphorylation at GluR1 (S845) (Du et al. 2007). Similarly, chronic lithium decreased hippocampal synaptosomal GluR1 levels and GluR1 phosphorylation at a specific PKA site (GluR1p845) that critically regulates AMPA receptor insertion and synaptic plasticity (Du et al. 2004). Regarding postmortem studies, few data are available. There is a single report of increased AMPA binding associated with a decreased GluR1 subunit expression in the striatum in BPD (Meador-Woodruff et al. 2001).

AMPA receptor antagonists, such as talampanel (GYKI 53773; LY 300164) are currently in Phase III clinical trials in epilepsy, and based on their anticonvulsant properties, may be potentially useful as mood stabilizers. Similarly, the competitive AMPA receptor antagonist NS1209, currently being tested for the treatment of refractory status epilepticus (Rogawski 2006), showed good central nervous system bioavailability and was well-tolerated in Phase I/II clinical trials. It also had faster and more consistent anticonvulsant properties than diazepam in animal models (Pitkanen et al. 2007). Further clinical studies are necessary to confirm the potential antidepressant efficacy of AMPA potentiators.

3.3 Metabotropic Glutamate Receptors

The metabotropic glutamate receptors (mGluRs) comprise eight subtypes (mGluR1 to GluR8) classified into three groups on the basis of their sequence homology, coupling to second messenger systems, and agonist selectivity. Group I mGluRs (mGluR1 and mGluR5) are coupled to the phospholipase C signal transduction pathway. Receptors in Groups II (mGluR2 and mGluR3) and III (mGluR4 and mGluR6 to mGluR8) are both coupled in an inhibitory manner to the adenylyl cyclase signal transduction pathway.

Group I mGluR1 and mGluR5 antagonists showed antidepressant-like effects in different preclinical paradigms (Machado-Vieira et al. 2009). The mGluR5-positive allosteric modulator 3-cyano-*N*-(1,3-diphenyl-1Hpyrazol-5-yl)benzamide reversed amphetamine-induced locomotor activity in rats, suggesting that it might be potentially useful in the treatment of mania (Kinney et al. 2005). Clinical studies conducted with the nonbenzodiazepine anxiolytic fenobam, a potent and selective mGluR5 antagonist, were discontinued because of psychostimulant effects (Palucha and Pilc 2007). The Group II mGluR2 and mGluR2/3 glutamate receptors are negatively linked to the adenylyl cyclase signal transduction pathway and limit excessive glutamate into the synapse. Different group II mGluRs modulators (e.g., LY341495) were shown to dose-dependently exert antidepressant-like effects in different models (Zarate et al. 2002). Group III mGluRs agonists were also found to have antidepressant-like effects in the forced swim and behavioral despair tests (Gasparini et al. 1999; Palucha and Pilc 2007). Antidepressant-like effects were also observed in the forced swim and tail suspension tests in mGluR7 knockout mice (Cryan et al. 2003).

To date, no Group III mGluR agonists have been tested clinically in mood disorders. However, this class of agents may ultimately be clinically useful in treating depressive episodes.

3.4 Glutamatergic Modulators: Riluzole

Riluzole, a blood–brain barrier-penetrant glutamatergic agent with well-defined neuroprotective properties, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of amyotrophic lateral sclerosis (ALS). Riluzole inhibits glutamate release and enhances AMPA trafficking by enhancing membrane insertion of the AMPA subunits GluR1 and GluR2 (Du et al. 2007). Riluzole also increases both glutamate reuptake and neurotrophic factor synthesis (Frizzo et al. 2004; Mizuta et al. 2001).

Riluzole showed antidepressant effects and was well-tolerated in patients with treatment-resistant MDD and bipolar depression. In the first trial, 13 patients (68%) with MDD completed the trial and all showed a significant improvement at week 6 (Zarate et al. 2004). In a study of 14 patients with bipolar depression, riluzole (100–200 mg/day) was used adjunctively to lithium for 6 weeks (Zarate et al. 2005). Depressive symptoms were significantly improved for those patients receiving riluzole, and there was no evidence of hypomania or mania.

Similar results have been obtained in animal models. Pretreatment with 10 mg/kg riluzole (but not 3 mg/kg) moderately reduced amphetamine-induced hyperlocomotion (Lourenco Da Silva et al. 2003), suggesting that riluzole has potential as an antimanic agent. Riluzole was also recently shown to reverse both the behavioral (anhedonia and helplessness) and biological changes (reduced glial dysfunction and glial fibrillary acidic protein (GFAP) expression) induced by an animal model of depression (Banasr et al. 2008).

3.5 *Cytidine*

Cytidine is a pyrimidine component of RNA that induces therapeutic effects by regulating dysfunctional neuronal–glial glutamate cycling. Pyrimidines affect cerebral phospholipid metabolism, catecholamine synthesis, and mitochondrial function, all of which have also been associated with the pathophysiology of bipolar depression. Recently, the therapeutic role of cytidine was evaluated in 35 individuals with BPD during a depressive episode. In this double-blind, placebo-controlled study, patients were assigned to valproate plus either cytidine or placebo for 12 weeks (Yoon et al. 2009). Cytidine was associated with earlier improvement of depressive symptoms; this finding was directly correlated with decreased mid-frontal glutamate/glutamine levels ($p = 0.001$) only in the active compound group. The study suggests that cytidine supplementation has therapeutic effects in bipolar depression mediated by decreased cerebral glutamate/glutamine levels.

4 The Purinergic System

Purinergic neurotransmission is mostly mediated by adenosine triphosphate (ATP) and adenosine, and plays an important role in regulating diverse neurotransmitters (Burnstock 2007). The purinergic system directly influences motor activity, cognition, sleep, appetite, memory, and social interaction (Machado-Vieira et al. 2002). Adenosine, a widespread neuromodulator acting mostly through adenosine 1 and 2A receptors, has been shown to have antidepressant-like effects in preclinical paradigms (Kaster et al. 2004).

More than 40 years ago, Anumonye and colleagues described that, in humans, remission from mania was associated with increased excretion of uric acid (Anumonye et al. 1968). Subsequently, it was hypothesized that purinergic system dysfunction was directly involved in the neurobiological basis of bipolar mania (Machado-Vieira et al. 2002). Supporting evidence for this theory includes the observation that adenosine antagonists such as caffeine are associated with increased irritability, anxiety, and insomnia in individuals with BPD. Similarly, sleep loss is a well-known trigger for manic episodes (Ogawa and Ueki 2003). In contrast, adenosine agonists appear to have sedative, anticonvulsant, antiaggressive, and antipsychotic properties in animal models (Lara et al. 2006). Furthermore, a single nucleotide polymorphism (SNP) in the purinergic P2RX7 gene was described as a susceptibility gene for BPD (Barden et al. 2006). In preclinical models, knockout of this gene led to antidepressant-like effects; animals also displayed better responsivity to imipramine (Basso et al. 2009). In addition, in preclinical studies, the P2 receptor antagonist PPADS blocked amphetamine-induced motor hyperactivity (Kittner et al. 2001). Recent genetic and clinical studies have reinforced the role of purinergic system dysfunction in the pathophysiology of BPD (Barden et al. 2006; Lucae et al. 2006; Machado-Vieira et al. 2008).

Our group also recently described increased plasma uric acid levels in treatment-naïve subjects with BPD during the first manic episode (Salvadore et al. 2010).

The purinergic modulator allopurinol was found to have antimanic properties (Akhondzadeh et al. 2006; Machado-Vieira et al. 2008). Allopurinol acts by inhibiting xanthine oxidase, which is the key enzyme transforming hypoxanthine to uric acid, and has been used for many years to treat gout (Machado-Vieira et al. 2001). Two recent, large, double-blind, placebo-controlled studies investigated the effects of allopurinol used adjunctively to a mood stabilizer in the treatment of bipolar mania. In the first study, Akhondzadeh and colleagues (2006) compared placebo and allopurinol (300 mg/day) added on to lithium plus haloperidol for 8 weeks. Posthoc comparisons demonstrated a significant improvement as early as Day 7 on YMRS scores, and the difference between the two groups was also significant at study endpoint (8 weeks). Another 4-week, double-blind, placebo-controlled study involving 180 subjects with acute bipolar mania compared the efficacy and safety of allopurinol (600 mg/day), the purinergic modulator dipyridamole (200 mg/day), and placebo added to lithium (Machado-Vieira et al. 2008). Antipsychotics were not allowed in this study. Allopurinol was found to be significantly superior to dipyridamole and placebo in reducing manic symptoms and was also well-tolerated. The antimanic effects of allopurinol were significantly associated with uric acid levels, reinforcing the notion that purinergic dysfunction plays a key role in mania. Additional large controlled studies with more selective purinergic modulators are necessary to determine what specific purinergic targets are relevant to antimanic effects and mood stabilization.

5 The Cholinergic System

Several decades ago, Janowsky first proposed that dysfunction of the cholinergic–adrenergic equilibrium, mostly related to increased cholinergic tone, could be related to the pathophysiology of mania and depression (Janowsky et al. 1972). This concept built on an earlier observation that insecticidal cholinesterase inhibitors induced depressive symptoms in individuals with BPD (Rowntree et al. 1950). The depressogenic effects of cholinomimetic drugs during manic episodes in turn suggested a role for decreased acetylcholine levels during mania (Davis et al. 1978).

5.1 The Muscarinic System

Kasper and colleagues (1981) noted that the anticholinergic agent biperiden had antidepressant effects in subjects experiencing a major depressive episode (Kasper et al. 1981). In a combined cohort of subjects with BPD, MDD, and seasonal mood disorders, an association study identified a SNP within the cholinergic muscarinic$_2$ receptor (CHRM2) gene as a risk gene (Luo et al. 2005). Preclinical studies have

noted that rats bred selectively for increased muscarinic receptor sensitivity display several depressive-like phenotypes, such as lethargy, despair, and anhedonia (Overstreet 1993). Neuroendocrine and pupillary responses to cholinergic activity also appear to be blunted in manic subjects, with normalization of pupillary responses accompanying treatment with lithium or valproate (Sokolski et al. 2000). PET studies using selective agonists have described decreased CHRM2 receptor binding in the anterior cingulate cortex of individuals with BPD but not MDD (Cannon et al. 2006). Additional evidence includes the finding of decreased muscarinic receptor binding in the frontal cortex of BPD subjects, suggesting abnormal expression of muscarinic receptors (Gibbons et al. 2009). Interestingly, lithium increases the expression of hippocampal cholinergic muscarinic receptors (Marinho et al. 1998).

In clinical studies, physostigmine, a short-acting cholinesterase inhibitor, showed rapid but not sustained improvement of manic symptoms after single or multiple injections in a small controlled trial of manic individuals (Davis et al. 1978; Khouzam and Kissmeyer 1996). The long-acting cholinesterase inhibitor donepezil (5–10 mg/day), used as add-on therapy, showed rapid and significant antimanic effects in more than half of patients with treatment-resistant mania (Burt et al. 1999); however, a subsequent double-blind, placebo-controlled study failed to show antimanic efficacy as add-on treatment in refractory mania (Eden Evins et al. 2006). Similarly, acute treatment with donepezil did not improve cognitive functioning in geriatric BPD (Gildengers et al. 2008). One case report also noted that donepezil induced hypomanic switch in a brain-injured patient during a depressive episode (Rao et al. 2008).

Recently, a double-blind, placebo-controlled, dose-finding study followed by a double-blind, placebo-controlled, clinical trial observed a rapid decrease in severity of depression (as measured by Montgomery-Asberg depression rating scale (MADRS) scores) following the administration of the antimuscarinic drug scopolamine hydrobromide compared with placebo in individuals with MDD and bipolar depression (Drevets and Furey 2010). In the first study, patients received a 15-min intravenous infusion of a saline placebo and three doses of scopolamine hydrobromide (2.0, 3.0, and 4.0 ug/kg). The second study included seven sessions with a 15-min intravenous infusion of a placebo saline solution or scopolamine hydrobromide (4.0 ug/kg). Despite previous reports suggesting that this class of agents was associated with potential psychotomimetic side effects and/or euphoria (Jellinek 1977), only one patient receiving scopolamine in this study experienced euphoria. Further controlled, short- and long-term studies with more selective compounds are warranted to evaluate the long-term efficacy, safety, and tolerability of these promising agents as therapeutics for the treatment of BPD.

5.2 The Nicotinic Acetylcholine Receptor System

The nicotinic acetylcholine receptor (nAChR) system involves 12 well-characterized neuronal nAChR subunits (α2–10 and β2–4). Nicotine and its analogs display

mood-elevating (hedonic) properties and antidepressant-like effects in preclinical models, and its withdrawal has been shown to induce anhedonic states (Epping-Jordan et al. 1998; Ferguson et al. 2000; Semba et al. 1998; Tizabi et al. 1999) in animal models. Similarly, the high-affinity nAChR agonist cytisine exhibited antidepressant-like properties in male C57BL/6J mice (Mineur et al. 2007).

Postmortem studies of individuals with BPD found increased mRNA levels of nAChR α7 (located at chromosome 15a13–14) and α7-like genes in the prefrontal cortex compared to patients with schizophrenia and healthy controls (De Luca et al. 2006). A small, double-blind, placebo-controlled study evaluating the antidepressant effects of transdermal nicotine (3.5–7.0 mg/day) compared to placebo showed superiority for the active compound at Day 8, with no difference from placebo at study endpoint (4 weeks). Few side effects were reported.

In preclinical studies, mecamylamine, a nicotinic antagonist, reduced drug-induced hyperactivity and induced antidepressant-like effects in rodents (Miller and Segert 2005; Tizabi et al. 1999). These effects seemed to be directly associated with $\beta 2$ and $\alpha 7$ subunits of the nAChR (Rabenstein et al. 2006). Based on preclinical models of depression, it was recently proposed that mecamylamine produced antidepressant-like effects via different mechanisms than nicotine (Andreasen and Redrobe 2009). For instance, nicotine (but not mecamylamine) enhanced the antidepressant-like effects of SSRIs. A placebo-controlled preliminary clinical study confirmed this effect, showing that mecamylamine added on to SSRIs was effective in patients with treatment-resistant MDD (George et al. 2008). The same compound (dose ranging from 2.5 to 7.5 mg/day) had mood-stabilizing effects in two individuals with BPD comorbid with Tourette's syndrome (Shytle et al. 2000). A small, 8-week, double-blind, placebo-controlled trial in children and adolescents with Tourette's syndrome comorbid with other psychiatric disorders also found that mecamylamine had mood-stabilizing and antidepressant effects (Shytle et al. 2002). Studies using specific nicotinic modulators in the treatment of mood disorders are currently underway, and these will hopefully help elucidate the role that these agents may ultimately play as therapeutics for BPD.

6 The Melatonergic System

Melatonin produces its biological effects mostly through G protein-coupled melatonin receptors (MT1 and MT2), which are highly expressed in the brain and regulate sleep–wake rhythms. This system is altered in the course of BPD, particularly the circadian system. To date, no controlled studies have explored the use of melatonin in patients with BPD, and case reports describe conflicting findings (Bersani and Garavini 2000; Nierenberg 2009; Van Oekelen et al. 2003). However, supersensitivity to melatonin suppression by light was described in patients with BPD, as well as in the nonaffected offspring of probands with BPD and in monozygotic twins discordant for BPD; these findings were not confirmed by another study of euthymic individuals with BPD (Hallam et al. 2005; Lewy et al.

1981, 1985; Nurnberger et al. 2000). Regarding genetic data, a significant association between the δ502 and 505 polymorphism in GPR50 (H9, melatonin-related receptor) and BPD risk was described, but this finding was not replicated in a subsequent association study (Alaerts et al. 2006; Thomson et al. 2005).

Agomelatine, a potent, nonselective agonist of melatonin MT1 and MT2 receptors has been shown to resynchronize a disrupted circadian rhythm and has circadian phase-advancement properties (Armstrong et al. 1993; Nagayama 1996; Redman and Francis 1998). Agomelatine is also a 5-HT2C antagonist and increases both norepinephrine and dopamine (Van Oekelen et al. 2003). Chronic agomelatine use increases cell proliferation and neurogenesis in the ventral dentate gyrus (Banasr et al. 2006). In animal models of anxiety and depression (the forced swim and chronic mild stress tests, learned helplessness paradigm, etc.), agomelatine exerted significant antidepressant-like effects (Bertaina-Anglade et al. 2006; Millan et al. 2005; Papp et al. 2003). Furthermore, in clinical studies, agomelatine was significantly more effective than placebo in several controlled, large, multicenter studies of individuals with MDD (Kennedy and Emsley 2006; Loo et al. 2002; Montgomery and Kasper 2007), and was also well-tolerated. A recent trial evaluating 21 patients with bipolar depression receiving agomelatine (25 mg/day) for 6 weeks noted that 81% of patients experienced significant improvement by study endpoint, and 47% showed response during the first week of treatment (Calabrese et al. 2007). Switch risk was considered very low. A recent open-label pilot study of agomelatine in bipolar depression found similar antidepressant effects (Eppel 2008).

7 Drugs with Multiple Targets and Potential Relevance in BPD

7.1 Modafinil

Modafinil is an FDA-approved wake-promoting agent for the treatment of narcolepsy (Littner et al. 2001). Its exact mechanism of action is unknown, but it is believed to target multiple neurotransmitter systems, including glutamate, gamma aminobutyric acid (GABA), dopamine, and noradrenaline. In a 6-week, randomized, double-blind, placebo-controlled study of individuals with bipolar I or II depression, modafinil used adjunctively to mood stabilizers with or without antidepressants ($n = 87$) was associated with superior improvement of depressive symptoms (mean dose: 177 mg/day) as early as Week 2 (Frye et al. 2007). No manic switch was observed. In another study, Frye and colleagues (2007) compared modafinil as add-on therapy (100 or 200 mg for 3 weeks) with placebo in BPD subjects exhibiting subsyndromal depressive symptoms, fatigue, or both. Those individuals receiving modafinil had significantly greater improvement on baseline-to-endpoint change measures on both the inventory for depressive symptoms (IDS) and clinical global impression (CGI) rating instruments, as well as response

and remission rates (Frye et al. 2007). However, two case reports evaluating the effects of modafinil described manic/hypomanic switch in patients with treatment-resistant bipolar depression (Plante 2008; Wolf et al. 2006), and two other cases showed treatment-induced irritability and aggression in BPD subjects (Ranjan and Chandra 2005). Another recent case report found that modafinil monotherapy exerted significant antimanic effect within 1 h of administration (Schoenknecht et al. 2010).

7.2 Uridine (RG2417) and Triacetyluridine (RG2133)

Uridine (RG2417) and its prodrug triacetyluridine (RG2133) (Repligen corporation) are biological compounds involved in the synthesis of DNA and RNA, and have been evaluated as putative therapeutics for diverse neuropsychiatric disorders. One preclinical investigation noted that RG2133 was associated with antidepressant-like effects. In a recent, 6-week, clinical study, the same compound (up to 18 g/day) was shown to decrease depressive symptoms in 11 individuals with bipolar depression as early as Week 2. Antidepressant response was associated with increased brain pH and improved mitochondrial function (Jensen et al. 2008).

In multicenter Phase IIb clinical trials of individuals with bipolar depression, uridine (administered twice daily) was found to be more effective than placebo (unpublished findings). Over the 6-week treatment period, patients taking uridine experienced a statistically significant improvement in depressive symptoms compared to placebo, as assessed by MADRS scores, and a strong trend towards improvement on the CGI-BP-C. This study was conducted under a development agreement with the Stanley Medical Research Institute (study ID # NCT00322764; study details are available at: http://www.medicalnewstoday.com/articles/88213.php).

8 Oxidative Stress and Bioenergetics

8.1 N-Acetyl Cysteine

Increasing evidence suggests the involvement of oxidative stress parameters in the pathophysiology of BPD (Machado-Vieira et al. 2007; Ng et al. 2008). Glutathione is the most abundant antioxidant substrate in all tissues and its altered levels have been described in individuals with BPD (Andreazza et al. 2007; Kuloglu et al. 2002). Glutathione production is regulated by its precursor, cysteine. Treatment with *N*-acetyl cysteine (NAC), a precursor of glutathione, increases glutathione levels. A recent, randomized, double-blind, multicenter, placebo-controlled study involving 75 patients with BPD evaluated NAC (1 g twice daily) used adjunctively to treatment as usual over 24 months, followed by a 4-week washout phase. By study

endpoint, NAC showed superior antidepressant effects compared to placebo as assessed by MADRS scores and most secondary scale scores (Berk et al. 2008). Notably, all interested patients could participate in the study; that is, patients were not necessarily selected for experiencing a major depressive episode. However, there was a considerable lag in the benefits obtained, and these benefits were lost shortly after discontinuing the study medication. There were no significant differences in side effects compared to placebo. The authors hypothesized that NAC's efficacy might be due to its ability to reverse the increased oxidative stress occurring during mood episodes. Notably, NAC has been also studied as a glutamatergic modulator in other psychiatric disorders, including obsessive compulsive disorder (OCD) spectrum disorders. Its potential glutamatergic effects may be based on its ability to increase glial cysteine levels and uptake mediated by a cysteine–glutamate antiporter, which in turn increases extrasynaptic glutamate levels. This effect is further believed to stimulate mGluR2 activity, thus reducing synaptic release of glutamate (Krystal 2008).

8.2 Creatine

Creatine plays a key role in brain energy homeostasis, and its dysfunction has been implicated in BPD. Individuals with BPD experiencing a manic episode display altered levels of brain creatine kinase in the hippocampus, an effect that has also been noted in animal models of mania (Ongur et al. 2009; Segal et al. 2007; Streck et al. 2008)). Investigators thus hypothesized that creatine supplementation might modify brain high-energy phosphate metabolism in subjects with BPD. A recent open-label study of ten treatment-resistant depressed patients (two of whom had BPD) found that 3–5 mg/day of creatine monohydrate added to ongoing treatment significantly improved depressive symptoms in patients with MDD (Roitman et al. 2007). However, the two subjects with BPD experienced transient hypomanic/manic symptoms. Further studies are necessary to clarify the role of creatine in the mitochondrially mediated pathophysiology of BPD (Quiroz et al. 2008).

9 The AA Cascade

The AA pathway exerts critical modulatory effects as an intermediary of second messenger pathways in the brain, thus resulting in the release of AA, and cyclooxygenase (COX)-mediated generation of eicosanoid metabolites such as prostaglandins and thromboxanes. The AA signaling pathway has been implicated in the pathophysiology and therapeutics of mood disorders, and strong evidence also suggests that cytokine dysregulation may play a role in the pathophysiology of depression (Khairova et al. 2009).

In this context, administration of the nonselective COX inhibitors indomethacin and piroxicam in rats prevented the arousal of manic-like effects in two animal models (amphetamine-stimulated locomotor activity and blocked cocaine sensitization) (Ross et al. 2002). In addition, chronic administration of lithium, carbamazepine, sodium valproate, or lamotrigine to rats downregulated AA turnover in brain phospholipids, formation of prostaglandin E(2), and/or expression of AA cascade enzymes, including cytosolic phospholipase A(2), COX-2, and/or acyl-CoA synthetase (Rapoport et al. 2009). Valproate decreased turnover of AA, protein levels of COX-1 and COX-2,203, and frontal cortex COX-2 mRNA (Rao et al. 2007). COX-2 also protected against neurotoxicity promoted by excessive concentrations of glutamate. With regards to antidepressants, preclinical studies noted increased AA signaling after chronic treatment with imipramine, but not bupropion (Lee et al. 2008).

In clinical studies, the COX-2 inhibitor celecoxib (400 mg/day) showed significant antidepressant effects compared to placebo when added on to reboxetine (Muller et al. 2006). More recently, a 6-week, double-blind, placebo-controlled study of individuals with BPD found superior antidepressant effects with celecoxib (400 mg/day) used adjunctively to mood stabilizers only during the first week of treatment (Nery et al. 2008). It is important to note that the degree of celecoxib's ability to penetrate the blood–brain barrier is not well established. Also, increased risk of adverse cardiovascular outcomes may limit the long-term use of selective COX-2 inhibitors (Velentgas et al. 2006). Another second-generation tetracycline (minocycline) has shown promising results in preclinical studies and may be putatively useful in treating MDD (Pae et al. 2008). Overall, targeting the AA cascade may represent a useful therapeutic approach in the treatment of mood disorders, and BPD in particular.

10 Intracellular Signaling Pathways and Targets Worthy of Further Study in BPD

10.1 Glycogen Synthase Kinase-3

GSK-3 is a multifunctional serine/threonine kinase that is normally highly active in cells and is deactivated by signals originating from numerous signaling pathways [e.g., the Wnt pathway, the phosphoinositide 3 (PI-3)-kinase pathway, protein kinase A (PKA), and PKC]. In general, increased activity of GSK-3 is proapoptotic, whereas GSK-3 inhibition attenuates or prevents apoptosis. It is a key modulator of glycogen synthesis, gene transcription, synaptic plasticity, apoptosis (cell death), cellular structure and resilience, and the circadian cycle (Jope 2003), all of which are directly involved in the pathophysiology of severe recurrent mood disorders. Mice overexpressing a constitutively active form of GSK-3β in the brain exhibited increased locomotor activity and decreased habituation in the open field test. Also,

the GSK-3 inhibitor AR-A014418 induced significant antidepressant-like behaviors in the forced swim test and attenuated D-amphetamine-induced hyperlocomotion (Gould et al. 2004, 2006), thus suggesting relevant antimanic and antidepressant effects for this class of compounds. In addition, the mood stabilizer lithium has neurotrophic and neuroprotective properties in rodent and *in vitro* models, and these effects may be partially due to GSK-3 inhibition (reviewed in Gould and Manji (2005)). Treatment with lithium was recently observed to significantly enhance initially decreased GSK-3β cytosolic and membrane expression in platelets from subjects with BPD but not MDD. Thus, GSK-3β may be a state rather than a trait marker in BPD (Pandey et al. 2009).

However, diverse pathways with multiple substrates are involved in GSK-3 inhibition, thus increasing the risk of side effects and toxicity (Rayasam et al. 2009). At this time, no blood–brain barrier-penetrant GSK-3-selective inhibitors are available for human use, and proof-of-principle studies with selective GSK inhibitors are needed in BPD to define the therapeutic relevance and safety of this target.

10.2 The PKC Signaling Cascade

PKC plays a key role in regulating neuronal excitability, neurotransmitter release, and long-term alterations in gene expression and plasticity. PKC isoforms differ in their structure, subcellular localization, tissue specificity, mode of activation, and substrate specificity. Diverse studies support the involvement of PKC and its substrates in the pathophysiology and therapeutics of BPD (Chen et al. 1994; Friedman et al. 1993; Hahn and Friedman 1999; Manji et al. 1993; Manji and Lenox 1999; Young et al. 1999; Zarate and Manji 2009). Diverse studies show that PKC is directly regulated by lithium and valproate, and a recent clinical trial using the PKC inhibitor tamoxifen provided further evidence for the involvement of this system in bipolar mania. Although well known for its antiestrogenic properties, tamoxifen is also a potent PKC inhibitor at high concentrations. Preclinical studies showed that tamoxifen decreased amphetamine-induced hyperactivity in a large open field (Einat et al. 2007). In clinical studies, a single-blind study found that tamoxifen had significant antimanic effects in five of seven individuals with BPD (Bebchuk et al. 2000). This initial finding was confirmed in a recent, double-blind, placebo-controlled study demonstrating that tamoxifen had significant antimanic effects at doses as high as 140 mg/day from Day 5 to 3 weeks (Zarate et al. 2007). This antimanic effect was not related to its sedative effects and no increased risk of depression was observed. A 28-day, double-blind, placebo-controlled study also showed a significant improvement in manic symptoms from baseline to final assessment with tamoxifen compared with placebo (Kulkarni et al. 2006).

Some of tamoxifen's antimanic effects could involve its antiestrogenic effects (see Goldstein (1986)). Interestingly, several other drugs tested as therapeutics for BPD such as omega-3 fatty acids and verapamil similarly inhibit PKC. Large

controlled studies with selective PKC inhibitors are necessary in acute bipolar mania to elucidate its potential therapeutic role.

11 Final Remarks

No currently available therapeutics for the treatment of BPD have been developed specifically based on an understanding of its neurobiological basis or the specific mechanism of action of existing effective medications. However, as this chapter has highlighted, novel, diverse, and promising compounds affecting a variety of targets are being carefully investigated, and these could ultimately result in new treatments for BPD. It is important to note that none of the new treatments reviewed in this chapter are FDA-approved for BPD. Indeed, most of the evidence presented here comes from case reports, case series, or proof-of-concept studies, some with small sample sizes. Nevertheless, these exciting and relevant findings may guide the development of much-needed novel and effective treatments for this devastating disorder.

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Bipolar Disorder: A Neurobiological Synthesis

Husseini K. Manji, Ioline D. Henter, and Carlos A. Zarate, Jr.

Contents

Bipolar disorder (BPD) is a common, chronic, recurrent mental illness affecting 1–2% of the general population (Goodwin and Jamison 2007). Clinically, it is one of the most debilitating medical illnesses, and a growing number of recent studies indicate that outcome is quite poor for many individuals with BPD. Afflicted patients generally experience high rates of relapse, a chronic recurrent course, lingering residual symptoms, cognitive and functional impairment, psychosocial disability, and diminished well-being. Furthermore, the disorder is frequently unrecognized, misdiagnosed, and mismanaged, and much still remains unknown about its pathophysiology.

With this book, we sought to bring together clinicians and researchers to provide a unique and broad perspective on BPD and to compile the most recent research drawn from a variety of disciplines investigating this complex disorder. Toward that

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end, the diverse chapters in this volume touch upon a broad swath of interrelated disciplines, from clinical phenomenology to basic molecular and cellular neurobiology, genetics, neuroimaging, and circadian physiology. The chapters in this volume clearly show that there have been tremendous advances in our understanding of the functioning (both normal and abnormal) of the brain. Indeed, we firmly believe that the impact of molecular and cellular biology–which has been felt in every corner of clinical medicine–will ultimately, and perhaps shortly, also have major repercussions for our understanding of the fundamental, core pathophysiology of BPD.

As the chapters in this volume highlight, recent years have witnessed a more wide-ranging understanding of the neural circuits and the various mechanisms of synaptic transmission, the molecular mechanisms of receptor and postreceptor signaling, and a finer understanding of the process by which genes code for specific functional proteins that in toto reduce the complexity of gene to behavior pathways (Gould and Manji 2004). In turn, a better understanding of the neurobiological underpinnings of this condition, informed by preclinical and clinical research, will be essential for the future development of targeted therapies that are more effective, act more rapidly, and are better tolerated than currently available treatments. Notably, advances in our understanding of the neurobiology of BPD continue to be made and do hold promise for future clinical applications.

As the information reviewed in these chapters has demonstrated, BPD is a multifactorial disorder, likely resulting from genetic vulnerability and environmental stressors interconnected and characterized by dysfunction in diverse biological systems. Indeed, the biological basis of its pathophysiology involves the dysfunction of an intricate network of interconnected limbic, striatal, and frontocortical neurotransmitter neuronal circuits that mediate mood state, cognition, self-awareness, insight, and functions, such as drive, and autonomic and circadian systems. Thus, BPD appears to arise from abnormalities within discrete brain networks (e.g., the anterior limbic network). Taken together, the information presented throughout these chapters makes it clear that abnormalities in multiple systems and at multiple levels characterize BPD. Here, we synthesize some of this available information.

1 Genetics

As Drs. McMahon and Wendland succinctly review in this volume, genetic factors clearly play a major role in the etiology of BPD. Indeed, the strong familiality and heritability of BPD have long been some of the best clues to its etiology. The most consistent data suggesting a role for genetic factors in BPD come from twin studies, which show a higher concordance in monozygotic compared to dizygotic twins (reviewed in Goodwin and Jamison 2007).

Furthermore, it is clear that we are on the verge of truly identifying susceptibility (and likely protective) genes for BPD. It is also clear that there is no one-to-one relationship between genes and behaviors, so that different combinations of genes – and the resultant changes in neurobiology – contribute to complex behaviors (normal or abnormal) (Hasler et al. 2006). It is also critically important to remember

that gene polymorphisms will likely simply be *associated* with BPD; that is, such genes are more likely to lend a higher probability for the subsequent development of BPD than invariably determine outcome. Obviously, genes will never code for abnormal behaviors per se, but rather code for proteins that make up cells, thereby forming circuits that in combination determine facets of both abnormal and normal behaviors. These expanding and interconnected levels of interaction have, in part, made the study of psychiatric diseases so difficult. The next task of psychiatric genetic research is to study how and why variations in these genes impart a greater probability of developing BPD and then to direct therapeutics at that pathophysiology (Gould and Manji 2004).

In recent years, epigenetics – the study of changes to the genome that, unlike mutations, do not alter DNA sequence – has emphasized the link between nature and nurture. Epigenetics purports to define the molecular mechanisms by which different cells from different tissues of the same organism, despite having identical DNA sequences, exhibit different cellular phenotypes and perform different functions. Presumably, phenotypic and functional differences are the cumulative result of a large number of developmental, environmental, and stochastic events, some of which are mediated through epigenetic modifications of DNA and chromatin histones. Epigenetic regulation is thus one of the molecular substrates for "cellular memory" that may extend our understanding of how environmental impacts result in temporally dissociated altered behavioral responses.

Epigenetic factors appear to influence the development of BPD, acting via stable but reversible modifications of DNA and chromatin structure. Indeed, the chapter by Dr. Petronis and colleagues in this volume argues that molecular studies of BPD will benefit significantly from adding an epigenetic perspective. Epigenetic mechanisms are consistent with various non-Mendelian features of BPD, such as the relatively high degree of discordance in monozygotic twins, the critical age group for susceptibility to the disease, clinical differences in males and females, and fluctuation of disease course, notably cycling between manic and depressive phases (Petronis 2003, 2004). Furthermore, recent studies have shown that the epigenomic state of a gene can be established through behavioral programming, and is potentially reversible (Weaver et al. 2004). This line of research is particularly notable because early life stressors (which have been associated with suicide attempts in later life) in BPD (Leverich et al. 2003) might be amenable to treatment with agents to "undo" the epigenetic changes (e.g., histone deactylase inhibitors (HDACs)) (Zarate et al. 2006). This work has great potential to enhance our understanding of the molecular basis of BPD.

The term "endophenotype" is also used with increasing frequency in relation to BPD, particularly because genes predisposing to BPD may be transmitted without expression of the clinical phenotype. Loosely defined as an internal, intermediate phenotype that fills the gap in the causal chain between genes and distal diseases (Gottesman and Shields 1973), the concept of endophenotypes in BPD may help to resolve key questions regarding the molecular genetic basis of this disorder. It is important to note that studies of endophenotypes in humans and in animal models of BPD are looking at specific aspects of behavior rather than trying to capture the broader spectrum of "mania" or "depression." Interestingly, individuals with BPD

have subtle neuropsychological abnormalities, even during periods of symptom remission. As Drs. Glahn and Burdick review in this volume, some of these neurocognitive deficits are present in unaffected family members of probands with BPD, suggesting that these measures may be quantitative endophenotypes for the disorder. Similarly, both individuals with BPD and their unaffected family members display specific personality traits (e.g., reduced inhibition, increased risk-taking). While much work remains to be done in further evaluating candidate endophenotypes with respect to specificity, heritability, temporal stability, and prevalence in unaffected family members, this research avenue has enormous potential for unraveling the etiology and pathophysiology of BPD.

2 The Neurobiological Evidence

Although genetic factors play a major, unquestionable role in the etiology of BPD, the biochemical abnormalities underlying the predisposition to, and the pathophysiology of, BPD remain to be fully elucidated. To date, the monoaminergic neurotransmitter systems have received the greatest attention in neurobiologic studies of these illnesses. Clinical studies over the past 40 years have attempted to uncover the biological factors mediating the pathophysiology of BPD using a variety of biochemical and neuroendocrine strategies. Indeed, assessments of cerebrospinal fluid (CSF) chemistry, neuroendocrine responses to pharmacological challenge, and neuroreceptor and transporter binding have, in fact, demonstrated a number of abnormalities of the serotonergic, noradrenergic, and other neurotransmitter and neuropeptide systems in mood disorders (summarized by Dr. Walderhaug and colleagues in this volume). While such investigations have been heuristic over the years, they have been of limited value in elucidating the unique biology of BPD, which must include an understanding of the underlying basis of the course of the illness characterized by episodic and often profound mood disturbance that can become progressive over time. Thus, BPD likely arises from the complex interaction of multiple susceptibility (and protective) genes and environmental factors, and the phenotypic expression of the disease must include a constellation of cognitive, motoric, autonomic, endocrine, and sleep/wake abnormalities.

Furthermore, while most antidepressants exert their initial effects by increasing the intrasynaptic levels of serotonin and/or norepinephrine, their clinical antidepressant effects are only observed after chronic (days to weeks) administration, suggesting that a cascade of downstream effects is ultimately responsible for their therapeutic effects. These observations have led to the sense that while dysfunction within the monoaminergic neurotransmitter systems is likely key to mediating some facets of the pathophysiology of BPD, such dysfunction likely represents the downstream effects of other, more primary abnormalities (Manji and Lenox 2000).

We should also keep in mind that a true understanding of the pathophysiology of BPD must address its neurobiology at different physiological levels (i.e., molecular, cellular, systemic, and behavioral). Abnormalities in gene expression undoubtedly

underlie the neurobiology of the disorder at the molecular level and, as noted previously, this will become evident as we identify the susceptibility and protective genes for BPD in the coming years. Once this has been accomplished, however, the even more difficult task of examining the impact of the faulty expression of these gene products (proteins) on integrated cell function must begin. The task becomes even more daunting when one considers the possibility that a major component of the pathophysiology of BPD may stem from discordant biological rhythms that ultimately drive the periodic recurrent nature of the disorder (see the chapter by Drs. Levenson and Frank in this volume for a thorough review of this topic).

Despite these formidable obstacles, there has been considerable progress in our understanding of the underlying molecular and cellular basis of BPD in recent years. In particular, recent evidence demonstrating that impaired signaling pathways may play a role in the pathophysiology of BPD, and that mood stabilizers exert major effects on signaling pathways that regulate neuroplasticity and cell survival have generated considerable excitement among the clinical neuroscience community, and are reshaping views about the neurobiological underpinnings of this disorder (Duman 2002; Manji et al. 2001; Nestler et al. 2002).

Overall, it should be clear from the information reviewed in this book that there are abnormalities in multiple systems and at multiple levels in BPD. It is our strong contention that BPD arises from abnormalities in cellular plasticity cascades, leading to aberrant information processing in synapses and circuits mediating affective, cognitive, motoric, and neurovegetative function. Cellular signaling cascades form complex networks that allow the cell to receive, process, and respond to information (Bhalla and Iyengar 1999; Bourne and Nicoll 1993). These networks facilitate the integration of signals across multiple time scales, the generation of distinct outputs depending on input strength and duration, and regulate intricate feed-forward and feedback loops (Weng et al. 1999). These signaling cascades play a critical role as molecular switches subserving acute and long-term alterations in neuronal information processing.

As the chapters by Drs. Young and Gawryluk, and by Dr. Du and colleagues in this volume ably review, a considerable body of evidence supports abnormalities in the regulation of signaling as integral to the underlying neurobiology of BPD. As noted previously, the pathophysiology of this illness must account for not only profound changes in mood seen in BPD, but also a constellation of neurovegetative features derived from dysfunction in limbic-related regions, such as the hippocampus, hypothalamus, and brainstem. Notably, the highly integrated monoamine and prominent neuropeptide pathways are known to originate and project heavily within these regions of the brain, and it is thus not surprising that abnormalities have been noted in their function across clinical studies. In fact, the contribution of these pathways to the pathophysiology of BPD must be reasonably robust, given the variability that might be expected in assessing such dynamic systems under the constraints in experimental design imposed upon such research (Manji and Lenox 2000).

Signaling cascades regulate the multiple neurotransmitter and neuropeptide systems implicated in BPD. While dysfunction within these neurotransmitter and

neuropeptide systems is likely to play an important role in mediating some facets of illness pathophysiology, they likely represent the downstream effects of other, more primary abnormalities in cellular signaling cascades. Indeed, even minor variations in ubiquitous regulators of signaling pathways can affect complex functions, yielding detrimental effects on behavior; this is clearly seen in many mouse models, where some genetic mutations in expressed proteins have little effect on non-CNS functions, but major effects on behavior (Manji et al. 2003). This observation also underscores the urgent need to develop more useful animal models for BPD (see the chapters by Dr. Einat and by Dr. Chen and colleagues in this volume for a comprehensive discussion of this topic). One issue of particular relevance to this area is the distinction between "animal models" and "model animals" (Chen et al. 2010). Loosely, the animal model approach begins by identifying behavioral stressors or chemical treatments that induce specific behavior(s) thought to cross-species phenocopy particular mood symptoms to study the biological basis of these induced behaviors. Conversely, the initial step of the model animal approach is to introduce specific gene or pathway alterations implicated in BPD into animals, which are then evaluated using batteries of behavioral tests. Both animal models and model animals can be used to evaluate novel therapeutics, but the increased use of model animals is expected due to the unique ability of such animals to evaluate pathophysiology-driven target treatments.

Abnormalities in cellular signaling cascades that regulate diverse physiologic functions also likely explain the tremendous comorbidity with a variety of medical conditions (notably cardiovascular disease, diabetes mellitus, obesity, and migraine) and substance abuse seen in BPD. As a corollary, it is worth noting that genetic abnormalities in signaling components are often fully compatible with life, and in many instances – despite the often-ubiquitous expression of the signaling protein – one sees relatively circumscribed clinical manifestations. These overt, yet relatively circumscribed, clinical manifestations are believed to ultimately arise from vastly different transcriptomes (all of the transcripts present at a particular time) in different tissues because of tissue-specific expression, haploinsufficiency, genetic imprinting, alternate splicing, varying stoichiometries of the relevant signaling partners in different tissues, and differences in the ability of diverse cell types to compensate for the abnormality (Manji et al. 2003).

Furthermore, signaling pathways are clearly major targets for hormones that have been implicated in the pathophysiology of BPD, including gonadal steroids, thyroid hormones, and glucocorticoids. In addition, alterations in signaling pathways likely represent the neurobiological substrates subserving the evolution of the illness over time (e.g., cycle acceleration). Signaling networks play critical roles in cellular memory; thus, cells with different histories, and that therefore express different repertoires of signaling molecules interacting at different levels, may respond quite differently to the same signal over time.

As noted previously, alterations in signaling pathways affect circadian rhythms known to be abnormal in BPD. It is important to note that although this tendency to recur is one of the most distinguishing features of BPD in both its bipolar and its unipolar forms, it is poorly described and not well understood. As Drs. Levenson

and Frank review in their excellent chapter in this volume, studies have begun to uncover the molecular underpinning of circadian cycles. The core clock mechanism appears to involve a transcriptional/translational feedback loop in which gene products are involved in negative feedback of themselves and other genes in the pathway. It is also important to note that cellular signal transduction cascades are clearly the targets for our most effective treatments for BPD. Indeed, it is likely that the identification of signaling cascades as targets for the actions of lithium and other mood stabilizers, such as valproate, has already had a profound impact upon our understanding of the cellular neurobiology of BPD (Bezchlibnyk and Young 2002; Manji and Lenox 2000). While most of our drug development efforts in the past have been aimed at treating the affective states of mania or depression, the unique clinical action of lithium is its ability to prophylactically stabilize the underlying disease process by effectively reducing the frequency and severity of profound mood cycling. Reasonable evidence exists to suggest that once the disease process has been triggered and clinically manifest, long-term adaptive changes in the central nervous signaling systems set the stage for predisposing an individual to more frequent and severe affective episodes over time. A correction of dysregulated trans-synaptic signaling by mood stabilizers represents a physiological process able to curtail the oscillations in behavioral states associated with BPD. Indeed, regulation of signal transduction within the critical regions of the brain by mood stabilizers affects the intracellular signal generated by multiple neurotransmitter systems; these effects undoubtedly represent targets for their therapeutic efficacy, since the behavioral and physiological manifestations of the illness are complex and are likely mediated by a network of interconnected neurotransmitter pathways.

Finally, abnormalities in cellular plasticity cascades likely also represent the underpinnings of the impaired structural plasticity seen in morphometric studies of BPD. Many of these pathways play critical roles not only in “here and now” synaptic plasticity, but also in long-term cell growth/atrophy and cell survival/cell death. For instance, the atrophic changes observed in multiple cell types (neurons and glia), as well as the reversibility of the changes with treatment, support a role for intracellular plasticity cascades. It is likely that the major defect is in the ability to regulate neuroplastic adaptations to perturbations (both physiological and pathophysiological) – an inability to handle “normal loads” (neurochemical, hormonal, stress-induced, pharmacologically induced, etc.) without failing or invoking compensatory adaptations that overshoot and predispose to oscillations. This allostatic load contributes to long-term disease progression (and potentially to cycle acceleration). Many of the very same “plasticity regulators” also play a critical role in cell survival, cell death, and cellular resilience. These observations serve to explain the atrophic, and perhaps degenerative, aspect of the illness in some patients, as well as the presence of signs normally associated with ischemic/hypoxic insults, such as white matter hyperintensities. This information is reviewed more fully in the chapters by Drs. Savitz and Drevets, and by Drs. Blond and Blumberg in this volume, which explore the most recent neuroimaging findings in BPD.

3 Conclusions

The last decade has been marked by tremendous advances in our understanding of the circuits, and especially of the molecular and cellular underpinnings of BPD. As discussed above, evidence consistently suggests that BPD involves structural impairments potentially related to dysfunctions in cellular plasticity and resilience, which may be prevented or even reversed with the use of mood stabilizers. Further insights into the pathophysiology of BPD have resulted from the use of technologies such as PET and fMRI, gene interaction analyses, and comprehensive gene expression analysis using DNA microarray. Future genetic linkage and association studies may be relevant, but it is important to emphasize that BPD is clearly a complex and multifactorial disorder and that the identification of the genes involved in the illness may remain elusive for some time. The related study of epigenetics and endophenotypes may soon yield profound insights into this condition.

Through functional brain imaging studies (see the chapters by Drs. Savitz and Drevets, and by Drs. Blond and Blumberg in this volume), affective circuits have been identified that mediate the behavioral, cognitive, and somatic manifestations of BPD. Key areas include the amygdala and related limbic structures, orbital and medial prefrontal cortex, anterior cingulate, medial thalamus, and related regions of the basal ganglia. Imbalance within these circuits, rather than an increase or decrease in any single region of the circuit, seems to predispose to and mediate the expression of BPD. Moreover, studies of cellular plasticity cascades in BPD are leading to a large-scale reconceptualization of the pathophysiology, course, and optimal long-term treatment of the illness. These data suggest that while BPD is clearly not a classic neurodegenerative disease, it is in fact associated with impaired cellular plasticity and resilience. As a consequence, there is a growing appreciation that optimal long-term treatment will likely be achieved by attempting to prevent underlying disease progression and its attendant cellular dysfunction, rather than exclusively focusing on treating signs and symptoms. The study of lithium (and other mood stabilizers)-responsive gene networks related to neuroprotection is promising and may provide a better understanding of critical nuclear downstream targets expressing key proteins and peptides. In addition, the search for neurobiological predictors of response, state, and trait markers is critically relevant and may provide new insights into potential biomarkers associated not only with the biological effects of lithium and other mood stabilizers but also with those relevant to clinical and translational paradigms.

As the last few chapters of this book have highlighted, little progress has been made in developing truly novel drugs specifically for the treatment of BPD; most recent additions to the pharmacopeia are brain-penetrant drugs developed to treat other disorders such as epilepsy or schizophrenia (although see the chapter by Dr. Bowden in this volume for an excellent review of pharmacological strategies for treating BPD with currently available therapeutics). More recently, the glutamate system has received much attention in the hope of developing improved therapeutics for BPD (see the chapter by Dr. Machado-Vieira and colleagues in this volume

for a review). In addition, a number of novel pharmacologic "plasticity-enhancing" strategies that may be useful in treating BPD are being developed. Indeed, these next-generation drugs, in addition to treating the core symptoms of BPD, might be able to target other important aspects of the illness. For example, they may be able to enhance cognition independent of whether mood symptoms improve, to prevent or reverse epigenetic factors that may negatively affect the long-term course of the illness, or to reduce certain medical comorbidities such as diabetes.

We are optimistic that the advances outlined throughout these chapters will result in an expanded understanding of this devastating disorder, and concomitantly, the discovery of new approaches to treat and ultimately prevent BPD.

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