Toward Constructing an Endophenotype Strategy for Bipolar Disorders

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Research aimed at elucidating the underlying neurobiology and genetics of bipolar disorder, and factors associated with treatment response, have been limited by a heterogeneous clinical phenotype and lack of knowledge about its underlying diathesis. We used a survey of clinical, epidemiological, neurobiological, and genetic studies to select and evaluate candidate endophenotypes for bipolar disorder. Numerous findings regarding brain function, brain structure, and response to pharmacological challenge in bipolar patients and their relatives deserve further investigation. Candidate brain function endophenotypes include attention deficits, deficits in verbal learning and memory, cognitive deficits after tryptophan depletion, circadian rhythm instability, and dysmodulation of motivation and reward. We selected reduced anterior cingulate volume and early-onset white matter abnormalities as candidate brain structure endophenotypes. Symptom provocation endophenotypes might be based on bipolar patients' sensitivity to sleep deprivation, psychostimulants, and cholinergic drugs. Phenotypic heterogeneity is a major impediment to the elucidation of the neurobiology and genetics of bipolar disorder. We present a strategy constructed to improve the phenotypic definition of bipolar disorder by elucidating candidate endophenotypes. Studies to evaluate candidate endophenotypes with respect to specificity, heritability, temporal stability, and prevalence in unaffected relatives are encouraged.

Key Words: Intermediate phenotype, biological marker, bipolar disorder, genetics, twins, families, endophenotypic

In seminal contributions, Angst and Perris proposed bipolar manic-depressive illness as a separate nosological group differing significantly in genetics, gender distribution, and course from unipolar depression (Angst 1966; Angst and Perris 1968; Perris 1966), with which it had been merged in Kraepelin's earlier and durable category of manic-depressive insanity since early in the 20th century. Understanding the etiology of manic-depressive illness, now referred to as bipolar disorder (BPD), requires a genetic diathesis interacting with environmental, epigenetic and stochastic components. Bipolar disorder, affecting approximately 1% of individuals (strictly diagnosed), is a chronic, disabling, and often life-threatening illness (Angst and Preisig 1995). Adding broader notions of the BP spectrum (Akiskal and Pinto 1999; Angst and Gamma 2002) would complicate our mission at this stage, so we must omit that rich literature.

Underlying genetic diatheses and environmental, epigenetic, and stochastic mechanisms have remained mostly uncharacterized (Lenox et al 2002). Recent scientific advances suggest that the time is at hand to begin to elucidate the genetic basis of BPD; these advances include 1) detection of genes causal for Mendelian brain diseases, such as Huntington's disease and early-onset Alzheimer's disease, and for some of the genes predisposing to complex diseases, such as diabetes and coronary artery blockage; 2) dramatic developments in molecular genetics, including the human genome project, Hapmap project, and increasing availability of low-cost genetic markers (single nucleotide polymorphisms) throughout the genome (Badner and Gershon 2002; Craddock et al 2005; Ogden et al 2004); and 3) continued consistent evidence from twin studies that concordance in BPD identical twins ranges from 40% (strict) to 97% (spectrum), in contrast to corresponding rates in nonidentical twins of 5%–38% (Angst et al 1980; Bertelsen 2004; Kieseppa et al 2004; McGuffin et al 2003).

Despite costly candidate gene association studies and genome-wide linkage scans, however, no genes for BPD have been identified definitively, though there are many promising leads (DePaulo 2004; Levinson et al 2003; McQueen et al 2005). The limited success of genetic studies of complex disorders has resulted in considerable debate regarding the reasons for the failures in the past, as well as the most appropriate methodological approaches to take in the future (Hirschhorn and Daly 2005; Kendler 2005). Questions have been raised concerning the definition of genetically relevant phenotypes and the nature of the underlying, partially overlapping sets of susceptibility genes. The diagnosis of BPD, as defined by current classification schemas, including DSM-IV, is based on clusters of symptoms and characteristics of clinical course that do not necessarily describe homogenous disorders but that rather reflect final common pathways of different pathophysiological processes involving genetic and environmental contributors (Charney et al 2002; Hasler et al 2004b). In addition, there is growing evidence that the boundaries between BPD and schizophrenia and between BPD and recurrent major depression might not be as distinct as previously assumed (Angst 1998; Lewis 2004; Maziade et al 2005).

In this review, we will present strategies to overcome some of the methodological difficulties impeding the elucidation of the genetic basis of BPD by proposing putative endophenotypes. The term "endophenotype" was described as an internal, intermediate phenotype (i.e., not obvious to the unaided eye) that fills the gap in the causal chain between genes and distal diseases (Gottesman and Shields 1973) and therefore might help to resolve questions about etiology. The endophenotype concept assumes that the number of genes involved in the variations of endophenotypes representing more elementary phenomena (as opposed to the behavioral macros found in the DSM) is less than the number involved in producing the full disease (Gottesman and Gould 2003). Endophenotypes provide a means for identifying the "upstream" traits underlying clinical phenotypes, as well as the "downstream" biological consequences of genes. The

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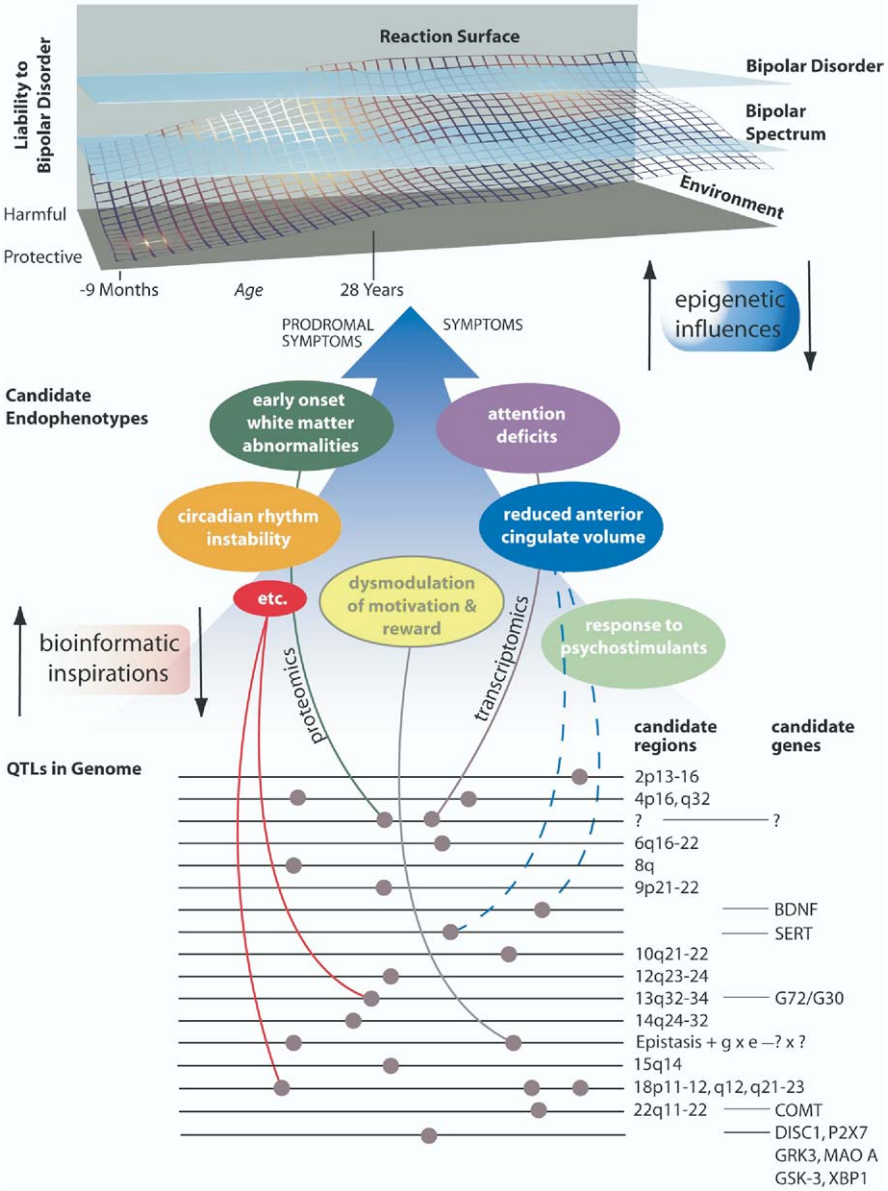

Figure 1. A heuristic model, whereby underlying bipolar disorders gene susceptibility loci and implicated genes, modulated by environmental, epigenetic, and stochastic events, predispose to the development of bipolar disorder. Along this lengthy continuum between genes and distal phenotype lie putative bipolar endophenotypes, the identification of which will be useful for studies of the underlying neurobiology and genetics of bipolar disorders, in addition to clear utility in preclinical investigations, such as the development of animal models. This figure is meant to represent a guide to future studies rather than a definitive portrait of loci, genes, and endophenotypes. QTL, quantitative trait locus. ©2005 I.I. Gottesman.

methods available to identify endophenotypes include neuropsychological, cognitive, neurophysiological, neuroanatomical, imaging, and biochemical measures (Figure 1). The evaluation criteria are based on the endophenotype concept developed by Gottesman and associates (Gottesman and Gould 2003; Gottesman and Shields 1973). Given the increasing recognition of the importance of epigenetic transformations and developmental factors in the expression of psychiatric phenotypes (Gottesman and Hanson 2004; Hasler et al 2005), the criterion "state independence" might be particularly difficult to achieve for candidate endophenotypes. Therefore, we slightly modified this criterion, emphasizing the role of time/age. Given the success of symptom provocation methods in genetic studies of medical diseases with variable course and important environmental influences over time (Kajantie et al 2004; Tripathy et al 2003), we also referred to these methods when claiming "state independence." Here are the modified criteria for the identification of endophenotypes:

1. An endophenotype is associated with illness, in the population.
2. An endophenotype is heritable.
3. An endophenotype is state independent (manifests in an individual whether or not illness is active) but age-normed and might need to be elicited by a challenge (e.g., glucose tolerance test in relatives of diabetics).
4. Within families, endophenotype and illness co-segregate.
5. An endophenotype identified in probands is found in their unaffected relatives at a higher rate than in the general population.

Apart from the criteria mentioned above, disease specificity and clinical and biological plausibility have also been discussed as evaluation criteria for endophenotypes (Tsuang et al 1993), to relate phenotypic definitions to clinically relevant outcomes, to enhance the elucidation of clinically relevant pathophysiological mechanisms (Lavori et al 2002), and to increase prior probability of utility in genetic studies (Freimer and Sabatti 2003, 2004). It should be emphasized, however, that endophenotypes, reflecting genetically relevant aspects of the heterogeneous pathophysiology of the disease, are clearly different from diagnostic markers, which

are evaluated by measures of sensitivity and specificity, because it cannot be assumed that the current definitions of psychiatric diseases are biologically valid. Claiming biological and clinical plausibility as endophenotype criteria prematurely or *a priori* might consequently impede discoveries of novel, unexpected disease mechanisms. We are not yet able to carve nature at its joints because we are uncertain as to what are the joints.

The Pheno–Geno Gradient of Endophenotypes

Within the broad class "endophenotypes," there is a gradient of closer to the gene and gene products ("geno") versus closer to the symptoms and the disease itself ("pheno"). In twin studies, broader diagnostic definitions (e.g., schizophrenia plus mood-incongruent affective disorders plus schizotypal personality disorder plus atypical psychosis) might provide higher heritability estimates than narrow diagnostic definitions (e.g., pure schizophrenia) (Farmer et al 1987). Likewise, in longitudinal studies, broader diagnostic categories (e.g., mood plus anxiety disorders) showed greater stability over time than narrow diagnostic definitions (e.g., pure panic disorder) (Angst et al 1990). By analogy, this might lead to the conclusion that relatively broad endophenotypes (brain function endophenotypes, e.g., cognitive performance) might be the most heritable and most appropriate for genetic studies. It has to be kept in mind, however, that although broad phenotypic constructs might show high familial transmission in twin and family studies, they might not represent alternative manifestations of a single liability distribution (McGue et al 1983). Genetic factors for intermediate traits that are closer to the genotype in the developmental scheme might generally be easier to identify because of the improved signal-to-noise ratio in the fraction of variance explained by any single factor (Carlson et al 2004).

The multifactorial threshold model of complex genetic disease assumes that 1) many factors contribute to a disorder ontogenetically; 2) the effects of each single factor are small, but the effects accumulate; and 3) once the combined effects of the factors pass some critical value, perhaps triggered by signaling or other cascades, the disorder becomes manifest (Gottesman and Shields 1967; McGue et al 1983). This model also can be applied to endophenotypes because we assume that multiple genetic and nongenetic factors contribute to an endophenotype that becomes manifest when the combined effects of the factors pass the endophenotype-specific threshold. Moreover, a certain endophenotype (e.g., cholinergic hypersensitivity) might, together with other endophenotypes and nongenetic factors, contribute to endophenotypes on more symptom-related levels (e.g., rapid-eye-movement [REM] sleep abnormality, clinical sleep characteristics), finally summing up to effects that pass the critical value for the macro phenotype. Again, the endophenotype approach assumes that the underlying liability of endophenotypes representing basic biological phenomena is less complex and easier to elucidate than the liability of complex behaviors, such as psychiatric diseases, irrespective of the magnitude of the phenotypic definition's total genetic risk.

Clinical and Preclinical Utilities of Endophenotypes

Although there exist select examples of success in psychiatry (e.g., the schizophrenia endophenotypes described below), the endophenotype idea remains a highly promising concept rather than a fully validated approach. The rationale for great expectations is a consequence of informed speculation and currently applicable procedures; specifically, endophenotypes are envisioned to aid in 1) diagnosis; 2) classification; 3) treatment; 4) clinical research; and 5) the development of preclinical models.

In contrast to other branches of medicine, psychiatry suffers from a diagnostic and classification system that is not based on pathophysiology and etiology, being dependent on nosological tradition, expert consensus, psychometric reliability, and clinical utility (First et al 2004). Therefore, it is not altogether surprising that studies of the underlying genetics and neurobiology have been fraught with a limited amount of success and an even more limited breadth of consensus. Dissecting psychiatric macro phenotypes into biologically valid components (whether they are biochemical, endocrinological, neurophysiological, neuroanatomical, cognitive, or psychopathological) presumes the ability to make diagnosis more certain, more specific, and more amenable to tailored treatment. Specifically, heterogeneity implicit in the current classification schema is a likely reason for the limited success of clinical studies, at the levels of treatment, neurobiology, and genetics.

The reductionist approach implicit in endophenotypes has clear parallels to the general mechanisms used in preclinical research and molecular genetics, having been successful in tracing pathways from potential susceptibility genes to psychiatric phenotypes. Neuregulin 1 knockout mice, for example, showed reduced expression of *N*-methyl-D-aspartic acid receptors and abnormalities in prepulse inhibition (Stefansson et al 2002), thus relating a schizophrenia candidate gene to putative endophenotypes of schizophrenia.

Selection of Endophenotypes

Unfortunately, there is no standardized algorithm for the selection of endophenotypes in genetic research. Generally, a putative endophenotype should be selected with respect to 1) empirical evidence of meeting endophenotype criteria; 2) feasibility and reliability of its measurement; and 3) possible relevance for the disorder/subject under study. For this article, we selected putative endophenotypes that seemed to be relatively specific for BPD. For example, we did not include P300 abnormalities in this review because they represent general markers of brain integrity, and their relationship to BPD is rather nonspecific (Lenox et al 2002). Likewise, we did not include promising putative endophenotypes that were primarily examined in major depression (e.g., return of depressive symptoms after tryptophan and catecholamine depletion, increased stress sensitivity, or dysfunctions of the hypothalamic–pituitary–adrenal axis) because they were discussed in a recently published review on endophenotypes in major depression (Hasler et al 2004b). In addition to the specificity criterion, we selected putative endophenotypes on the basis of empirical studies in euthymic patients and in unaffected subjects at substantially increased risk for BPD.

Brain Function Endophenotypes

One of the most consistent findings in behavioral genetics is that general intellectual functioning is highly heritable (Plomin and Spinath 2004). Twin and family studies consistently indicate that 65%–80% of individual differences in variation in adult intelligence test scores is accounted for by genetic factors, although the heritability of specific cognitive functions might be considerably lower. Cumulative data have identified stable and inherent cognitive impairments in psychiatric disorders (Goldberg and Weinberger 2004). The potentially high heritability and the reliable measurement of cognitive functions suggest that useful BPD endophenotypes can be derived from such impair-

ments, if they are not the consequence of the illness (Glahn et al 2004). In genetic studies of schizophrenia, for example, impaired working memory has seemed to be a useful neurocognitive endophenotype involved in schizophrenia-related functional and structural prefrontal cortex abnormalities and to a functional polymorphism in the catechol-O-methyl transferase (COMT) gene, which is thought to play a role in schizophrenia vulnerability (Egan et al 2001; Zammit et al 2004). In recent years, there has been increasing recognition of the role played by particular subcortical structures (e.g., nucleus accumbens, amygdala) in the regulation of motivation, sleep–wake cycle, and social behavior, domains that are prominently impaired in affective disorders (Nestler et al 2002). Twin and family studies provide evidence for high heritability for deficits in reward function (Fu et al 2002; Kendler et al 1991), and longitudinal research studies have demonstrated that symptoms of impaired reward mechanisms, including anhedonia and antisocial traits, emerge early in life, representing important precursors of a substantial portion of adult mental disorders (Kim-Cohen et al 2003; Luby et al 2004).

Attention Deficits

Deficits in attention have been proposed as a neuropsychological core vulnerability marker of BPD (Clark et al 2002; Harmer et al 2002). The specificity of this finding is questionable, however, because attention deficits have also been reported in patients with recurrent major depression in full remission (Weiland-Fiedler et al 2004), patients with schizophrenia (Addington and Addington 1997), and subjects with attention-deficit/hyperactivity disorder (Doyle et al 2005). In a report by Clark and Goodwin (2004), attention deficits seemed to be present early in the course of BPD but became more pronounced with repeated episodes. The same deficits have been identified in euthymic bipolar subjects (Clark et al 2002, 2005a), though the degree of impairment might be exacerbated during acute manic episodes. Functional neuroimaging studies have revealed several anatomical networks involved in functions of attention, such as alerting, orienting, and executive control (Fan et al 2002). Among the different attentional functions, executive attention, a process that involves dopamine-rich frontal areas (including the anterior cingulate), was found to be highly heritable (Fan et al 2001; Swan and Carmelli 2002). Executive attention has been assessed by the Stroop paradigm, attentional set shifting tasks, or the Attention Network Test. Impairments in executive attention were found to be mood state independent: in euthymic patients, decreased performance on the Stroop color and word test were not correlated to illness severity or duration (Zubieta et al 2001), and a functional neuroimaging study on attention in symptomatic and euthymic subjects with BPD, using the Stroop interference task, revealed a trait abnormality in the ventral prefrontal cortex related to mood-independent attentional deficits (Blumberg et al 2003). Unaffected offspring of bipolar probands showed evidence for deficit in tasks of ventral, but not dorsal, prefrontal cortex function (Frangou et al 2005). Moreover, increased slowness in the Stroop test, attentional set shifting, and deficits in executive control seemed to be specifically associated with genetic risk of BPD (Clark et al 2005b; Ferrier et al 2004; Zalla et al 2004). Taken together, attention deficit represents a potential endophenotype for BPD, although the neurobiological heterogeneity of attentional functions has to be taken into account to further decipher the molecular and genetic determinants (Fan et al 2001).

Deficits in Verbal Learning and Memory

Comparative studies on neuropsychological dysfunctions in severe psychiatric disorders showed that impairments were qualitatively similar in schizophrenia and BPD, with impairments being more severe in schizophrenia than in BPD; however, particularly poor performance on tests of verbal memory was consistently found as a characteristic of BPD (Johnson and Magaro 1987; Seidman et al 2002). Brain lesion studies and functional imaging studies identified a brain-wide distributed network in the medial temporal lobe, the temporal cortex, and the frontal cortex as a neural correlate of declarative memory function (Miyashita 2004). It has long been hypothesized that memory engrams of declarative knowledge in the cortex develop with structural reorganization of neural circuits. Neurobiological mechanisms that are potentially involved in the synaptic plasticity required for learning and memory include glutamatergic neurotransmission (Bannerman et al 1995) and changes in gene expression brought about by neurotrophic factors, such as cyclic adenosine monophosphate response element binding protein (CREB) and brain-derived neurotrophic factor (BDNF) (Bourtchuladze et al 1994; Egan et al 2003). In healthy subjects, verbal learning and memory were found to have a particularly high heritability: a twin study on memory functions showed that the intraclass correlations between monozygotic and dizygotic twins were significantly different for verbal learning and memory, whereas they were not different for response discrimination, learning strategy, and recognition (Swan et al 1999). Poor performance on measures of verbal learning and memory was found in euthymic bipolar patients irrespective of a history of alcohol abuse (Altshuler et al 2004; van Gorp et al 1998; Zubieta et al 2001), thus providing evidence for the state independence of this dysfunction. Unaffected twins of bipolar patients performed significantly worse than normal control subjects on short-term and long-term verbal learning and memory tasks (Gourovitch et al 1999), and deficits in verbal long-delay free recall and verbal recognition were found in healthy siblings of BPD patients (Keri et al 2001; Sobczak et al Sobczak et al 2002b, 2003). Tryptophan depletion enhanced verbal memory deficits in unaffected relatives of BPD patients (Sobczak et al 2002b, 2003). Some studies, however, failed to show such impairment in relatives of subjects with BPD (Clark et al 2005b; Ferrier et al 2004), suggesting mixed evidence for the association between verbal memory deficit and genetic risk of BPD. More research regarding the specific components of learning and memory deficits associated with genetic risk of BPD is warranted.

Cognitive Deficits After Tryptophan Depletion

Investigators have examined the possibility that sensitivity to the deleterious mood and cognitive effects of lowered serotonin might represent an endophenotype for BPD by studying unaffected relatives of BPD patients. Unlike control subjects, unaffected relatives showed increased impulsivity during acute tryptophan depletion. Baseline measurements indicated that, relative to control subjects, unaffected relatives exhibited lower serotonin platelet concentrations, lower affinity, and fewer binding sites of the serotonin transporter for imipramine; these differences were unaffected by tryptophan depletion (Quintin et al 2001). Sobczak et al (2002a) found that speed of information processing on a planning task (Tower of London Task) after tryptophan depletion was impaired in relatives of BPD patients but not in the control group. Furthermore, subjects with a BPD type I relative showed impairments in planning and memory, independent of tryptophan depletion, representing potentially

specific familial trait abnormalities related to BPD. In concert, these results suggest that impaired planning after reduced tryptophan availability might represent an endophenotype for BPD.

Circadian Rhythm Instability

Clinical features of BPD, such as diurnal variation in mood, early morning awakening, and cyclicity and seasonality of recurrences, have led to speculation that abnormalities in circadian rhythm might play an important role in its pathophysiology. Although circadian abnormalities have also been found in other psychiatric disorders, including unipolar depression and schizophrenia, they seemed to be particularly important in BPD: disturbance of the sleep–wake cycle was found to be the most common prodrome of mania (Jackson et al 2003; Wehr et al 1987); experimentally induced sleep deprivation is associated with the onset of hypomania or mania in a considerable portion of patients (see Response to Sleep Deprivation, below); and antimanic drugs were shown to stabilize circadian rhythms (Klemfuss 1992; Klemfuss and Kripke 1995). Although abnormalities in the circadian rhythm of body temperature and neuroendocrine profiles seem to be disease state dependent (Linkowski 2003; Souetre et al 1988), there is some evidence that the circadian rhythm in euthymic bipolar patients is persistently unstable (Jones et al 2005) and sensitive to environmental influences, such as weather conditions and seasonal changes (Hakkarainen et al 2003), and that euthymic patients show important impairments of sleep-related functioning, such as low daytime activity levels and nocturnal insomnia (Harvey et al 2005). Twin research in healthy individuals provided evidence for the heritability of circadian clinical characteristics (Dauvilliers et al 2005) and for a genetic control of the human circadian clock (Linkowski et al 1993). A mutation in a human clock gene, hPER2, has been specifically associated with a familial variant of human sleep behavior (Toh et al 2001), and a polymorphism in the human CLOCK gene has been associated with circadian mood fluctuation and illness recurrence in BPD (Benedetti et al 2003).

Lithium, which has been shown to modify the phase and period of circadian rhythms in a variety of species, ranging from unicellular organism and insects to mice and even humans, is a glycogen synthase kinase 3 (GSK-3) inhibitor (Gould et al 2004; Klein and Melton 1996). Interestingly, Martinek et al (2001) identified the *Drosophila* orthologue of GSK-3, SHAGGY, as a component of the circadian cycles. Overexpression of SHAGGY lengthened the *Drosophila* free-running circadian cycle. Additionally, a decrease in SHAGGY activity resulted in an increase in circadian period length (Martinek et al 2001), the effect (increase in circadian period) that has been noted in numerous species, including *Drosophila*, after treatment with lithium (Klemfuss 1992; Padiath et al 2004). Taken together, these data suggest that lithium's effect on circadian cycles (discussed in Gould and Manji 2002) might bring about some of its therapeutic effects in bipolar patients, supporting the hypothesis that circadian rhythm instability is etiologically associated with BPD and a candidate endophenotype. Finally, preliminary evidence on an association between a polymorphism in the GSK-3-β promoter gene and BPD suggest that genetic factors involved in the regulation of the human circadian clock might represent vulnerability factors of BPD (Benedetti et al 2004a).

Dysmodulation of Motivation and Reward

Loss of interest, lack of reactivity to positive events, and anhedonia are core features of the depressive phase of BPD, whereas heightened incentive motivation and compulsiveness toward reinforced behaviors are characteristic symptoms of the manic phase of the disorder. Presumed associations between dysfunction of the brain reward system and alterations between anhedonia and enhanced response to rewarding stimuli provide a potential biological basis of reward-related endophenotypes in BPD.

A wide variety of evidence in humans and nonhuman primates has associated brain reward functions with neural activity in the ventral striatum and mesial prefrontal cortex (Knutson et al 2001, 2003; Schultz 2002). Interestingly, gray matter deficits in these brain regions have been associated with genetic risk for BPD (McDonald et al 2004a). Euphoria has been related to amphetamine-induced dopamine release in human ventral striatum (Drevets et al 2001), and enhanced rewarding effects of psychostimulants in patients with affective illness and induction of mania in individuals with BPD might represent a trait-like dysfunction of the dopaminergic system associated with impairment of the brain reward function (Tremblay et al 2002). In individuals at risk for affective disorders, depletion of dopamine and norepinephrine by α-methyl-para-tyrosine (AMPT) induced anhedonia after 24 hours, followed by hypomanic symptoms, such as increased sexual interest and decreased need for sleep, 24–48 hours after the last AMPT dose, suggesting rebound sensitivity to AMPT depletion as an endophenotype for BPD (Anand et al 1999; Bunney et al 1977). Preliminary evidence of the heritability of these findings includes a functional polymorphism of the COMT gene that has been associated with the individual variation in the brain response to dopaminergic challenge (Mattay et al 2003).

In animals, the reward pathway circuitry has been intricately studied. Dopaminergic pathways originating in the ventral tegmental area and substantia nigra terminate in the nucleus accumbens and dorsal striatum. Glutamate, in addition to dopamine, is critical for plasticity-related events that lead to the identification of salience to rewarding stimuli. On the molecular level, increased function of the neurotrophic factor CREB in the nucleus accumbens, in response to stress or to overstimulation by rewarding stimuli, has been found to dampen the interest for natural rewards, such as sucrose drinking (Nestler 2004). In contrast, accumulations of δ-FosB, another reward-related transcription factor, has been shown to increase incentive motivation. δ-FosB persists in neurons for relatively long periods of time and might initiate and sustain changes in gene expression (Nestler et al 2001). Transgenic mouse studies have identified a large array of genes that regulate activity and function of brain reward pathways, although it should be mentioned that many of the studies were in the context of the effects of drugs of abuse (Ogden et al 2004).

More research in animal models of impaired brain reward pathways will be necessary to specifically address the hypothesis that dysregulation of these transcription factors might play a role in the intracellular pathophysiology of BPD. Future clinical studies will determine the relevance of specific reward pathways and brain areas to bipolar and unipolar depression.

Brain Structure Endophenotypes

The identification of pathologic lesions in specific regions of the central nervous system has contributed importantly to rapid progress in the understanding and treatment of neurodegenerative disorders, including Parkinson's and Alzheimer's diseases. Neuropathological findings are extremely useful for defining nosological subtypes of these conditions. For example, clinical features alone can be used to diagnose parkinsonism; postmor-

tem examination is needed for the definite diagnosis of the underlying disease, including classic Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, and frontotemporal dementia (Giasson and Lee 2003).

Increasing evidence suggests that BPD is accompanied by brain structural changes that might be mediated by interactions between hypercortisolemia, glutamate neurotoxicity, stress-induced reduction in neurotrophic factors, and stress-induced reduction in neurogenesis (Manji and Duman 2001). The relationship between these factors and changes in brain function on the cellular and molecular levels has been extensively studied and lays the foundation for most current hypotheses. Advanced imaging technology is beginning to describe subtle changes in brain structures that are associated with specific pathophysiological processes and genes (Hariri and Weinberger 2003). For example, a variation in the BDNF gene that has been found as a vulnerability factor of BPD (Craddock et al 2005) seems to affect the anatomy of the hippocampus and prefrontal cortex (Pezawas et al 2004). In vivo imaging allows the potential to connect findings in genetic neuroscience obtained from animal experiments and postmortem human studies to clinical characteristics of subjects suffering from BPD.

Anterior Cingulate Volume Reduction

Volume reductions in the anterior cingulate cortex (ACC) located ventral ("subgenual") and anterior ("pregenual") to the genu of the corpus callosum have been implicated by numerous studies of mood disorders (Drevets 2001). Specifically, a volume reduction in the left subgenual ACC has been associated with familial unipolar and bipolar disorders by magnetic resonance imaging (MRI) morphometric measures (Drevets et al 1997; Hirayasu et al 1999) and by postmortem neuropathological studies, which have shown glial reduction in the corresponding gray matter (Öngür et al 1998). This reduction in volume exists early in the illness in major depressive disorder (MDD) and BPD (state independence) (Botteron et al 2002; Hirayasu et al 1999) but seems to become more pronounced after illness onset, according to preliminary evidence in twins discordant for MDD (Botteron et al 1999). A volumetric MRI study found reduced subgenual PFC volume in subjects at high familial risk for mood disorders (Drevets et al 2004). Consistently, another volumetric MRI study in healthy subjects at risk for BPD or schizophrenia showed that alterations in the anterior ACC were specifically associated with genetic risk of BPD (McDonald et al 2004a).

The ACC contains abundant concentrations of glucocorticoid receptors that have been shown to play a major role in attenuating the glucocorticoid response to stress (Diorio et al 1993); in rats, left-sided lesions of the ACC increase sympathetic arousal and corticosterone responses to restraint stress (Sullivan and Gratton 1999). In addition, the ventral ACC and prelimbic cortex receive and send extensive neuronal projections from/to the ventral tegmentum, which have been shown to modulate the burst-firing dopamine neurons during reward learning (Drevets et al 1998). Humans with lesions that include the ventral ACC show abnormal autonomic responses to emotional stimuli, an inability to experience emotion related to concepts, and inability to use information regarding the probability of aversive social consequences versus reward in guiding social behavior (Damasio et al 1990). In four of six severely depressed patients, chronic deep stimulation of white matter tracts adjacent to the subgenual cingulate gyrus was associated with a sustained remission of depression (Mayberg et al 2005). Together, dysfunctions of this region conceivably could relate to the reductions in incentive, motivation, and hedonic capacity in depression, as well as the hypermotivational state and elevated hedonic capacity in mania. The mechanisms and genes underlying volume loss in the ACC have not yet been determined. Preclinical studies on the role and genetics of neurotrophic factors and the signaling cascade neurotrophic factor/mitogen-activated protein kinase/bcl-2 involved in the fine balance maintained between the levels and activities of cell-survival and cell-death factors (Manji et al 2003) might inform clinical studies associating ACC volume loss to genes. In humans, there is preliminary evidence that serotonin transporter gene s-allele carriers have significantly reduced bilateral gray matter volumes in the subgenual anterior cingulate (Pezawas et al 2005).

Early-Onset White Matter Abnormalities

White matter abnormalities (WMA) are abnormalities in the brain that are seen as bright foci on T2-weighted MRI scans. Dupont et al (1987) first reported that 8 of 14 bipolar patients had WMA findings on MRI. Two meta-analyses revealed that the risk of white matter abnormalities is more than threefold higher in patients with BPD than in healthy control populations (Altshuler et al 1995; Videbech 1997). A study in 43 bipolar patients and 39 healthy control subjects, using contiguous 3-mm-thick MR slices, confirmed increased occurrence of WMA in BPD: deep grade-2 WMA were found in 14% of bipolar patients and in none of the healthy control subjects (Ahn et al 2004). Alhthough WMA are not present in all subjects with BPD, WMA are thought to be relatively specific for BPD as compared with other primary affective disorders arising in early to mid-life (Dupont et al 1995), although WMA have also been found in schizophrenia (McDonald et al 2005). In addition, WMA (in contrast to gray matter or periventricular abnormalities) were found to be predictive of lithium response in BPD patients (Kato et al 2000), suggesting a role of WMA in the pathophysiology of BPD; however, the etiology of the WMA identified in BPD is unknown. White matter abnormalities are associated with a number of events, such as aging, cerebrovascular disorders, and migraine headaches (Altshuler et al 1995). Furthermore, it is unclear whether the cause of WMA is directly related to the pathophysiology of BPD or whether they are simply a coincident finding. The presence of WMA in young bipolar patients, however, is particularly noteworthy (Lyoo et al 2002; Pillai et al 2002; Stoll et al 2000). Although the histopathological correlates and the functional significance of WMA have not yet been determined, these findings are potentially consistent with increasing evidence suggesting that cell loss and atrophy occur in the brains of patients with BPD (Drevets 2000; Vawter et al 2000) and the possibility that BPD might be associated with impairments of neuroplasticity and cellular resilience (Manji et al 2000).

It remains to be shown convincingly that WMA are significantly more genetic than environmental in origin. In fact, supporting an environmental cause, Moore et al (2001) reported that WMA were correlated with season of birth in a group of bipolar patients. To our knowledge, a single study has examined the incidence of abnormal MRI findings in a single family with a strong history of BPD. In a group of 21 family members (8 with BPD), these investigators noted a "high prevalence of MRI findings." Of the 21 family members, 15 had abnormal findings, including 6 of 10 non-bipolar members. These abnormalities, however, were primarily lesions in the gray matter. One of the 10 non-bipolar members had a white matter lesion (Ahearn et al 1998). In addition to more extensive pedigree studies, experiments examining postmortem brains from bipolar patients imaged before death will be required to fully understand the

etiology of WMA in BPD. Continued studies that include relatives of patients with BPD will provide further data to make conclusions about the viability of WMA as an endophenotype.

Although anterior cingulate volume reduction and WMA are among the more consistent and specific neuroimaging findings in BPD, others, such as increased right lateral ventricular volume and changes in amygdala and hippocampal volume, might equally qualify as putative brain structure endophenotypes for BPD (McDonald et al 2004b).

Symptom Provocation Endophenotypes

In the symptom provocation (challenge) paradigm, a psychopharmacological or behavioral stimulus is presented to humans or animals under controlled conditions to elicit target psychiatric or neurobiological responses. The target symptoms or responses are selected to provide insight into basic biological mechanisms or into signs and symptoms that have pathophysiological relevance (e.g., the use the glucose tolerance test in the unaffected relatives of diabetics). Variations in behavioral or neurobiological responses might serve as quantitative endophenotypes in genetic studies. Endophenotypes based on symptom provocation methods are usually more disorder specific than brain function and brain structure endophenotypes, particularly when typical symptoms of the disorder are elicited in remitted patients. Ethical restraints must be observed at all times and should serve as an incentive to develop in vitro challenges to relevant tissue. In the "bottom-up" approach, symptom provocation methods help to test the roles played by genetically controlled neurobiological mechanisms, mainly derived from animal research, in the pathophysiology of a psychiatric disorder, whereas the "top-down" approach helps to generate clinically based hypotheses on the neurobiological and genetic underpinnings of psychiatric diseases that can be tested in the laboratory. In both instances, the use of symptom provocation endophenotypes provides a conceptual bridge between basic science and clinical symptomatology (D'Souza et al 1999).

Sensitivity to Psychostimulants

Psychostimulants, including amphetamines and cocaine, induce manic symptoms in some non-bipolar individuals and might induce full mania in individuals with BPD (Mamelak 1978). In addition, enhanced rewarding effects of psychostimulants in patients with affective illness have been reported (Tremblay et al 2002). Anatomically, the euphoric response to stimulants seemed to be related to dopamine release in the human ventral striatum (Drevets et al 2001). There is preliminary evidence for specific genetic variance explaining some of the individual variance in brain response to psychostimulants (Mattay et al 2003). Together, these findings suggest that behavioral changes (i.e., manic-like behavior) observed after exposure to amphetamines might be useful as markers for BPD.

Studies in rodents suggest a genetic foundation to behavioral response after stimulant administration. For example, the hyperactive response to psychostimulants measured in open-field models of hyperactivity might considerably differ between inbred rat and mouse strains (George et al 1991; Moisset and Welch 1973; Stohr et al 1998). Moisset and Welch used BALB/cJ and C57BL/10J mice to show such a difference. In an initial control experiment including 5 days of habituation, there was no difference in the locomotion activity in BALB/cJ and C57BL/10J mice. After amphetamine administration, they found significantly greater activity levels in C57BL/10J mice than in BALB/cJ mice. Furthermore, a common model observes the response of laboratory animals to amphetamine. Lithium attenuates amphetamine-induced hyperactivity in rodents and represents one of the most popular and reproducible models of antimanic drug efficacy (Einat et al 2003). Stimulant-induced hyperactivity is attenuated by antipsychotic drugs and anticonvulsants often used for the treatment of BPD (Lamberty et al 2001). It also has face validity in the sense that amphetamine commonly precipitates manic episodes in susceptible bipolar individuals, presenting an effect that seems to be attenuated by lithium (Huey et al 1981; Van Kammen and Murphy 1975).

There is some evidence that these results from animals generalize to humans. Johanson, Uhlenhuth, and others provided evidence for differential behavioral and discriminatory sensitivities to amphetamine administration in a series of studies conducted in the 1980s. They showed that among healthy volunteers, there was a broad range of differences in the ability to discriminate between amphetamine and placebo effects. Subjects who were good at identifying amphetamine effects had higher scores on personality measures of anxiety, depression, and confusion. Another study by the same group investigated differences between choosers of amphetamine and non-choosers in a choice procedure (de Wit et al 1986). The response to amphetamine was considerably different between the two groups. Choosers experienced increased positive mood and euphoria, whereas non-choosers experienced increased anxiety and depression after amphetamine administration. Kavoussi and Coccaro (1993) studied behavioral responses to amphetamine and placebo in 11 healthy volunteers by clinical interview and self-report. They found a positive association between the magnitude of the mood response to amphetamine and scores on the Affective Liability Scale.

There is preliminary evidence for the heritability of the behavioral response to amphetamine from twin studies. In a sample of 13 pairs of normal monozygotic twins, amphetamine-induced behavioral responses were highly correlated within twin pairs (Nurnberger et al 1982). In a sample six pairs of monozygotic twins, these results were replicated. The detailed analysis of this second twin study suggested that concordance rates were higher on behavioral than on pharmacokinetic measures, higher on objective behavioral measures than on self-report behavioral measures, and that different sets of genes are likely to be involved in the heterogeneous behavioral response to amphetamine (Crabbe et al 1983).

There is only limited and mixed evidence for the association between behavioral response to amphetamine and vulnerability to BPD. Anand et al (2000) found in 13 euthymic bipolar patients a greater increase in scores on the Brief Psychotic Rating Scale and the Young Mania Rating Scale after amphetamine administration than in 13 age- and gender-matched healthy comparison subjects, whereas there was no evidence for increased striatal dopamine release in patients relative to control subjects. An early study, however, did not find a difference in the behavioral response to amphetamine administration between control subjects and patients with BPD (Nurnberger et al 1982). Nevertheless, genes that affect variability of the responses to amphetamines also might reflect vulnerability to BPD. For example, a polymorphism in the promotor of the G-protein receptor kinase 3 gene, which is involved in the brain's homeostatic response to dopamine/amphetamine, has been associated with risk of BPD (Barrett et al 2003). Because psychostimulant use can also precipitate psychosis (especially in patients with a history of schizophrenia), it will remain critical that the specificity of any findings be tested.

Sensitivity to psychostimulants is worthy of future study because many of the human behavioral responses to amphetamine, including hyperactivity, increased novelty seeking, and changes in sleep–wake behaviors, can be modeled in animals (Stewart and Badiani 1993). Therefore, a better understanding of the human responses to amphetamine and their possible associations with vulnerability to BPD has the potential to improve animal models for BPD. Conversely, insights into the genetic factors responsible for differences in behavioral responses to amphetamine in animals might help to elucidate the genetic underpinnings of BPD in humans. Given the mixed evidence for associations between the behavioral response to amphetamine and risk of BPD, as well as ethical concerns regarding the use of amphetamines in subjects at risk of BPD, it seems to be warranted to evaluate the use of other promanic medications (Peet and Peters 1995) as putative symptom provocation endophenotypes in BPD.

Cholinergic Sensitivity

Dysfunctions of the cholinergic–adrenergic balance might be associated with etiologic factors of BPD. Evidence for anomalies of the cholinergic system in affective disorders has derived from studies conducted in symptomatic patients. Decreased cholinergic activity has been found in mania and cholinergic hypersensitivity in depression. Janowsky et al (1972, 1974, 1981) reported that a cholinergic challenge (using the anticholinesterase inhibitor physostigmine) induced depressive symptoms in manic subjects, and cholinergic activity induced a worsening of symptoms in unipolar depressed subjects; these results have been replicated by others (Davis et al 1978; Nurnberger et al 1983b; Risch et al 1981). The anergic–anhedonic syndrome following a cholinergic agonist was found to be dose dependent (Fritze and Beckmann 1988), suggesting that the percent change (and perhaps the speed of change) in intrasynaptic acetylcholine concentration is critical. In contrast, anticholinergic drugs, such as scopolamine, that target the muscarinic cholinergic receptors are associated with mood elevation and mania, and some tricyclic antidepressant drugs have relevant antimuscarinic effects (Raisman et al 1979; Stanton et al 1993). The neuroendocrine and pupillary responses to cholinergic activity are increased in depressed subjects (Dilsaver 1986), whereas manic subjects are hyporesponsive to cholinergic agents with respect to pupillary responses (Sokolski and DeMet 2000), and improvement in mania with lithium and valproate is associated with normalization of pupillary responses (Sokolski and DeMet 1999), confirming the hypotheses that depression is associated with cholinergic overreactivity, whereas mania is associated with a hypocholinergic state. A recent positron emission tomography study using [F-18]3-(3-((3-fluoropropyl)thio)-1,2,5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1methlpyridine (FPTZTP) showed a relatively specific reduction in muscarinic cholinergic-2 receptor binding in the depressed state of BPD (Cannon et al 2004), possibly reflecting excessive extracellular acetylcholine concentrations. Although there has been mixed evidence for the cholinergic hypothesis (Katerina et al 2004), the challenge paradigms used to test it might be useful in identifying endophenotypes in BPD. Given the role of the cholinergic system in the sleep–wake cycle (Szymusiak 1995), in learning, memory, and attention (Murray and Fibiger 1985; Wesnes and Warburton 1984), and in motivation and reward (Picciotto 1998), dysfunctions of the cholinergic system are likely related to circadian abnormalities, cognitive deficits, and impaired reward function in patients with BPD.

Rapid eye movements occur during discreet periods of sleep, and their onset can be induced by cholinergic agents (Gillin et al 1978; Sitaram et al 1978a, 1978b, 1978c, 1979). Bipolar patients seemed to differ from control subjects regarding the induction of REM sleep by cholinergic agents (Berger et al 1989; Nurnberger et al 1989; Sitaram et al 1980, 1982). There is evidence for mood state independence of this anomaly. Sitaram et al (1980) described faster induction of REM sleep with the cholinergic agonist arecoline in drug-free euthymic patients with BPD than in healthy control subjects matched for age and gender. The same research team also showed that the second REM period occurred significantly earlier in 14 euthymic bipolar patients than in control subjects (Sitaram et al 1982). Other researchers, however, found that increased susceptibility to cholinergic induction of REM sleep was state dependent (Berger et al 1989).

There is some evidence for the heritability of this trait. Nurnberger et al (1983a) examined the induction of REM sleep by cholinergic agents in seven monozygotic pairs. They reported an intraclass correlation of 0.69 for REM latency time after cholinergic stimulation, suggesting that this trait is heritable. In first-degree relatives of patients with both major depression and supersensitivity to cholinergic activity, Sitaram et al (1987) showed that 66% of the depressed relatives and 22% of the unaffected relatives also showed supersensitive REM induction, suggesting that this marker co-segregates in families with affective illness. Because this informative study did not include control subjects and did not rule out the effects of prior depressive episodes or treatment on cholinergic sensitivity, the results have to be interpreted with caution. Taken together, supersensitive REM sleep induction by cholinergic agents has been consistently associated with BPD; however, there is only preliminary evidence regarding the mood state independence, heritability, and familiality of this biological marker.

Response to Sleep Deprivation

Some symptoms of affective disorders might show diurnal variations (mood, psychomotor activity, accessibility of memories of positive and negative experiences), and a subgroup of patients with BPD might have a circadian rhythm disorder (Bunney and Bunney 2000). In healthy young subjects, moderate changes in the timing of the sleep–wake cycle had specific effects on subsequent mood (Boivin et al 1997). The association between phase advance of the sleep–wake cycle and phase advances in nocturnal cortisol secretion, as well as the effect of antidepressant and antimanic drugs on circadian rhythms of behavior, physiology, and endocrinology suggest sleep–wake cycle abnormalities as a source of putative endophenotypes for BPD (Bunney and Bunney 2000; Duncan 1996). Because manipulations of the circadian rhythms (light therapy, phase advance treatment, sleep deprivation—though it has to be acknowledged that sleep deprivation is more than a simple circadian manipulation) can have antidepressant efficacy, circadian abnormalities have been hypothesized to be etiologically associated with affective disorders.

Studies of sleep deprivation used as a therapy for the treatment of BPD suggested that decreased sleep duration might play a role in the origin of mania (Colombo et al 1999; Kasper and Wehr 1992; Szuba et al 1991; Wehr et al 1987; Wirz-Justice and Van den Hoofdakker 1999). The assessment of patients enrolled in sleep deprivation studies is usually conducted in a controlled environment, which makes this setting scientifically attractive. There is consistent evidence that sleep deprivation is highly effective in the treatment of both unipolar and bipolar depression (Wirz-Justice and Van den Hoofdakker 1999). The benefits are gener-

ally short lived, and chronic sleep deprivation might have negative health consequences (Hasler et al 2004a), thus reducing its use as a long-term treatment for depression (Wu and Bunney 1990). The risk of switching into mania during sleep deprivation therapy in patients with BPD has not been sufficiently evaluated, because most studies did not assess changes in manic symptoms, and the study samples included both unipolar and bipolar depressed patients. Colombo et al (1999) reported that 4.85% switched into mania and 5.83% switched into hypomania in a sample of 206 bipolar patients who underwent sleep deprivation as antidepressive treatment. Others found much higher rates of subjects with BPD vulnerable to mania/hypomania after disrupted sleep (Kasper and Wehr 1992). The potential state independence of hypomanic symptoms after sleep deprivation and the clinical and biological plausibility of this marker suggest that sleep deprivation might qualify as an endophenotype of BPD; however, heritability and association with genetic risk of BPD of this symptom provocation method have yet to be determined. Because sleep deprivation is related to a potentially heritable marker of affective illness, circadian rhythms, one might hypothesize that the genetic underpinnings could possibly be related to circadian cycles.

Because mania is associated with a reduced need of sleep and reduced sleep duration, sleep deprivation might be both an inducing and a self-reinforcing mechanism in the development and maintenance of a manic episode (Wehr et al 1987). Sleep deprivation might also be an important mechanism by which other promanic behaviors, including stimulant use, increase the risk of mania. Growing insight into the neurobiology of sleep deprivation (Spiegel et al 1999) and studies on the differential effects of sleep deprivation in susceptible individuals might provide relevant cues about the pathophysiology and etiological heterogeneity of BPD. Although sleep symptoms in affective illness might not be familial, there is some evidence for familiality of sleep physiological abnormalities related to affective illness (Hasler et al 2004b). For example, a study in unaffected individuals at high genetic risk for depression or BPD found abnormalities in the electroencephalographic coherence that were related to the risk of the disorders (Fulton et al 2000): beta–delta coherence was lower bilaterally in male high-risk subjects, whereas right-hemispheric theta–delta coherence was also lower in the same subjects. These findings are similar to those reported in subjects suffering from current affective illness. Further studies are warranted to examine relationships between electroencephalographic abnormalities and response to sleep deprivation. Electroencephalographic studies in euthymic patients with BPD and in unaffected relatives of patients with BPD will be necessary to determine whether endophenotypes for BPD can be derived from sleep physiological abnormalities.

Very recent molecular and cellular biological studies have reinvigorated the interest in sleep deprivation as a possible model. Thus, there is now incontrovertible evidence that the expression of selected critical genes varies dramatically during sleep and waking events, which likely plays a major role in regulating various, long-term neuroplastic events. Microarray, messenger ribonucleic acid differential display, and biochemical studies have shown that short-term sleep deprivation is associated with a rapid increase in various plasticity-related genes. Notably, these are precisely the plasticity-related molecules whose expression is increased by chronic antidepressant treatment. In an extension of the gene expression studies, Cirelli and Tononi (2000a, 2000b) hypothesized that a key factor responsible for the induction of the plasticity genes might be the level of activity of the neuromodulatory noradrenergic and serotonergic systems. Both of these systems project diffusely to most of the brain, where they regulate gene expression and are only quiescent during REM sleep (Cirelli and Tononi 2000a). There is thus a striking similarity between the effects of chronic antidepressants and short-term sleep deprivation on the BDNF signaling cascade. Do these alterations play a role in their ability to induce switches in susceptible individuals? As discussed already, some studies have suggested excess transmission of the valine allele of amino acid 66 of BDNF in BPD. Interestingly, this is the form of BDNF that has been associated with enhanced stimulated release in vitro (Egan et al 2003) and with younger age of onset in BPD (Rybakowski et al 2003). Thus, although quite preliminary, the data raise the intriguing possibility that bipolar individuals with the val/val BDNF genotype might be at greater risk for antidepressant- or sleep-deprivation–induced switches into mania; studies are currently underway to address this possibility. Further experiments have also linked the lithium target gene GSK-3 to response to sleep deprivation (Benedetti et al 2004b).

Concluding Remarks

In this article, we have discussed the advantages of applying an endophenotype strategy to the study of BPD. The endophenotype approach, applied to studies of BPD, presents a heuristic research strategy that will be necessary for major advances to take place. Numerous domains of study deserve further investigation, including neuropsychological deficits, circadian rhythm instability, dysmodulation of motivation and reward, neuropathological abnormalities, and symptom provocation responses. Given the relative scarcity of well-designed twin, family, and prospective studies evaluating candidate endophenotypes for BPD, future research has the potential to improve the phenotypic definition of BPD. Progress in developing economical and easy-to-apply neurobiological markers and the feasibility of genome-wide association studies might considerably facilitate the discovery of biological endophenotypes. In the long run, the discovery and systematic evaluation of BPD endophenotypes, along with identification of specific environmental risk factors, will provide the basis of a new classification system (Hasler et al 2004b). Such a classification system, based on etiology and pathophysiology, is badly needed because the improvement of the phenotypic definition of BPD will likely facilitate the identification of vulnerability genes and possibly the development of better preventive strategies and treatments for this disabling and often life-threatening illness.

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