Researching the Pathophysiology of Pediatric Bipolar Disorder

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We suggest that the core feature of bipolar disorder (BPD) is marked state fluctuations. The pathophysiology of switches into depressed, irritable, and extreme positive valence states requires study, with the latter deserving particular focus because it represents a pathognomonic feature of BPD in both adults and children. Hypotheses regarding the pathophysiology of pediatric BPD must account for these marked state fluctuations as well as for specific developmental aspects of the illness. These developmental aspects include marked irritability (in addition to euphoria and depression) and very rapid cycles, along with high rates of attention-deficit/hyperactivity disorder. We review research on neural mechanisms underlying positive valence states and state regulation, focusing on those data relevant to BPD and to development. Researchers are beginning to explore the response of manic patients and control subjects to positive affective stimuli, and considerable research in both nonhuman primates and humans has focused on the cortico–limbic–striatal circuits mediating responses to rewarding stimuli. In control subjects, positive affect affects cognition, and data indicate that prefrontal electroencephalogram asymmetry may differ between control subjects with consistently positive affect and those with more negative affect; however, this latter generalization may not apply to adolescents. With regard to the pathophysiology of state switching in pediatric BPD, data in control subjects indicating that attention regulation plays a role in emotion regulation may be germane. In addition, research detailing physiologic and psychological responses to negative emotional stimuli in bipolar patients and control subjects may increase our understanding of the mechanisms underlying both irritability and rapid cycling seen in children with BPD. Potential foci for research on the pathophysiology of pediatric BPD include reactivity to standardized positive and negative emotional stimuli, and the interaction between emotion regulation and attentional processes.
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Introduction

In recent years, researchers and clinicians have made considerable progress characterizing the phenomenology and course of pediatric bipolar disorder (BPD) (Geller et al 2002a, 2002b; National Institute of Mental Health 2001). Family and genetic studies, longitudinal studies, and clinical trials are also underway. Studies that begin to elucidate the pathophysiology of pediatric BPD are an important complement to these other research endeavors. Pathophysiologic studies are feasible in children because noninvasive methods exist to study psychophysiology, neuropsychology, neurochemistry, and brain structure and function. Clearly, such studies in bipolar children face major obstacles, including complex state–trait issues, and the ethical and practical problems involved in studying medication-free manic patients. Nevertheless, it is both possible and important for researchers to study the neural phenomena mediating the symptoms of pediatric BPD. Our purpose here is to suggest an approach to doing so.

Our approach to the study of pediatric BPD centers on the hypothesis that the core abnormality in BPD is marked state fluctuations. Although the states experienced by patients with BPD include depression, irritability, and mania, we suggest that, of all these switches, those into mania deserve particular research focus because sustained fluctuations into an extreme positive valence state represent a pathognomonic feature of BPD that differentiates it from other psychiatric illnesses. Indeed, given the nosologic confusion and controversy surrounding "mixed mania," "dysphoric mania," "agitated depression," and "irritable mania," there is a rationale for limiting the narrowest phenotype of BPD to individuals with a lifetime history of at least one episode of euphoric mania (Cassidy and Carroll 2001; Cassidy et al 2001; Geller et al 1998, 2001a; Leibenluft et al, in press).

In discussing the fluctuations that occur in BPD, we use the word "state" rather than "mood" because mania and depression are characterized by marked episodic alterations in behavior, cognition, and level of arousal, as well as by alterations in mood. Importantly, pediatric mania can be

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differentiated from attention-deficit/hyperactivity disorder (ADHD) and from the giddiness of healthy children by the extremity, frequency, and duration of such fluctuations, as well as by the fact that switches into mania involve not only mood changes, but also the appearance of cognitive and behavioral symptoms unique to mania (decreased need for sleep, grandiosity, increased goal-directed activity, increased pleasure-seeking) (Geller et al 1998, 2002b).

In describing mania as an extreme positive valence state, we draw on a large literature characterizing emotional states in terms of valence and arousal (Davidson and Irwin 1999; Lang et al 1998). Psychological researchers typically define an emotion as an evoked response to an environmental stimulus with motivational salience (Lang et al 1998). Motivational stimuli, in turn, are typically categorized in terms of their valence. Appetitive or positive stimuli are rewarding, and organisms will expend energy to approach them. Alternatively, organisms expend energy to avoid negative or aversive stimuli. Within these psychological models, the term *arousal* is used in a somewhat nonspecific manner to indicate the intensity of the activation evoked by the emotional stimulus, or the amount of resources mobilized in response to it (Lang et al 1998), without specific inferences as to the physiologic mechanisms mediating arousal. Importantly, although a number of other pathologic mood states are characterized by high arousal but *negative* valence (i.e., agitated depression, anxiety, mixed mania), euphoric mania is the only extreme *positive* valence state. Consequently, this unique characteristic of mania deserves particular attention in pathophysiologic studies. Similarly, although patients with other disorders may switch clinical state, such transitions are more frequent, more sustained, and more extreme in BPD than in other illnesses

Thus, marked state fluctuations and the ability to switch into an extreme positive-valence state differentiate BPD from other psychiatric illnesses and provide reasonable foci for pathophysiologic research. Therefore, after a brief summary of the clinical characteristics that differentiate childhood- from adult-onset BPD, we will review research on neural mechanisms underlying positive valence states and state regulation. We will first discuss neuropsychological and psychophysiologic studies, and then review neuroimaging studies. We will concentrate on studies with particular relevance for BPD, on developmental considerations, and on the implications of the literature for future research on pediatric BPD.

Developmental Differences in the Clinical Presentation of Bipolar Disorder

Hypotheses regarding the pathophysiology of pediatric BPD should account for phenomenologic differences between children and adults with the illness. That is, most investigators agree that even children who meet full DSM-IV criteria for mania (those with "narrow phenotype" illness [National Institute of Mental Health 2001]) have a characteristic clinical presentation that differs from that described for "classic" mania in adults. Unlike "classic" mania in adults (but like adults with rapid-cycling BPD), children with BPD tend to have relatively rapid mood cycles, with multiple short episodes interspersed between those meeting DSM-IV duration criteria (Geller et al 1998; Wozniak et al 1995). While manic or depressed, children with "narrow phenotype" BPD frequently experience irritability in addition to euphoria or dysphoria. This irritability, which is characterized by extreme, often physical, responses to frustration and other negative emotional stimuli, is one of the most impairing symptoms of the illness. Although irritability occurs in adults with euphoric and mixed mania, both its prevalence and its severity appear to be more marked in juvenile, as compared with adult, BPD (Geller et al 1998, 2002b; Wozniak et al 1995).

In addition to relatively short cycles and irritability, hypotheses regarding the pathophysiology of juvenile BPD should also account for the exceptionally high comorbidity with ADHD that has been reported. This comorbidity is particularly marked in children with a prepubertal onset of BPD (Geller et al 1998; Wozniak et al 1995). The observed comorbidity is not due to diagnostic uncertainty, because trained raters using standardized diagnostic instruments can reliably differentiate BPD, ADHD, and co-occurring BPD and ADHD in children (Geller 1998, 2001b; Milberger 1995). Controversy regarding how such differential diagnoses could be made arose when researchers suggested that children with BPD might present with chronic irritability, rather than the episodic course of classic adult BPD (Wozniak et al 1995). However, emerging data indicate that the presence of clear affective episodes (i.e., in the case of mania, increased irritability, or euphoria that represents a distinct change from baseline) may be associated with external validators of the diagnosis of BPD, including parental history of BPD, and a lifetime history of psychosis (Bhangoo et al, unpublished data), whereas the nosologic status of children with chronic irritability remains unclear and requires further study. ADHD can be diagnosed in the presence of BPD because, although symptoms such as distractibility and hyperactivity often worsen during a manic episode, children with comorbid ADHD and BPD also exhibit symptoms of ADHD inter-episodically, when they are euthymic.

In adult patients with BPD, there is a dearth of research on the comorbidity of ADHD, although studies suggest that 21% of adults with BPD report a lifetime history of

childhood traits consistent with ADHD (Winokur et al 1993) and that such a history may be associated with a relatively early age of onset of BPD (Sachs et al 2000). Clearly, more research is needed on the important question of whether ADHD, attention deficit disorder, or symptoms of executive dysfunction are present in adult, euthymic patients with BPD. Such studies would help to clarify whether the high prevalence of ADHD in children with BPD is an age-dependent expression of the illness or reflects a familial subtype of BPD characterized by early onset and comorbidity with ADHD (Faraone et al 1997). In any case, this high prevalence of ADHD may provide important clues regarding both the pathophysiology and genetics of juvenile BPD.

Marked, Frequent State Alterations

Bipolar disorder is distinguished from other psychiatric illnesses by the variety of mood states that patients experience, including mania, depression, euthymia, hypomania, dysthymia, and subsyndromal affective symptoms (Judd et al 2002). Dramatic shifts in mood state are accompanied by equally marked physiologic and cognitive changes, and transitions between states (in particular, the switch into mania) can be abrupt. An important, and unresolved, question is the extent to which such state shifts are endogenous, rather than influenced by environmental factors. Whereas some bipolar patients have regular endogenous cycles, data also indicate that environmental factors can influence the onset of both depressive and manic episodes in adults (Hammen and Gitlin 1997; Johnson et al 2000; Malkoff-Schwartz et al 1998).

Although research has not yet addressed the extent to which environmental emotional stimuli precipitate mood fluctuations in bipolar children, two factors indicate that the question may be particularly important in this population. First, emerging data indicate that pathologic mood states in children and adolescents are generally more closely tied to environmental emotional stimuli than are similar states in adults. Examples of such developmental differences include the greater effects of contagion or media exposure on suicide attempts and completion in adolescents, as well as the stronger relationship between stressful events and major depression in adolescents, relative to adults (Gould et al 1994; Pine et al 2002). It is therefore conceivable that bipolar children are more reactive to such influences than are either bipolar adults or control children, although the question has not yet received systematic attention; if confirmed, this hypothesis may help to explain the relatively rapid cycles seen in bipolar children. Second, as noted above, the clinical presentation of bipolar children is frequently characterized by irritability. Because irritability can be conceptualized as increased reactivity to negative emotional stimuli, this symptom could also result from increased responsiveness to emotional stimuli in bipolar children, as compared with both control children and bipolar adults.

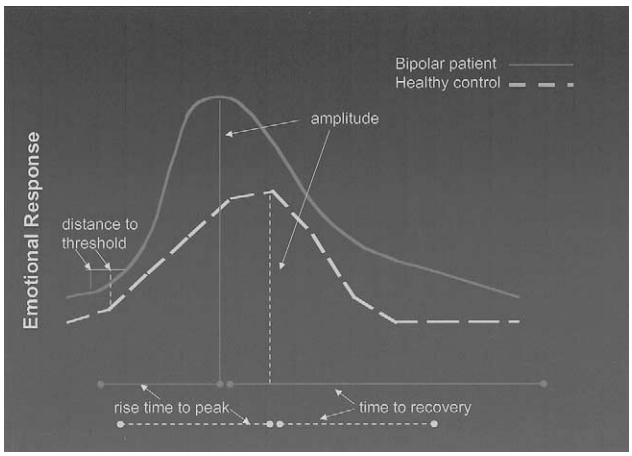

Figure 1. Hypothesized time course of the response to an emotional stimulus in a bipolar patient and a healthy volunteer. The bipolar patient has a higher baseline (therefore creating a lower threshold for response), faster rise time to peak, higher amplitude response, and slower time to recovery. Concept adapted from Davidson 1998.

A useful framework for considering this question has been provided by Davidson (1998), who has suggested that interindividual differences in emotional reactivity can be described in terms of "affective chronometry," a systematic description of the course of an emotional response to an affective stimulus (Figure 1). Individuals differ in the threshold that a discrete stimulus must exceed to evoke a response. A highly reactive child might respond to a minor stimulus (i.e., a negative comment from a playmate) with an instantaneous rageful response, whereas another child might have no response at all. Individuals may also differ in the peak or amplitude of their response, the rise time to that peak, and/or their recovery time (i.e., the time from peak response back to baseline). For example, compared with their more sanguine counterparts, highly reactive individuals might have a rapid rise to a high peak, followed by a relatively slow return to baseline. Indeed, the extent to which a subject's increased reactivity to a stimulus is due to a quick rise to the peak of the emotional response, rather than to a slow return to baseline, is an empirical question. In addition, whereas patients with a number of mood and anxiety disorders may exhibit increased responsiveness to emotional stimuli, the exact nature of their abnormality may differ. For example, patients may differ in the particular type of emotional stimulus that triggers an extreme reaction (threat in an anxious patient, reward in a manic patient) or in the time course of the reaction.

Research on affective chronometry is possible because of the development of standardized stimuli that elicit emotional responses and the identification of physiologic measures that can index those responses. In addition to positive reinforcement (reward) or punishment paradigms like those described above, standardized emotional stimuli include pictures designed to elicit emotional responses and startle stimuli (which are both arousing and aversive) (Lang et al 1998). In response to such stimuli, valence is assessed by recording heart rate and corrugator and zygomatic electromyography, whereas arousal is assessed by measures of skin conductance and cortical event-related potentials (Lang et al 1998). Researchers have developed standardized emotional stimuli for use in infants and young children (e.g., Balaban 1995), although considerably less work has been done with older children, adolescents, and children with psychiatric illness (exceptions include Grillon et al 1997; McManis et al 2001; Ornitz et al 1999). Paradigms that track physiologically the entire time course of an emotional response might be particularly informative and help to distinguish a propensity toward extreme responses to stimuli from a failure of regulatory mechanisms. We are currently employing one such paradigm in bipolar children and control subjects (Skolnick and Davidson 2002).

The observation that children with BPD are particularly responsive to emotional stimuli would necessarily lead to the more challenging question of how such deficits might develop. As noted above, the development of emotion regulation in children has been the subject of considerable research. One such line of research that is particularly relevant to early onset BPD concerns interactions between the development of attentional and emotion regulation mechanisms. Mischel and colleagues have suggested that, in children, the ability to deploy attention strategically (which typically increases throughout childhood and adolescence) is associated with the ability to delay gratification and to tolerate frustration (Mischel et al 1989; Sethi et al 2000). For example, if children can focus their attention away from a reward, they are able to wait longer for the reward (Mischel et al 1989). Similarly, in a series of studies, Posner, Rothbart, and colleagues have demonstrated that children's ability to attend was inversely related to their level of negative affect (Harmon et al 1997; Posner and Rothbart 1998).

Studies linking the development of attention regulation to that of emotion regulation are germane to pediatric BPD because of the observed high comorbidity between ADHD and early-onset BPD and because of attentional difficulties that have been documented in adult patients with BPD. In children at risk for BPD, symptoms of ADHD are often the first signs of psychopathology (Chang et al 2000; DelBello and Geller 2001). It is interesting to speculate that these children's genetic vulnerability to mood lability may be manifest first by attentional deficits that (along with other deficits) prevent the development of effective mood regulation mechanisms.

In adult bipolar patients, studies using the continuous performance test to study attention regulation have found performance deficits in patients who are currently manic (Clark et al 2001; Fleck et al 2001; Liu et al 2002; Sax et al 1995, 1998, 1999) and, in some studies, in euthymic bipolar patients (Clark et al 2001; Liu et al 2002; Wilder-Willis et al 2001; negative studies are Sax et al 1998; Swann et al 2001). In mania, few studies have attempted to directly link deficits in attention regulation, as measured on neuropsychological tests, to clinical measures of attention dysregulation. In ADHD, on the other hand, recent efforts following such a strategy have yielded interesting data. That is, whereas initial studies found only moderate associations between the diagnosis of ADHD and measures of abnormal attention derived from tasks such as the continuous performance test (Barkley et al 1992; Grodzinsky and Barkley 1999), recent studies employing more comprehensive cognitive assessments of attention have demonstrated associations between specific symptom patterns and specific attention dysfunction (Solanto et al 2001; Sonuga-Barke 2002). Importantly, these studies suggest that some subgroups of children with ADHD may exhibit specific cognitive deficits in tasks that directly manipulate aspects of reward, rather than on tasks that manipulate aspects of inhibitory demands. Studies of pediatric BPD might follow these efforts, focusing specifically on both reward-related and attention- or inhibition-related processes. For example, future studies might quantify the precise nature of attentional deficits in clinical terms, measuring the extent to which these deficits occur across times, across contexts, or in response to emotionally evocative stimuli or differing reward contingencies. These measures might then be linked to behavioral measures of attention collected in the laboratory under similar conditions. In other words, one manifestation of bipolar children's increased responsiveness to emotional stimuli could consist of increased attentional dysfunction in the presence of emotional cues. Moreover, such alterations in responsiveness could vary as a function of stimulus properties, including valence and level of arousal. Such associations between specific clinical symptoms and specific neuropsychological deficits, once identified, would have implications for subtyping presentations of mania and suggesting targets for therapeutic intervention. In addition, well-targeted functional magnetic resonance imaging (fMRI) studies might identify the neural circuitry mediating such associations.

The Extreme Positive-Valence State

Because of the difficulties involved in performing physiologic studies on highly active patients, the manic state has received relatively little research attention beyond clinical description; however, researchers have recently begun to explore manic patients' response to rewarding stimuli, both because of the theoretical importance of such stimuli in the generation of positive valence emotion and because several manic symptoms may be related to a deficit in processes engaged by the presentation of reward. For example, pleasure-seeking and increased goal-directed activity might both reflect a failure of manic patients to experience goal attainment as sufficiently rewarding. Alternatively, elation could represent an exaggerated response to a rewarding stimulus. To differentiate these opposing hypotheses, researchers must carefully characterize the way in which manic patients' responses to positive emotional stimuli differ from those of control subjects. The development of laboratory paradigms that can generate quantifiable behavioral indices of such differences is a necessary prerequisite to functional imaging studies designed to elucidate the neural mechanisms underlying them.

Researchers have therefore begun to characterize systematically manic patients' response to positive emotional stimuli. Studies using a set-shifting task with affective cues (Murphy et al 1999) and an emotion recognition task (Lembke and Ketter 2002) have demonstrated such quantifiable differences manifest as a bias toward positive-valence stimuli in manic patients. With regard to behavior on tasks in which subjects attempt to earn reward, one study was unable to demonstrate patient–control subject performance differences (Clark et al 2001); however, another study using a decision-making task found that manic patients made more risky decisions (i.e., chose the less likely option) more often than did depressed patients or control subjects (Murphy et al 2001).

Research on the manic state should also be informed by data regarding the physiology of positive affective states in psychiatrically healthy individuals. Investigators have examined inter-individual physiologic differences between healthy subjects who display consistent positive valence affect at baseline, compared with those whose "affective style" is more negatively valenced (Davidson and Irwin 1999). One such body of research was motivated by early imaging studies indicating that patients with left-sided cortical lesions tend to exhibit depressive syndromes, whereas those with right-sided or midline lesions are more likely to exhibit disinhibited or even manic behavior (Morris et al 1996; Starkstein and Robinson 1997). Based on these observations and relevant animal studies, researchers hypothesized that right anterior prefrontal areas may be particularly involved in the mediation of avoidance behaviors and negative affect, whereas left anterior prefrontal areas might play a parallel role with regard to approach behaviors and positive affect (Davidson and Irwin 1999). Consistent with this hypothesis, studies of frontal electroencephalogram (EEG) activity in infants and young children demonstrated that increased right prefrontal activation was associated with a more marked response to maternal separation in 10-month-olds and with social withdrawal in 4-year-olds (Davidson and Fox 1989; Fox et al 1995). Moreover, several studies find an absolute decrease in left frontal activity among infants of mothers with major depression (Dawson et al 1992, 1997; Jones et al 1997). Subsequent studies in adults suggested that EEG prefrontal asymmetry may be a trait marker that is relatively stable (Sutton and Davidson 1997) and predicts response to emotional stimuli independent of current mood state. Specifically, adults with left-sided asymmetry tend to have more positive emotional responses to standardized stimuli than do those with right-sided asymmetry (Tomarken et al 1990; Wheeler et al 1993). In addition, longitudinal studies of depressed children followed into adulthood find abnormal frontal asymmetry in formerly depressed subjects, particularly if they also exhibit current depression (Miller et al 2002). This study also found particularly high levels of asymmetry in subjects exhibiting a bipolar course. However, two studies in adolescents failed to find such associations with frontal regions, though findings in posterior regions were similar to those among adults (i.e., posterior symmetry favoring the left hemisphere) (Graae et al 1996; Kentgen et al 2000). This provides evidence suggesting that the relationship between frontal asymmetry and depression changes during development.

Because adolescence is a time when the risk for major affective syndromes (including BPD) increases markedly, these negative data regarding frontal asymmetry in adolescents may raise essential questions regarding the development of mood regulation, and the relationship of changes in asymmetry to the risk for such syndromes across development. That is, associations between approach or withdrawal tendencies and frontal asymmetry patterns consistently emerge in studies of both young children and adults, yet not in adolescents. If, indeed, the physiology of emotion regulation is similar in children and adults, but differs in adolescents, this may suggest that adolescence is characterized by a reorganization of frontally based neural systems involved in affective processes (see below). We are currently pursuing this line of research, both by examining developmental changes in frontal systems during adolescence and by testing the hypothesis that, given their marked mood lability, anterior cortical asymmetry will be less stable in adolescents with BPD than in control subjects.

In addition to comparing subjects who differ in their baseline level of positive affect, investigators have also examined the cognitive impact of positive emotion experimentally induced in the laboratory. These studies indicate that individuals in positive moods appear to rely on heuristics and general rules to make decisions, whereas those in negative moods use a more systematic approach to problems, focusing more attention on detail (Bodenhausen et al 1994; Park and Banaji 2000). Thus, congruent with the suggestion that BPD is particularly prevalent among highly creative people (Jamison 1995), positive mood appears to increase creativity, whereas negative mood may increase precision (Isen et al 1987). Similarly, in a finding that may relate to the distractibility seen in (hypo)mania, individuals in negative moods tend to assess critically the merits of persuasive arguments, whereas those in positive moods are more likely to be influenced by irrelevant peripheral cues (Schwarz et al 1991). Finally, individuals in positive moods are more likely to see outcomes as dependent on internal rather than external factors (Forgas, 1998); these data may be relevant to the grandiosity seen in mania. The possible adaptive value of these relationships between mood and cognition may be intuitively obvious, in that the decision-making style associated with a positive mood would foster risk-taking, exploration, and individual initiative, whereas that associated with a negative mood would foster conservative, focused problem solving. A testable hypothesis (similar to one that has been confirmed in depression) is that (hypo) manic patients (or perhaps even those at risk for BPD) are particularly susceptible to such influences of emotional state on cognition.

To understand the pathophysiology of pediatric mania, it will be important to consider the developmental trajectory of processes mediating positive affect states and the response to rewarding stimuli. Consistent with the observation that first episodes of mania frequently occur at adolescence, research in community-based samples of children, adolescents, and adults indicates an increase in the propensity to experience high arousal positive states at this time (Csikszentmihaly and Larson 1984). Studies using event-sampling methods note that, compared with children or adults, adolescents experience more markedly positive mood following naturally occurring rewards, as well as greater fluctuations in mood states throughout a typical week (Larson et al 2002). These developmental changes might reflect changes in reward processes or in cognitive processes that impact on them; indeed, evidence exists to support both of these possibilities. With respect to primary changes in reward processes, adolescents, but not children, show mood elevation in response to psychostimulant medications (Rapoport et al 1980). With regard to relevant cognitive processes, adolescents are better able than children to delay gratification or to invoke other cognitive processes that eventually lead to larger reward deliveries (Mischel et al 1989).

Studies in rodents and nonhuman primates document interesting parallels with these human developmental changes. Across a range of mammalian species, adolescence is associated with an increase in efforts to procure naturally occurring rewards, as well as robust changes in sensitivity to drugs of abuse (Spear 2000). Hence, adolescence, which in humans represents a developmental period during which there is an increase in the risk for mania, also represents a time when reward-related processes change rapidly in both humans and animals.

Functional Neuroimaging Data

For the reasons noted above, functional neuroimaging studies of particular relevance to the study of BPD would include studies of subjects experiencing high-arousal, positive valence emotions, or performing tasks with the potential for reward. Appropriate subjects for these studies would include patients with the illness, their relatives, and children at high risk, as well as control subjects. With regard to reward-related tasks, experiments using pharmacologic self-stimulation or feeding paradigms in animals have identified a neural system engaged by reward-related processes, and positron emission tomography (PET) and fMRI studies in control subjects performing relevant tasks have confirmed the existence of a similar circuit in humans. This “reward circuit” includes dopamine-containing neurons in the ventral tegmental area (VTA), prefrontal cortical areas (PFC) (particularly ventral and medial PFC, including prominent connections between the VTA and anterior cingulate [AC]), portions of the basal ganglia (particularly nucleus accumbens and ventral striatum), and medial temporal areas, including the amygdala and the hippocampus (Figure 2) (Breiter and Rosen 1999; Rolls 2000). In general, ascending dopamine neurons are hypothesized to signal changes in reward delivery, relative to expectancy, whereas the PFC is hypothesized to represent the nature of expected reward (Rolls 2000). In addition to the medial and ventral PFC, basal ganglia structures are activated by the expectation and detection of reward in both animals and humans (Pagnoni et al 2002; Schulze et al 2000). Animal studies also indicate that the striatum is involved in the preparation and execution of motor responses to rewarding stimuli (Schultze et al 2000) and that distinct amygdalar nuclei participate in various aspects of reward-related processes, including weighing the salience of rewarding stimuli and orienting attention toward such stimuli (Parkinson et al 2000).

In both nonhuman primates and humans, there is evidence that mature prefrontal function does not emerge

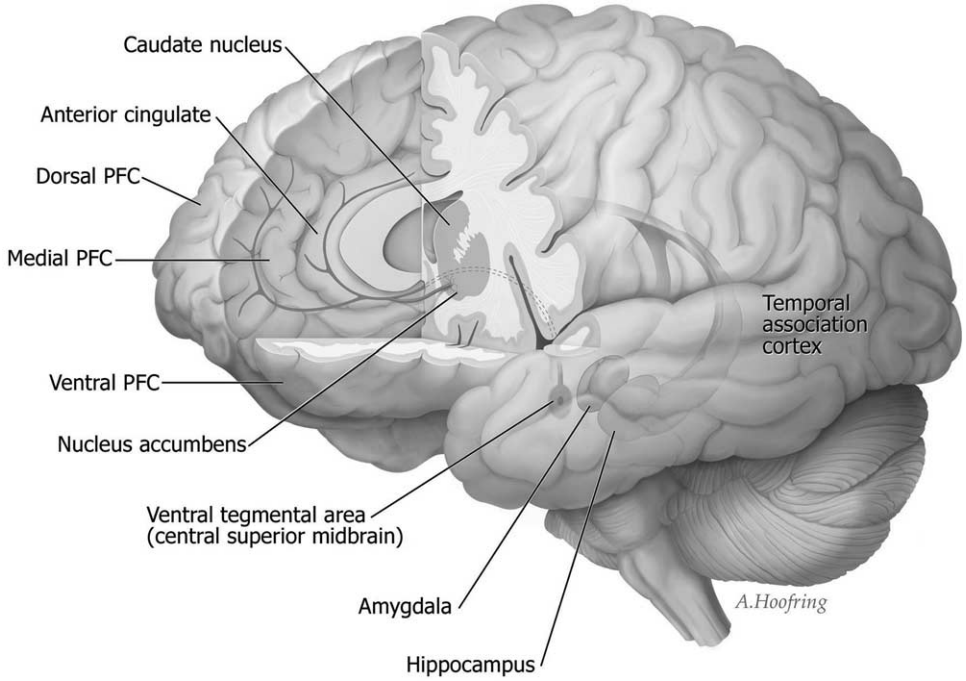

Figure 2. Neural circuit hypothesized to mediate responses to rewarding stimuli, including relevant brain structures and dopaminergic innervation. See text for references. PFC, prefrontal cortex.

before late adolescence or early adulthood, and that ventral aspects of the PFC may mature before dorsal regions (Alexander 1982; Thompson et al 2000). Given the role that the ventral PFC may play in assessing or coding the reward value of stimuli (Rolls 2000) and the putative role of the dorsal PFC in mediating executive functions that can modulate reward-related behavior, further study should focus on the interactions between dorsal PFC, ventral PFC, and other components of the reward circuit over development. In nonhuman primates, there is evidence that, in addition to the remodeling of prefrontal circuits mediating reward behavior, there is also considerable development in dopaminergic function during adolescence. Specifically, data indicate that dopamine turnover and synthesis in the PFC increases at that time, and that there is a shift in activity from mesolimbic to mesocortical dopaminergic systems (Spear 2000). Such changes in dopamine systems may in turn relate to the developmental changes in dorsal, medial, and ventral frontal regions, each of which receive considerable dopaminergic input from the VTA (Figure 2). The possible relevance of these processes to the increased risk for mood disorders, including BPD, at adolescence bears further study.

Not surprisingly, studies involving the induction of positive valence emotion in control subjects demonstrate the involvement of a similar circuit. Emotion induction in these studies has been accomplished by film clips (sometimes erotic), words with emotional salience, music, happy faces, recall of pleasant experiences, or other pleasant stimuli (e.g., Blood and Zatorre 2001; Karama et al 2002; Lane et al 1997). Again, ventral and medial PFC, amygdala, and the ventral striatum have been identified as key components in the circuit activated by pleasant stimuli (Aalto et al 2002; Aharon et al 2001; Bartels and Zeki 2000; Blood and Zatorre 2001; Canli et al 2002; Hamann and Mao 2002; Karama et al 2002; Lane et al 1997). The AC has also been implicated in many of these studies, perhaps particularly in those in which the emotion induction task has a significant cognitive component (Phan et al 2002; Bush et al 2000). Comparisons both between and within studies have allowed investigators to ask whether particular brain regions appear to be uniquely activated by positive stimuli. Although there are more similarities than differences in the structures activated by positive versus negative emotional stimuli, the literature does indicate that striatal structures may be particularly involved in mediating response to positive valence stimuli (Phan et al 2002). It is also important to note that, although early imaging studies seemed to indicate that the amygdala was most likely to be activated by negatively valenced emotional stimuli, more recent data indicate that the amygdala may instead be involved in processing any salient emotional stimuli, including stimulus–reward associations (Baxter and Murray 2002).

Compared with this body of literature, there are relatively few functional neuroimaging studies in manic patients. Similar to findings in depressed patients, ventral and medial PFC activation may differ in manic patients versus control subjects. (Indeed, given the fact, noted

above, that positive and negative emotions are largely mediated by the same brain regions, it would not be surprising if patient–control subject differences that are found in mania resemble to some degree those found in depression.) Compared with control subjects, one study found decreased orbitofrontal activity in manic patients (on the right side during a word generation task, and bilaterally at rest) (Blumberg et al 1999), whereas another (Curtis et al 2001) found increased medial and left inferior frontal activation in bipolar patients performing a verbal fluency task.

Considerably more research is needed to understand how temporal and striatal function may differ between manic patients and control subjects. Temporal areas have been of interest in mania because of pathophysiologic and therapeutic correspondences between BPD and temporal lobe epilepsy (Flor-Henry 1969), structural imaging studies and theoretical considerations implicating the amygdala in the illness (Altshuler et al 2000; Strakowski et al 1999), and the verbal learning deficits that have been reported in patients with the illness (Clark et al 2001; van Gorp et al 1999). However, the literature is limited and mixed, in that functional imaging studies have reported both decreased (Migliorelli et al 1993) and increased (al-Mousawi et al 1996; Gyulai et al 1997; O'Connell et al 1995) right temporal activity in patients with BPD. One study found evidence of increased amygdala activity in subjects with bipolar or unipolar depression (Drevets et al 2002). Given the possible role of the striatum in mediating reward responses and positive emotion, it is interesting that several studies have found increased basal ganglia activity in manic patients (Blumberg et al 2000; O'Connell et al 1995). For example, in a PET study of manic patients at rest, Blumberg et al (2000) found increased activity in the left head of the caudate, ipsilateral to changes in the dorsal AC.

Finally, a number of studies have found an association between increased AC activity and mania (Blumberg et al 2000; Drevets et al 1997; Goodwin et al 1997; Rubinsztein et al 2001). These findings were obtained at rest (Blumberg et al 2000; Drevets et al 1997), after lithium withdrawal (Goodwin et al 1997), and when subjects were performing a decision-making task on which behavioral abnormalities had previously been demonstrated (Rubinsztein et al 2001). In the latter study, the degree of task-related activation in the AC correlated with the Young Mania Rating Scale score (Rubinsztein et al 2001). Although the precise location of AC activation varies between studies, both the dorsal AC, thought to mediate processes related to attention allocation and response selection, and more ventral areas, thought to mediate processes related to vegetative emotional responses (Bush et al 2000), have been implicated.

Because neuroimaging studies in control subjects indicate that the AC may be involved in stimulus and/or response selection (Miller and Cohen 2001), the possibility that attentional deficits in bipolar patients are related functionally to differences in AC activation between patients and control subjects bears further study. As noted above, such studies may be particularly important in bipolar children, given the marked attentional deficits in this population and the role that the development of attention regulation may play in the concurrent development of emotion regulation. In addition, because of the reciprocal connections between the ventral AC and the hypothalamus, periaqueductal gray, and brainstem nuclei mediating arousal, Drevets (2001) has suggested that the ventral AC and adjacent medial frontal areas may be of particular importance in mediating the switches, often abrupt, into the extreme state of hyperarousal that characterizes mania. If this suggestion is correct, then AC function would be particularly important to study developmentally, given the increased switch rate in early- compared with later-onset BPD. Developmental changes in the AC have received relatively little attention, although one study showed a significant correlation between children's performance on measures of attention and volume of the right AC (Casey et al 1997), whereas another found that gray matter loss (i.e., maturation) in the AC lagged behind even the relatively late-maturing frontal or temporal lobes (Sowell et al 2002).

Conclusion

In conclusion, we suggest that, in bipolar children as in bipolar adults, the neural mechanisms mediating extreme fluctuations in behavioral state, as well as the physiology of extreme positive valence states, are particularly important targets for research. Longitudinal studies tracking the course of impulsivity and inattentiveness in children with BPD and comparing these clinical features with the symptoms of adults with BPD would yield important data. It will be important to study children with BPD both while ill and while euthymic (to differentiate state from trait effects); to study children at high risk for BPD as well as the family members of children with BPD; and to study the effects of medications (such as lithium) that are effective in the illness (Manji and Zarate 2002). In addition, the impact of severe affective symptoms on neurodevelopment in bipolar children bears further study. It is clear that marked brain plasticity exists throughout childhood, adolescence, and early adulthood; if neurons that "fire together wire together" (Casey et al 2000), how does the experience of a manic episode affect the developing neural circuitry of a child? Clearly, such research, although essential, will be challenging, because it will be

difficult to disentangle the effects of extended medication treatment from the neurodevelopmental effects of the illness itself.

As noted above, bipolarity in children is characterized by relatively rapid mood cycles, high comorbidity with ADHD, and significant irritability. Both rapid mood cycles and irritability may result from markedly increased reactivity to both positive and negative emotional stimuli. This hypothesis is amenable to testing in both laboratory and naturalistic settings. In addition, the interaction between emotion and cognition (particularly attentional processes) is a most important target for research in pediatric bipolar disorder. In this regard, both longitudinal questions (the impact of attentional dysfunction of the development of emotion regulation) and cross-sectional questions (the increase in attentional dysfunction and impulsivity in the presence of emotional stimuli) bear further study in children with BPD.

Finally, it is clear that progress in understanding the pathophysiology of pediatric BPD will rely in part on increased knowledge regarding the neural processes mediating emotional development and mood regulation in healthy children. As noted above, research should focus on the developmental trajectory of reward-related processes and on the cortico–limbic–striatal circuits that appear to mediate mood in both depressed and healthy adults. In addition, recent work by Cohen and colleagues, Cameron and colleagues, and others has begun to describe neural mechanisms that involve the AC and prefrontal cortex and mediate "cognitive control" (i.e., the ability to direct the allocation of attention to stimuli as well as the choice of behavioral responses to those stimuli) (Carter et al 1999; Miller and Cohen 2001). Given both the impulsivity and inattentiveness of bipolar children, further work on the development of such mechanisms in both healthy and bipolar children may be informative.

Research on BPD presents many challenges, particularly in the case of patients who experience an early onset of the illness. Children with BPD tend to experience severe symptoms and only a modest response to treatment. The pathophysiology of their illness deserves systematic study, to facilitate the development of novel, and hopefully more effective, treatments.

This paper contains the private views of the authors and should not be construed as official or as reflecting the views of the Federal Government or the Department of Health and Human Services.

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References

Aalto S, Naatanen P, Wallius E, Metsahonkala L, Stenman H, Niem PM, Karlsson H (2002): Neuroanatomical substrata of amusement and sadness: A PET activation study using film stimuli. *Neuroreport* 13:67–73.

Aharon I, Etcoff N, Ariely D, Chabris CF, O'Connor E, Breiter HC (2001): Beautiful faces have variable reward value: fMRI and behavioral evidence. *Neuron* 32:537–551.

Alexander GE (1982): Functional development of frontal association cortex in monkeys: Behavioral and electrophysiological studies. *Neurosci Res Prog Bull* 20:471–479.

al-Mousawi AH, Evans N, Ebmeier KP, Roeda D, Chaloner F, Ashcroft GW (1996): Limbic dysfunction in schizophrenia and mania. A study using 18F-labelled fluorodeoxyglucose and positron emission tomography. *Br J Psychiatry* 169:509–516.

Altshuler LL, Bartzokis G, Grieder T, Curran J, Jimenez T, Leight K, et al (2000): An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. *Biol Psychiatry* 48:147–162.

Balaban MT (1995): Affective influences on startle in five-month-old infants: Reactions to facial expressions of emotion. *Child Dev* 66:28–36.

Barkley RA, Grodzinsky G, DuPaul GJ (1992): Frontal lobe functions in attention deficit disorder with and without hyperactivity: A review and research report. *J Abnorm Child Psychol* 20:163–188.

Bartels A, Zeki S (2000): The neural basis of romantic love. *Neuroreport* 11:3829–3834.

Baxter MG, Murray EA (2002): The amygdala and reward. *Nat Rev Neurosci* 3:563–573.

Blood AJ, Zatorre RJ (2001): Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc Natl Acad Sci U S A* 98:11818–11823.

Blumberg HP, Stern E, Martinez D, Ricketts S, de Asis J, White T, et al (2000): Increased anterior cingulate and caudate activity in bipolar mania. *Biol Psychiatry* 48:1045–1052.

Blumberg HP, Stern E, Ricketts S, Martinez D, de Asis J, White T, et al (1999): Rostral and orbital prefrontal cortex dysfunction in the manic state of bipolar disorder. *Am J Psychiatry* 156:1986–1988.

Bodenhausen GV, Kramer GP, Susser K (1994): Happiness and sterotypic thinking in social judgment. *J Pers Soc Psychol* 66:621–632.

Breiter HC, Rosen BR (1999): Functional magnetic resonance imaging of brain reward circuitry in the human. *Ann N Y Acad Sci* 877:523–547.

Bush G, Luu P, Posner MI (2000): Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 4:215–222.

Canli T, Sivers H, Whitfield SL, Gotlib IH, Gabrieli JD (2002): Amygdala response to happy faces as a function of extraversion. *Science* 296:2191.

Carter CS, Botvinick MM, Cohen JD (1999): The contribution of the anterior cingulate cortex to executive processes in cognition. *Rev Neurosci* 10:49–57.

Casey BJ, Giedd JN, Thomas KM (2000): Structural and functional brain development and its relation to cognitive development. *Biol Psychol* 54:241–257.

Casey BJ, Trainor R, Giedd J, Vauss Y, Vaituzis CK, Hamburger S, et al (1997): The role of the anterior cingulate in automatic and controlled processes: A developmental neuroanatomical study. *Dev Psychobiol* 30:61–69.

Cassidy F, Carroll BJ (2001): Frequencies of signs and symptoms in mixed and pure episodes of mania: Implications for the study of manic episodes. *Prog Neuropsychopharmacol Biol Psychiatry* 25:659–665.

Cassidy F, Pieper C, Carroll BJ (2001): Subtypes of mania determined by grade of membership analysis. *Neuropsychopharmacology* 25:373–383.

Chang KD, Steiner H, Ketter TA (2000): Psychiatric phenomenology of child and adolescent bipolar offspring. *J Am Acad Child Adolesc Psychiatry* 39:453–460.

Clark L, Iversen SD, Goodwin GM (2001): A neuropsychological investigation of prefrontal cortex involvement in acute mania. *Am J Psychiatry* 158:1605–1611.

Csikszentmihalyi M, Larson R (1984): *Being Adolescent: Conflict and Growth in the Teenage Years.* New York: Basic Books.

Curtis VA, Dixon TA, Morris RG, Bullmore ET, Brammer MJ, Williams SC, et al (2001): Differential frontal activation in schizophrenia and bipolar illness during verbal fluency. *J Affect Disord* 66:111–121.

Davidson RJ (1998): Affective style and affective disorders: Perspectives from affective neuroscience. *Cogn Emotion* 12:307–330.

Davidson RJ, Fox NA (1989): Frontal brain asymmetry predicts infants' response to maternal separation. *J Abnorm Psychol* 98:127–131.

Davidson RJ, Irwin W (1999): The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci* 3:11–21.

Dawson G, Frey K, Panagiotides H, Osterling J, Hessl D (1997): Infants of depressed mothers exhibit atypical frontal brain activity: A replication and extension of previous findings. *J Child Psychol Psychiatry* 38:179–186.

Dawson G, Klinger LG, Panagiotides H, Hill D, Spieker S (1992): Frontal lobe activity and affective behavior of infants of mothers with depressive symptoms. *Child Dev* 63:725–737.

DelBello MP, Geller B (2001): Review of studies of child and adolescent offspring of bipolar parents. *Bipolar Disord* 3:325–334.

Drevets WC (2001): Neuroimaging and neuropathological studies of depression: Implications for the cognitive-emotional features of mood disorders. *Curr Opin Neurobiol* 11:240–249.

Drevets WC, Price JL, Bardgett ME, Reich T, Todd RD, Raichle ME (2002): Glucose metabolism in the amygdala in depression: Relationship to diagnostic subtype and plasma cortisol levels. *Pharmacol Biochem Behav* 71:431–447.

Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, et al (1997): Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386:824–827.

Faraone SV, Biederman J, Wozniak J, Mundy E, Mennin D, O'Donnell D (1997): Is comorbidity with ADHD a marker for juvenile-onset mania? *J Am Acad Child Adolesc Psychiatry* 36:1046–1055.

Fleck DE, Sax KW, Strakowski SM (2001): Reaction time measures of sustained attention differentiate bipolar disorder from schizophrenia. *Schizophr Res* 52:251–259.

Flor-Henry P (1969): Schizophrenic-like reactions and affective psychoses associated with temporal lobe epilepsy: Etiological factors. *Am J Psychiatry* 126:400–404.

Forgas JP (1998): On being happy and mistaken: Mood effects on the fundamental attribution error. *J Pers Soc Psychol* 75:318–331.

Fox NA, Rubin KH, Calkins SD, Marshall TR, Coplan RJ, Porges SW, Long JM, Stewart S (1995): Frontal activation asymmetry and social competence at four years of age. *Child Dev* 66:1770–1784.

Geller B, Craney J, Bolhofner K, DelBello M, Williams M, Zimmerman B (2001a): One-year recovery and relapse rates of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry* 158:303–305.

Geller B, Craney JL, Bolhofner K, Nickelsburg MJ, Williams M, Zimerman B (2002a): Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry* 159:927–933.

Geller B, Williams M, Zimerman B, Frazier J, Beringer L, Warner KL (1998): Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. *J Affect Disord* 51:81–91.

Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, DelBello MP, et al (2001b): Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. *J Am Acad Child Adolesc Psychiatry* 40:450–455.

Geller B, Zimerman B, Williams M, DelBello MP, Bolhofner K, Craney JL, et al (2002b): DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. *J Child Adolesc Psychopharmacol* 12:11–25.

Goodwin GM, Cavanagh JT, Glabus MF, Kehoe RF, O'Carroll RE, Ebmeier KP (1997): Uptake of 99 mTc-exametazime shown by single photon emission computed tomography before and after lithium withdrawal in bipolar patients: Associations with mania. *Br J Psychiatry* 170:426–430.

Gould MS, Petrie K, Kleinman MH, Wallenstein S (1994): Clustering of attempted suicide: New Zealand national data. *Int J Epidemiol* 23:1185–1189.

Graae F, Tenke C, Bruder G, Rotheram MJ, Piacentini J, Castro-Blanco D, et al (1996): Abnormality of EEG alpha asymmetry in female adolescent suicide attempters. *Biol Psychiatry* 40:706–713.

Grillon C, Dierker L, Merikangas KR (1997): Startle modulation in children at risk for anxiety disorders and/or alcoholism. *J Am Acad Child Adolesc Psychiatry* 36:925–932.

Grodzinsky GM, Barkley RA (1999): Predictive power of frontal lobe tests in the diagnosis of attention deficit hyperactivity disorder. *Clin Neuropsychol* 13:12–21.

Gyulai L, Alavi A, Broich K, Reilley J, Ball WB, Whybrow PC (1997): I-123 iofetamine single-photon computed emission tomography in rapid cycling bipolar disorder: A clinical study. *Biol Psychiatry* 41:152–161.

Hamann S, Mao H (2002): Positive and negative emotional verbal stimuli elicit activity in the left amygdala. *Neuroreport* 13:15–19.

Hammen C, Gitlin M (1997): Stress reactivity in bipolar patients and its relation to prior history of disorder. *Am J Psychiatry* 154:856–857.

Harman C, Rothbart MK, Posner MI (1997): Distress and attention interactions in early infancy. *Motivation Emotion* 21:27–43.

Isen AM, Daubman KA, Nowicki GP (1987): Positive affect facilitates creative problem solving. *J Pers Soc Psychol* 52:1122–1131.

Jamison KR (1995): Manic-depressive illness and creativity. *Sci Am* 272:62–67.

Johnson SL, Sandrow D, Meyer B, Winters R, Miller I, Solomon D, Keitner G (2000): Increases in manic symptoms after life events involving goal attainment. *J Abnorm Psychol* 109:721–727.

Jones NA, Field T, Fox NA, Lundy B, Davalos M (1997): EEG activation in 1-month-old infants of depressed mothers. *Dev Psychopathol* 9:491–505.

Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al (2002): The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59:530–537.

Karama S, Lecours AR, Leroux JM, Bourgouin P, Beaudoin G, Joubert S, Beauregard M (2002): Areas of brain activation in males and females during viewing of erotic film excerpts. *Hum Brain Mapp* 16:1–13.

Kentgen LM, Tenke CE, Pine DS, Fong R, Klein RG, Bruder GE (2000): Electroencephalographic asymmetries in adolescents with major depression: Influence of comorbidity with anxiety disorders. *J Abnorm Psychol* 109:797–802.

Lane RD, Reiman EM, Ahern GL, Schwartz GE, Davidson RJ (1997): Neuroanatomical correlates of happiness, sadness, and disgust. *Am J Psychiatry* 154:926–933.

Lang PJ, Bradley MM, Cuthbert BN (1998): Emotion, motivation, and anxiety: Brain mechanisms and psychophysiology. *Biol Psychiatry* 44:248–263.

Larson RW, Moneta G, Richards MH, Wilson S (2002): Continuity, stability, and change in daily emotional experience across adolescence. *Child Dev* 73:1151–1165.

Leibenluft E, Charney DS, Towbin K, Bhangoo R, Pine DS (in press): Defining clinical phenotypes of juvenile mania. *Am J Psychiatry*.

Lembke A, Ketter TA (2002): Impaired recognition of facial emotion in mania. *Am J Psychiatry* 159:302–304.

Liu SK, Chiu CH, Chang CJ, Hwang TJ, Hwu HG, Chen WJ (2002): Deficits in sustained attention in schizophrenia and affective disorders: Stable versus state-dependent markers. *Am J Psychiatry* 159:975–982.

Malkoff-Schwartz S, Frank E, Anderson B, Sherrill JT, Siegel L, Patterson D, Kupfer DJ (1998): Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes: A preliminary investigation. *Arch Gen Psychiatry* 55:702–707.

Manji HK, Zarate CA (2002): Molecular and cellular mechanisms underlying mood stabilization in bipolar disorder: Implications for the development of improved therapeutics. *Mol Psychiatry* 7(suppl 1):S1–S7.

McManis MH, Bradley MM, Berg WK, Cuthbert BN, Lang PJ (2001): Emotional reactions in children: Verbal, physiological, and behavioral responses to affective pictures. *Psychophysiology* 38:222–231.

Migliorelli R, Starkstein SE, Teson A, de Quiros G, Vazquez S, Leiguarda R, et al (1993): SPECT findings in patients with primary mania. *J Neuropsychiatry Clin Neurosci* 5:379–383.

Milberger S, Biederman J, Faraone SV, Murphy J, Tsuang MT (1995): Attention deficit hyperactivity disorder and comorbid disorders: Issues of overlapping symptoms. *Am J Psychiatry* 152:1793–1799.

Miller A, Fox NA, Cohn JF, Forbes EE, Sherrill JT, Kovacs M (2002): Regional patterns of brain activity in adults with a history of childhood-onset depression: Gender differences and clinical variability. *Am J Psychiatry* 159:934–940.

Miller EK, Cohen JD (2001): An integrative theory of prefrontal cortex function. *Annu Rev Neurosci* 24:167–202.

Mischel W, Shoda Y, Rodriguez MI (1989): Delay of gratification in children. *Science* 244:933–938.

Morris PL, Robinson RG, Raphael B, Hopwood MJ (1996): Lesion location and poststroke depression. *J Neuropsychiatry Clin Neurosci* 8:399–403.

Murphy FC, Rubinsztein JS, Michael A, Rogers RD, Robbins TW, Paykel ES, et al (2001): Decision-making cognition in mania and depression. *Psychol Med* 31:679–693.

Murphy FC, Sahakian BJ (2001): Neuropsychology of bipolar disorder. *Br J Psychiatry* 178:S120–S127.

Murphy FC, Sahakian BJ, Rubinsztein JS, Michael A, Rogers RD, Robbins TW, et al (1999): Emotional bias and inhibitory control processes in mania and depression. *Psychol Med* 29:1307–1321.

National Institute of Mental Health (2001): National Institute of Mental Health Research Roundtable on Prepubertal Bipolar Disorder. *J Am Acad Child Adolesc Psychiatry* 40:871–878.

O'Connell RA, Van Heertum RL, Luck D, Yudd AP, Cueva JE, Billick SB, et al (1995): Single-photon emission computed tomography of the brain in acute mania and schizophrenia. *J Neuroimaging* 5:101–104.

Ornitz EM, Russell AT, Hanna GL, Gabikian P, Gehricke JG, Song D, Guthrie D (1999): Prepulse inhibition of startle and the neurobiology of primary nocturnal enuresis. *Biol Psychiatry* 45:1455–1466.

Pagnoni G, Zink CF, Montague PR, Berns GS (2002): Activity in human ventral striatum locked to errors of reward prediction. *Nat Neurosci* 5:97–98.

Park J, Banaji MR (2000): Mood and heuristics: The influence of happy and sad states on sensitivity and bias in stereotyping. *J Pers Soc Psychol* 78:1005–1023.

Parkinson JA, Robbins TW, Everitt BJ (2000): Dissociable roles of the central and basolateral amygdala in appetitive emotional learning. *Eur J Neurosci* 12:405–413.

Phan KL, Wager T, Taylor SF, Liberzon I (2002): Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 16:331–348.

Pine DS, Cohen P, Johnson JG, Brook JS (2002): Adolescent life events as predictors of adult depression. *J Affect Disord* 68:49–57.

Posner MI, Rothbart MK (1998): Attention, self-regulation and consciousness. *Philos Trans R Soc Lond B Biol Sci* 353:1915–1927.

Rapoport JL, Buchsbaum MS, Weingartner H, Zahn TP, Ludlow C, Mikkelsen EJ (1980): Dextroamphetamine. Its cognitive and behavioral effects in normal and hyperactive boys and normal men. *Arch Gen Psychiatry* 37:933–943.

Rolls ET (2000): The orbitofrontal cortex and reward. *Cereb Cortex* 10:284–294.

Rubinsztein JS, Fletcher PC, Rogers RD, Ho LW, Aigbirhio FI, Paykel ES, et al (2001): Decision-making in mania: A PET study. *Brain* 124:2550–2563.

Sachs GS, Baldassano CF, Truman CJ, Guille C (2000): Comorbidity of attention deficit hyperactivity disorder with early- and late-onset bipolar disorder. *Am J Psychiatry* 157:466–468.

Sax KW, Strakowski SM, Keck PE Jr, McElroy SL, West SA, Stanton SP (1998): Symptom correlates of attentional improvement following hospitalization for a first episode of affective psychosis. *Biol Psychiatry* 44:784–786.

Sax KW, Strakowski SM, McElroy SL, Keck PE Jr, West SA (1995): Attention and formal thought disorder in mixed and pure mania. *Biol Psychiatry* 37:420–423.

Sax KW, Strakowski SM, Zimmerman ME, DelBello MP, Keck PE Jr, Hawkins JM (1999): Frontosubcortical neuroanatomy and the continuous performance test in mania. *Am J Psychiatry* 156:139–141.

Schultz W, Tremblay L, Hollerman JR (2000): Reward processing in primate orbitofrontal cortex and basal ganglia. *Cereb Cortex* 10:272–284.

Schwarz N, Bless H, Bohner G (1991): Mood and persuasion: Affective states influence the processing of persuasive communication. In: Zanna MP, editor. *Advances in Experimental Social Psychology*, volume 24. San Diego: Academic Press, 161–197.

Sethi A, Mischel W, Aber JL, Shoda Y, Rodriguez ML (2000): The role of strategic attention deployment in development of self-regulation: Predicting preschoolers' delay of gratification from mother-toddler interactions. *Dev Psychol* 36:767–777.

Skolnick AJ, Davidson RJ (2002): Affective modulation of eyeblink startle with reward and threat. *Psychophysiology* 39:835–850.

Solanto MV, Abikoff H, Sonuga-Barke E, Schachar R, Logan GD, Wigal T, et al (2001): The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: A supplement to the NIMH multimodal treatment study of AD/HD. *J Abnorm Child Psychol* 29:215–228.

Sonuga-Barke EJ (2002): Psychological heterogeneity in AD/HD—a dual pathway model of behaviour and cognition. *Behav Brain Res* 130:29–36.

Sowell ER, Trauner DA, Gamst A, Jernigan TL (2002): Development of cortical and subcortical brain structures in childhood and adolescence: A structural MRI study. *Dev Med Child Neurol* 44:4–16.

Spear LP (2000): The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev* 24:417–463.

Starkstein SE, Robinson RG (1997): Mechanism of disinhibition after brain lesions. *J Nerv Ment Dis* 185:108–114.

Strakowski SM, DelBello MP, Sax KW, Zimmerman ME, Shear PK, Hawkins JM, et al (1999): Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. *Arch Gen Psychiatry* 56:254–260.

Sutton SK, Davidson RJ (1997): Prefrontal brain asymmetry: A biological substrate of the behavioral approach and inhibition systems. *Psychol Sci* 8:204–210.

Swann AC, Anderson JC, Dougherty DM, Moeller FG (2001): Measurement of inter-episode impulsivity in bipolar disorder. *Psychiatry Res* 101:195–197.

Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW (2000): Growth patterns in the developing brain detected by using continuum mechanical tensor maps. *Nature* 404:190–193.

Tomarken AJ, Davidson RJ, Henriques JB (1990): Resting frontal brain asymmetry predicts affective responses to films. *J Pers Soc Psychol* 59:791–801.

van Gorp WG, Altshuler L, Theberge DC, Mintz J (1999): Declarative and procedural memory in bipolar disorder. *Biol Psychiatry* 46:525–531.

Wheeler RE, Davidson RJ, Tomarken AJ (1993): Frontal brain asymmetry and emotional reactivity: A biological substrate of affective style. *Psychophysiology* 30:82–89.

Wilder-Willis KE, Sax KW, Rosenberg HL, Fleck DE, Shear PK, Strakowski SM (2001): Persistent attentional dysfunction in remitted bipolar disorder. *Bipolar Disord* 3:58–62.

Winokur G, Coryell W, Endicott J, Akiskal H (1993): Further distinctions between manic-depressive illness (bipolar disorder) and primary depressive disorder (unipolar depression). *Am J Psychiatry* 150:1176–1181.

Wozniak J, Biederman J, Kiely K, Ablon JS, Faraone SV, Mundy E, Mennin D (1995): Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry* 34:867–876.