Neural and Behavioral Substrates of Mood and Mood Regulation

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A review of behavioral and neurobiological data on mood and mood regulation as they pertain to an understanding of mood disorders is presented. Four approaches are considered: 1) behavioral and cognitive; 2) neurobiological; 3) computational; and 4) developmental. Within each of these four sections, we summarize the current status of the field and present our vision for the future, including particular challenges and opportunities. We conclude with a series of specific recommendations for National Institute of Mental Health priorities. Recommendations are presented for the behavioral domain, the neural domain, the domain of behavioral–neural interaction, for training, and for dissemination. It is in the domain of behavioral–neural interaction, in particular, that new research is required that brings together traditions that have developed relatively independently. Training interdisciplinary clinical scientists who meaningfully draw upon both behavioral and neuroscientific literatures and methods is critically required for the realization of these goals. Biol Psychiatry 2002;52:478–502

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Introduction

This article summarizes the deliberations and recommendations of the workgroup on the Neural and Behavioral Substrates of Mood and Mood Regulation. The article is divided into two major sections. In the first section, we summarize the current status of the field, present our vision for the future, and in so doing, discuss the various challenges and available opportunities. The second section contains specific recommendations for National Institute of Mental Health (NIMH) priorities in these areas. In each section, we consider research using the following four approaches, which together constituted the subject matter of this workgroup: 1) behavioral and cognitive; 2) neurobiological; 3) computational; and 4) developmental.

Current Status, Future Vision, Challenges, and Opportunities

Behavioral and Cognitive Approaches

Research in this area has generated some consistent findings regarding the course and characteristics of depression (Abramson et al 2001) and bipolar disorder (BPD). Eight of these findings are enumerated here. We then describe our current knowledge base of cognitive and psychosocial processes involved in depression and BPD onset and maintenance. Finally, we explore opportunities for future research.

THE CONSISTENT FINDINGS ABOUT DEPRESSION. First, depression is a highly recurrent disorder (Belsher and Costello 1988; Judd 1997) as is BPD (Goodwin and Jamison 1990). Second, life events may play a role in triggering episodes of depression (Brown and Harris 1978; Monroe and Simons 1991) and of mania/hypomania (Johnson and Roberts 1995), though the likelihood of such events exerting a causal role in triggering depression is a function of both the number of previous episodes and genetic risk (Kendler et al 2001). In particular, individuals with low genetic risk exhibit a decrease in the impact of stressful life events as the number of previous depressive episodes increases. In the absence of previous depressive

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episodes, those at high genetic risk frequently experience depressive episodes without any major environmental stressors.

Third, the presence of intimate others is associated with a lowered risk of depressive and bipolar episodes (Brown and Harris 1978; Johnson et al 1999; Panzarella et al 2001). Fourth, depression and BPD can be lethal, as they clearly increase risk for suicide (Davila and Daley 2000; Goodwin and Jamison 1990). People with major depression are at 11 times greater risk of making a suicide attempt, and those with BPD are at 30 times greater risk for making a suicide attempt than people without a mood disorder (Kessler et al 1999).

Fifth, depression is a common disorder (Kessler et al 1994). This fact suggests that common, as opposed to rare, factors cause depression. Sixth, the rates of depression surge during middle-to-late adolescence (Hankin et al 1998) and onset of subsyndromal forms of BPD (e.g., cyclothymia) rise rapidly during mid-adolescence (Alloy and Abramson 2000; Goodwin and Jamison 1990). Seventh, gender differences in depression exist among adults, with twice as many women experiencing depression as men (Hankin and Abramson, 2001; Nolen-Hoeksema 1987). In contrast, there are no gender differences in BPDs (Goodwin and Jamison 1990). Finally, depression long has been viewed as heterogeneous with multiple causes (Abramson et al 1989; Craighead 1980).

COGNITIVE VULNERABILITY IN DEPRESSION AND BIPOLAR DISORDER. Over the past 30 years, some investigators have emphasized the importance of cognitive processes in the etiology, maintenance, and treatment of depression. According to the major cognitive vulnerability–stress theories of depression (Abramson et al 1989; Beck 1967), individuals who exhibit negative cognitive styles (e.g., the tendency to make stable, global attributions, infer negative consequences, and infer negative self-characteristics in response to negative life events; dysfunctional attitudes involving the belief that one's happiness and self-worth depend on being perfect or on others' approval) or negative information processing about the self are vulnerable to developing episodes of depression when they experience stressful life events. These negative cognitions lead people to expect negative events to occur in the future in many domains and to blame themselves for these events, contributing to hopelessness, low self-worth, guilt, and sadness.

One specific cognitive model of depression, the Hopelessness Theory (Abramson et al 1989), suggests that the expectation that highly desired outcomes will not occur or that highly aversive outcomes will occur and that one cannot change this situation—hopelessness—is a proximal cause of depression, specifically the proposed hypothesized subtype of "hopelessness depression" (HD). Symptoms of HD are hypothesized to include sadness, retarded initiation of voluntary responses, suicidality, low energy, apathy, psychomotor retardation, sleep disturbance, poor concentration, and mood-exacerbated negative cognitions, but not other symptoms of depression, such as appetite disturbance, guilt, irritability, anhedonia, and somatic complaints. In turn, hopelessness is more likely to occur when an individual with negative cognitive styles experiences negative life events (i.e., the cognitive vulnerability–stress interaction).

Recent evidence from adult samples including both men and women and different ethnic groups indicates that hopelessness does mediate the relation between the cognitive vulnerability–stress combination and increases in depression (Alloy and Clements 1998; Hankin et al 2001) and that the cognitive vulnerability–stress interaction predicts changes in HD symptoms specifically (Alloy and Clements 1998). In addition, hopelessness prospectively predicts HD symptoms better than other depression symptoms or symptoms of other psychopathology (Alloy and Clements 1998). Moreover, there is preliminary evidence that the HD symptom cluster is a cohesive and distinct syndrome (Alloy and Clements 1998). Finally, hopelessness is perhaps the best single psychological predictor of suicidal ideation, attempts, and completions (Abramson et al 2000; Beck et al 1985, 1990). Whether hopelessness should be best regarded as a prodromal symptom or a cause of depression remains to be more fully explored in future research.

Rumination, the tendency to repetitively focus on one's symptoms of depression and the causes and consequences of one's depressive symptoms (Nolen-Hoeksema 1991), exacerbates and/or mediates cognitive vulnerability to depression. A ruminative coping style in response to sad mood is predictive of onsets of major depressive episodes (Nolen-Hoeksema 2000a; Just and Alloy 1997), longer and more severe episodes (Just and Alloy 1997; Nolen-Hoeksema et al 1993, 1994), and gender differences in vulnerability to depression (Nolen-Hoeksema 1987; Nolen-Hoeksema et al 1999) in adult samples representative of the community. Further, rumination mediates the effects of negative cognitive styles and other vulnerability factors for depression, including past history of depression and personality vulnerabilities, in predicting onsets of major depressive episodes (Spasojevic and Alloy, 2001). Some mechanisms by which rumination increases and maintains depression have been identified in experimental studies. Rumination enhances negative cognitions about the past, present, and future, interferes with effective interpersonal problem solving, depletes motivation to engage in instrumental behavior, and impairs social relationships (Nolen-Hoeksema 2000b).

It must be noted that the cognitive vulnerabilities described briefly above and identified in the psychological research on depression might also reflect early signs of disease. Although prospective studies can establish temporal precedence, they cannot definitively establish cause. Moreover, it is also possible that cognitive vulnerabilities reflect learned behavior from a parent with a similar cognitive style that may both reflect or emerge from genetic vulnerabilities that constitute the more distal diathesis. Experimental studies manipulating cognitions have shown the predicted effects on negative mood, however, providing more evidence of the role of cognitions in the production of at least depressive symptoms, if not major depressive disorders (Nolen-Hoeksema 2000b).

Much recent work has begun to identify some of the psychosocial origins of vulnerability to depression (Garber and Flynn 1998; Rose and Abramson 1992). A history of childhood maltreatment, including emotional and sexual maltreatment, is associated with adult cognitive vulnerability to depression and the actual development of major depressive episodes, and suicidality (Gibb et al 2001; Gibb et al, in press; Rose and Abramson 1992) Similarly, negative parenting practices, in particular a pattern referred to as "affectionless control" (Parker 1983) involving lack of emotional warmth and negative psychological control, is related to cognitive vulnerability to depression and onsets of depressive episodes (Alloy et al 2001a; Garber and Flynn 2001). Finally, maladaptive inferential feedback from parents and other adults regarding the causes and consequences of stressful events in children's lives is associated with children's cognitive vulnerability to depression and later onsets of major depression (Alloy et al 2001a; Dweck et al 1978; Garber and Flynn 2001).

Of course, all of these toxic psychosocial environments would be expected to act initially by inducing plastic changes in brain function and structure that would be expressed as cognitive vulnerabilities. An additional possibility that has been considered though not well-studied is that early individual differences in affective style, both genetically influenced and experientially shaped, bias a person's emotional reactivity and mood, and the consistent experience of low levels of positive affect and/or high levels of certain forms of negative affect induces a shift toward a more depressogenic cognitive style (e.g., Davidson 1994).

LIFE EVENTS AND DEPRESSION AND BIPOLAR DISORDER. As noted above, life events play a role in triggering episodes of depression and mania/hypomania (Alloy et al 2001b; Brown and Harris 1978; Johnson and Roberts 1995; Monroe and Simons 1991); however, recent evidence suggests that various kinds of life events may not be equivalent in their depressogenic and manicogenic potential. For example, recent (within 3 months), major negative events that signify loss or exits from the social network appear to be especially likely to trigger major depression (Brown and Harris 1978; Monroe and Simons 1991). With regard to mania/hypomania, it is less clear whether positive or negative life events are crucial for triggering manic symptoms (Alloy et al 2001b). Events that disrupt circadian rhythms, in particular the sleep/wake cycle (Ehlers et al 1988; Malkoff-Schwartz et al 1998), or that involve goal attainment or "challenge" (Johnson et al 2000) may be especially likely to trigger mania/hypomania. Further, events that occur in domains that "match" specific content areas of vulnerability for individuals (e.g., interpersonal rejection for an individual who is highly dependent or sociotropic) may be especially likely to trigger depressive and manic/hypomanic episodes (Coyne and Whiffen 1995; Hammen et al 1992).

Life events that interact with cognitive vulnerabilities may predict onsets of depressive and manic/hypomanic symptoms (Alloy and Clements 1998; Alloy et al 1999c; Hammen et al 1992; Metalsky et al 1987b); however, the precise manner in which vulnerability and stress combine to lead to depression or mania/hypomania is unknown (Monroe and Simons 1991). Does a synergistic vulnerability–stress model, in which only high-risk individuals (with negative cognitive styles) who experience high stress develop depression, or a titration vulnerability–stress model, in which high "doses" of stress can precipitate depression in individuals with low cognitive vulnerability and low "doses" of stress are sufficient to trigger depression in highly vulnerable individuals, better explain the interaction between cognitive vulnerability and stress in promoting onsets of depression (Abramson et al 1997)? Moreover, cognitive vulnerability and stress may combine in yet another way to precipitate depressive and manic/hypomanic episodes. According to a stress generation model (Daley et al 1997; Hammen 1991; Monroe and Simons 1991), high-risk individuals navigate a life course that promotes differential exposure to greater life stress, and this greater stress, in turn, precipitates depressive or manic symptoms. The developmental antecedents of cognitive vulnerability are also not well known.

Several other issues are worth noting in the consideration of the role of life stress in mood disorders. First, depression can cause life events such as marital breakup and job loss. Such life events might be interpreted by an individual as playing a causal role in her depression but may actually reflect a consequence of the disorder rather than a cause; however, such life events may contribute to the maintenance or exacerbation of the depression. Second, another set of life events that play a causal role in the development of mood disorders are certain medical conditions, such as major fluctuations in gonadal steroids (e.g., having a baby or being premenopausal) or cerebro-

vascular disease (e.g., stroke). Both of these have been found to significantly increase the risk of depression (e.g., O'Hara et al 1991).

SOCIAL SUPPORT AND DEPRESSION AND BIPOLAR DISORDER. Social support appears to protect against depression when people experience stressful events (Cohen and Wills 1985; Roberts and Gotlib 1997). Similarly, social support may protect individuals with BPD from mood episodes (Johnson et al 1999). The protection conferred by social support against mood disorders may be part of a more general protection provided by social support for medical conditions per se (e.g., Sharpe et al 1990). Recent work indicates that social support, and in particular the offering of adaptive explanations for negative events by persons in the support network, may provide "resilience" by preventing the development of hopelessness through three mechanisms (Panzarella et al 2001): 1) by decreasing the number and severity of stressful life events a person experiences; 2) by decreasing maladaptive inferences for stressful events; and 3) by decreasing or attenuating negative cognitive styles.

FUTURE RESEARCH DIRECTIONS AND CHALLENGES. The knowledge base of cognitive and psychosocial processes involved in depression and BPD reviewed herein provides a foundation and the opportunity for addressing the following issues. Given the role that negative cognitive styles and information processing play as potential vulnerabilities for depression and possibly for BPD as well, what are the precise psychological and biological mechanisms by which cognitive vulnerability is translated into mood disorder? Does cognitive vulnerability also have a role to play in the onset and course of BPD? Are the same cognitive and psychosocial processes involved in first onsets versus recurrences of mood disorders, or do these factors combine differently for first versus subsequent episodes? Does cognitive vulnerability change over time as a function of intervening mood episodes, intervening stressors, or intervening inferential feedback and, if so, does this lead to attendant changes in vulnerability to future mood episodes? What are the developmental origins of cognitive vulnerability to mood disorders, and how do these antecedent factors promote vulnerability at different developmental stages? Why do the gender differences in depression emerge in adolescence, and are these gender differences smaller for some ethnic groups than others? Precisely how do vulnerability and stressful events combine to trigger episodes of mood disorder (synergistic model, titration model, or stress-generation model)? What properties of life events are crucial to their depressogenic and manicogenic effects? Finally, to what extent are the cognitive style variables that have been featured in the cognitive vulnerability theories actual causes or consequences of other variables that themselves may play a more proximal role in the etiology of mood disorders?

Given the major advances that have occurred in understanding both the cognitive and psychosocial antecedents of depression and the biological and neural bases of emotional and motivational systems, respectively, the time is ripe for an integration of the cognitive and biological approaches to depression and BPD. Work on two fundamental psychobiological systems, the Behavioral Activation System (BAS), which regulates approach behavior to attain rewards and goals, and the Behavioral Inhibition System (BIS), which regulates withdrawal and/or inhibition of behavior in response to threat and punishment, may dovetail with the cognitive vulnerability–stress models of depression (Gotlib and Abramson 1999). For example, when a cognitively vulnerable individual experiences a negative life event and makes inferences about that event that lead to hopelessness about achieving important current and future goals, the substrate for this set of cognitive processes may be the relative deactivation of the BAS (Abramson et al 2001); however, it must be noted that the circuitry that supports the BAS and BIS is likely to be complicated and distributed across a number of interconnected structures, including the prefrontal cortex, anterior cingulate, amygdala, and hippocampus (see Davidson et al, 2002, for review) and it is surely overly simplistic to describe global changes in the activation of these hypothetical systems. We now have the tools to interrogate the detailed circuitry underlying these systems, and future research will need to harness these methods to better understand the neural substrates of these hypothesized diathesis–stress interactions.

Similarly, work on the cognitive vulnerability–stress models of depression and BPD may be integrated with circadian rhythm perspectives on mood disorders (Ehlers et al 1988; Malkoff-Schwartz et al 1998). Stressful life events may be especially likely to disrupt sleep/wake cycles in cognitively vulnerable individuals who make negative inferences about the stressors and ruminate on the negative cognitions and their emerging negative affect. Consequently, the integration of cognitive, psychosocial, and neurobiological approaches to mood disorders is both an important gap in existing research and opportune at this time. To take full advantage of the opportunity to integrate cognitive, psychosocial, and neurobiological approaches to mood disorder vulnerability, prospective, longitudinal, high-risk designs are needed, in which both behavioral and biological variables are assessed.

Neurobiological Approaches

NEUROCHEMICAL CORRELATES OF MOOD DISORDERS: NEUROTRANSMITTER AND NEUROPEPTIDE SYSTEMS. Primary major depressive disorder (MDD) and BPD have been associated with a variety of neuroendocrine, neurochemical, neurophysiological, and neuromorphometric abnormalities (see Davidson et al, 2002; Drevets and Todd 1997; Drevets et al 1999; Manji et al 2001, for recent reviews with extensive citations). There is a wealth of data at the animal level that provides an important foundation for the understanding of the neurobiology of mood, mood regulation, and mood disorders in humans. Work that is especially pertinent to a number of central points in our review will be briefly considered, but such data are not treated at length because one of the workgroups included within this series has focused on animal models. It is not known whether these comprise the vulnerability to abnormal mood episodes, compensatory changes to other pathogenic processes, or sequelae of recurrent illness. None of these abnormalities has had sufficient sensitivity and specificity with respect to diagnosis or predictors of treatment outcome to justify their application in routine clinical care.

The brain systems that have heretofore received the greatest attention in mood disorders research have been the monoaminergic neurotransmitter systems, which were implicated by discoveries that effective antidepressant drugs exerted their *primary* biochemical effects by regulating intrasynaptic concentrations of serotonin, norepinephrine, and dopamine, and that antihypertensives that depleted these monoamines precipitated major depressive episodes. Assessments of cerebrospinal fluid (CSF) chemistry, neuroendocrine responses to pharmacological challenge, and neuroreceptor and transporter binding also demonstrated abnormalities of the monoamine systems in mood disorders (Maes and Meltzer 1995; Schatzberg and Schildkraut 1995; Willner 1995). For example, neuroimaging, postmortem, and pharmacological challenge studies have all shown abnormalities of serotonin$_{1A}$ receptor function and binding and serotonin transporter binding in mood disorders (reviewed in Drevets et al 2000). Serotonin transporter availability also appears to be reduced in depression. Less consistency among studies has been found for the serotonin$_{2A}$ receptor (reviewed in Dhaenen 2001). Preclinical studies indicate that somatic antidepressant treatments effect changes in the function of these sites that are relevant to their therapeutic mechanisms. (Blier and diMontigny 1999). The monoaminergic systems are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits thought to support the behavioral and visceral manifestations of mood disorders.

Abnormalities have also been demonstrated in a variety of neuropeptide, neuroendocrine, and other neurotransmitter systems in mood disorders. For example, elevated activity of the hypothalamic–pituitary–adrenal (HPA) axis is one of the most replicated biological findings in major depression. Relative to healthy control subjects, people with depression have elevated levels of cortisol in 24-hour collections of plasma and urine, hypertrophy of the adrenal and pituitary glands, and exaggerated cortisol response to adrenocorticotropic hormone (ACTH) stimulation (reflecting adrenal hypertrophy) (reviewed in Drevets et al 2002; Garlow et al 1999). The diathesis toward HPA axis dysfunction in MDD appears associated with both a negative feedback disturbance and an increased drive by central processes. (reviewed in Drevets et al, 2002). The latter is evidenced in unmedicated MDD samples by increased CSF levels of corticotropin-releasing hormone (CRH), pituitary enlargement, and blunted ACTH response to CRH (presumably reflecting desensitization of the pituitary CRH receptors) in vivo, and by increased numbers of CRH-secreting neurons, increased CRH mRNA expression in the paraventricular nucleus (PVN) of the hypothalamus, and down-regulation of frontal cortex CRH receptor density postmortem (Garlow et al 1999; Holsboer 2000; Young et al 1991). These findings may be specific to depressives who are melancholic, bipolar, or severely depressed, as distinct patterns of HPA axis dysfunction are reported in people with atypical depression. Although dysfunction within these neurotransmitter and neuroendocrine systems is likely to play a role in the pathophysiology of MDD, there is a growing expectation that they may represent downstream effects of other, *more primary abnormalities.* The signaling networks that integrate multiple chemical signals and regulate the functional balance between interacting neuronal circuits have been hypothesized to constitute a common downstream abnormality that could account for the dysfunction in so many neurotransmitter, neuroendocrine, and physiologic systems in mood disorders (Manji et al 2001). Compatible with this hypothesis, the activity of these signaling pathways is modulated by most effective pharmacological treatments for mood disorders (Manji et al 2001).

NEUROANATOMICAL AND NEUROPATHOLOGICAL CORRELATES OF MOOD DISORDERS. Neuroimaging studies reveal multiple abnormalities of regional cerebral blood flow (CBF) and glucose metabolism in limbic and prefrontal cortical (PFC) structures in mood disorders (for early reports, see Baxter et al 1985; Mayberg et al 1994), although disagreement exists regarding the specific locations and the direction of these abnormalities (see Davidson et al, 2002; Drevets 2000 for reviews). Data from

unmedicated, early-onset, familial, or melancholic depressives show that CBF and metabolism are increased in the amygdala, orbital cortex, and medial thalamus, and decreased in the dorsomedial/dorsal anterolateral PFC, the anterior cingulate cortex (ACC) ventral to the genu of the corpus callosum (i.e., subgenual PFC), and the dorsal ACC, relative to healthy control subjects. The overall pattern of these metabolic changes during major depressive episodes suggests that structures implicated by other types of evidence in mediating emotional and stress responses are pathologically activated; brain areas thought to modulate or inhibit emotional expression are also activated (e.g., posterior orbital cortex), and areas implicated in attention and sensory processing are deactivated (e.g., dorsal ACC). However, it should be noted that not all patients with MDD exhibit this particular pattern of abnormalities. In particular, several investigators have not found increased amygdala activation in patients with major depression (e.g., Abercrombie et al 1998). Davidson et al (2002) have suggested that high levels of amygdala activation are associated with an increased prevalence of anxiety symptoms and dispositional negative affect. Likewise, both decreased glucose metabolism and decreased volume in the orbitofrontal cortex have been reported for certain subtypes of depression (Bremner et al 1997a, 2002). It is likely that the variations among different studies are associated with heterogeneity among different subtypes of depression.

During antidepressant drug treatment, some of these neurophysiological abnormalities reverse in treatment-responders, whereas others do not (Brody et al 2001; Drevets 2000). Most of the regions where neurophysiological abnormalities persist independently of mood-state have been shown to contain structural brain changes in morphometric magnetic resonance imaging (MRI) and/or postmortem studies of primary mood disorders. Some studies have demonstrated reduced gray matter volumes in parts of the orbital and medial prefrontal cortex, the striatum, and the amygdala, and enlargement of third ventricles in mood disorders. In addition, postmortem histopathological studies have shown abnormal reductions in glia cell counts, neuron size and/or synaptic proteins in the subgenual PFC, orbital cortex, dorsal anterolateral PFC, and amygdala (Cotter et al 2001; Ongur et al 1998b; Rajkowska 2000). The marked reduction in glial cells in these regions is intriguing in view of the growing appreciation that glia play critical roles in regulating synaptic glutamate concentrations and central nervous system energy homeostasis, and in releasing trophic factors that participate in the development and maintenance of synapses.

The neuroimaging and histopathological findings described above pertain to MDD subjects with an early age of depression onset, and in contrast, elderly subjects who have a late age of MDD onset instead have MRI and hemodynamic correlates of cerebrovascular disease (reviewed in Drevets et al 1999). The disparate findings between early- and late-onset cases nevertheless affect a common neural circuitry.

AMYGDALA. In familial MDD, the abnormal elevation of resting CBF and glucose metabolism in the amygdala ranges from 5% to 7%, which when corrected for spatial resolution effects, would reflect an increase in actual CBF and metabolism of 50%–70%. This range is physiologic, based upon CBF increases measured invasively in experimental animals during exposure to fear-conditioned stimuli (LeDoux et al 1983). Amygdalar CBF and metabolism correlate positively with depression severity and with dispositional negative affect. During antidepressant treatment that both induces and maintains symptom remission, amygdala metabolism decreases to normative levels, compatible with preclinical evidence that chronic antidepressant drug administration has inhibitory effects on amygdala function. It must be stressed, however, that this pattern of amygdala function is not present in all patients with MDD and appears to be associated with a specific symptom cluster that includes high levels of dispositional negative affect and anxiety.

Neuroimaging, electrophysiological and lesion analysis studies in humans and experimental animals demonstrate that the amygdala is involved in the acquisition and recall of emotional or arousing memories. In humans, bursts of electroencephalogram (EEG) activity have been recorded in the amygdala during recollection of specific emotional events (Halgren 1981). Moreover, electrical stimulation of the human amygdala can evoke emotional experiences (especially fear or anxiety) and recall of emotionally charged life events from remote memory (Gloor et al 1982). Taken together with the finding of elevated amygdala metabolism in MDD, these observations suggest the hypothesis that excessive amygdalar stimulation of cortical structures involved in declarative memory may account for the tendency of depressed subjects to ruminate on memories of emotionally aversive or guilt-provoking life events (Cahill 2000). Amygdala dysfunction in mood disorders may also conceivably alter the initial evaluation and memory consolidation related to sensory or social stimuli with respect to their emotional significance (Davidson et al, 2002; Drevets 2001). The amygdala is involved in recognizing fear and sadness in facial expression and fear and anger in spoken language (Adolphs et al 1996; Morris et al 1996), and studies examining hemodynamic responses in the amygdala to facially expressed emotion demonstrate abnormalities in children with MDD (Thomas et al 2001). Norepinephrine release in the amyg-

dala plays a critical role in at least some types of emotional learning, and the activation of norepinephrine release is facilitated by glucocorticoid secretion (Ferry et al 1999). At least some depressed subjects have abnormally elevated secretion of both norepinephrine and cortisol (Schatzberg and Schildkraut 1995), which in the presence of amygdala activation may conceivably increase the likelihood that ordinary social or sensory stimuli are perceived or remembered as being aversive or emotionally arousing (Davidson and Irwin 1999; Drevets 2001).

Although the amygdala may be critically involved in the initial learning of emotional associations, it may not be required for the expression of well-learned emotional dispositions. In rhesus monkeys with bilateral destruction of the amygdala using excitotoxic lesions, preserving fibers of passage, Kalin et al (2001) reported no change in behavioral or biological manifestations of temperamental fearfulness and behavioral inhibition, yet they did find reductions in behavioral measures of acute fear. These and other similar findings argue for a role of the amygdala in the initial learning of emotional associations and in the expression of acute fear responses to biologically prepared (in this case, snakes) stimuli; however, the data also question the role of the amygdala in the expression of more tonic dispositional characteristics of mood. These issues still require further study.

PREFRONTAL CORTEX. Consistent with prior literature, recent reports have documented decreased activation in both dorsolateral and dorsomedial prefrontal cortex as well as the pregenual region of the anterior cingulate gyrus in depressed patients (see Bush et al 2000 for review of ACC in normal function and Davidson et al, 2002; Drevets, 2000, 2001, for reviews of PFC and ACC function in depression). The reduction in activation in this latter region, particularly on the left side, appears to be at least partially a function of a reduction in the volume of gray matter as revealed by MRI-derived morphometric measures (Drevets et al 1997) and confirmed by postmortem measures of gray matter volume (Ongur et al 1998b). Consistent with the notion that the metabolic reduction found in this region is at least partially a function of the volume reduction, Drevets et al (1997) have reported that remission of symptoms associated with successful treatment is not accompanied by a normalization of activation in this area.

This general decrease in physiologic activity in the dorsolateral PFC and in the subgenual region of the ACC is sometimes accompanied by an increase in other regions of the PFC, particularly in the ventrolateral and orbital (lateral and medial) (reviewed in Drevets 2000; Rajkowska 2000). Treatment studies have found that activation in dorsolateral PFC, particularly on the left side, increases following successful antidepressant treatment (Kennedy et al 2001). Less consistent are findings for ventrolateral and orbital PFC regions. Some studies have found increases in these regions (Kennedy et al 2001), whereas others have reported decreases (e.g., Brody et al 2001; Drevets 2000; Mayberg et al 1999). In contrast to clinically depressed patients in whom a reduction in metabolic rate has been observed in subgenual PFC (particularly on the left side), studies of induced sadness in normal subjects reported an increase in activation in this region (Liotti et al 2000; Mayberg et al 1999). This apparent discrepancy may be resolved by considering the effects of the reduction in cortex volume found in this area in MDD and BPD on relatively low-resolution positron emission tomography (PET) measures: computer simulations that correct PET data for the partial volume effect of reduced gray matter volume conclude the "actual" metabolic activity in the remaining subgenual PFC tissue is *increased* in people with depression relative to control subjects, and decreases to normal with effective antidepressant drug treatments (Drevets 2000).

As suggested above, of critical import to any claims made about functional differences between depressed patients and normal control subjects are recent reports of anatomical differences in the prefrontal cortex. Based on the neuroimaging observations of reduced blood flow and metabolism and diminished volume of the subgenual portion of Brodmann area 24 in subjects with familial MDD and BPD (Drevets et al 1992, 1997), Ongur et al (1998b) evaluated this cortical region in postmortem samples from two separate cohorts of subjects. Using state-of-the-art stereological techniques, they found that both the density and total number of glial cells were reduced in subjects with MDD or BPD compared to unaffected comparison subjects, with the findings most robust in those with a family history of illness. In contrast, neither the density nor total number of neurons was altered. The regional specificity of these findings was supported by the absence of such changes in the primary somatosensory cortex of the same subjects with MDD and BPD. Furthermore, the diagnostic specificity of these observations was suggested by the failure to find similar changes in subjects with schizophrenia. Rajkowska et al (1999) also observed reductions in the density of glial cells in the orbital and dorsolateral PFC of subjects with MDD, with a suggestion that these changes may be more marked in certain cortical layers (III–VI). In addition, the size of glia nuclei were reported to be increased in these brain regions. A preliminary report from the same group indicates that similar alterations in glia density and size are present in these brain regions in subjects with BPD (Rajkowska 2000). These authors also found reductions in

neuronal size and in cortical thickness in these brain regions.

Two other recent studies provide additional data consistent with a disturbance in glial cells in mood disorders, although the findings differ from those summarized above in several respects. Using tissue specimens containing Brodmann area 24 (although whether the subgenual portion or another subdivision was examined was not specidifed) provided by the Stanley Foundation Neuropathology Consortium, Cotter et al (2001) found that glial density was significantly reduced in layer VI from subjects with MDD or schizophrenia, but not in subjects with BPD (most of whom were receiving mood stabilizers, which appear to exert neurotrophic/neuroprotective effects; Manji et al 2001). Although neuronal density was not altered in any subject group, the mean size of neurons was reported to be reduced in the deep layers of subjects with MDD. Using the same cohort of subjects, Uranova et al (2001) examined area 10 in the dorsal PFC. They found that the density of glia was significantly reduced in layer VI in subjects with BPD and in subjects with schizophrenia. Among the subjects with MDD, only those with a family history of "severe mental disorder" showed decreased glial densities.

Taken together, the findings from these four research groups converge upon the hypothesis that a subset of subjects with MDD and BPD (most likely those with a positive family history of mood disorder) share a deficit in prefrontal cortical glial density. The stereology-based findings of reduced total glial number in the Ongur et al (1998b) study, and the observations from at least some structural neuroimaging studies that gray matter volume is reduced in these cortical regions, suggest the reduced glia density represents actual reduction in the number of glia as opposed to alterations in the distribution volume of the glia secondary to medication (e.g., lithium-related gray matter volume increases) or other factors. Given the multiple roles that glia appear to serve (e.g., neuronal energetics, neurotransmitter uptake, and metabolism, etc.), alterations in glia number may have substantial and widespread affects on brain function.

The potential pathophysiological significance of these findings depends on the consideration of a number of issues. For example, the apparent presence of reduced glial density in multiple major domains of the prefrontal cortex (medial, orbital, and dorsal anterolateral) suggests that the disturbance may have an impact on multiple prefrontal networks that differ substantially in their connectivity with other brain regions (Barbas and Rempel-Clower 1997; Carmichael and Price 1995a, 1995b, 1996). This apparent relative lack of regional specificity presents challenges to clinicopathological correlations between disturbances in a given region with signs or symptoms of the disorder. This type of observation also raises the question of whether the finding of reduced glia density actually represents part of the causal pathophysiology of mood disorders or a consequence of these illnesses or their treatments. The latter view may be supported by the observation in two of three studies that subjects with schizophrenia also show a reduction in glial density. Clearly, further studies are needed to clarify the diagnostic specificity of the observation and to determine whether subjects with different psychiatric disorders may differ in the type of glial disturbance that they exhibit. The fact that these anatomical differences in the brains of patients with mood disorders might account for some of the functional differences as noted by Drevets et al (1997) does not in itself provide any direct measures of causal influence. Longitudinal studies of patients at risk for mood disorders are needed to ascertain whether these structural differences are present before the onset of a depressive episode. Heritable factors can be examined by studying monozygotic twins discordant for mood disorders to ascertain whether the anatomical abnormalities are found in the affected twin only. Finally, these observations raise questions regarding the extent to which they may be associated with other reported abnormalities in mood disorders. For example, to what extent does a reduction in glial cell number contribute to the reported reduction in hippocampal volume in structural imaging studies of depression (Sheline et al 1996, 1999)?

The common observation in EEG studies of an altered pattern of asymmetric activation in anterior scalp regions in the direction of reduced left relative to right activation in depressed or dysphoric individuals has also been replicated several times in recent years (Bell et al 1998, Bruder et al 1997a, Debener et al 2000, Gotlib et al 1998, Pauli et al 1999, Reid et al 1998, Weidemann et al 1999); however, it should be noted that this asymmetry is not invariably found (e.g., Kentgen et al 2000; Reid et al 1998). Reid et al (1998) and Davidson (1998) have discussed various methodological and conceptual issues related to the inconsistencies in the literature. In an important extension of the work on electrophysiological asymmetries, Bruder et al (2001) examined whether brain electrical asymmetry measures acquired during a pretreatment period predicted response to selective serotonin reuptake inhibitor (SSRI) treatment. They found that among women in particular, the treatment responders had significantly less relative right-sided activation compared to the nonresponders, though this effect was present in both anterior and posterior scalp regions. Based on the role of right prefrontal regions in components of negative affect (Davidson 2000) and right posterior regions in arousal and anxiety (Heller and Nitschke 1998), these findings imply that those subjects with global right-activation who would be ex-

pected to have symptoms of negative affect and anxious arousal are least likely to show improvements with SSRI treatment.

Anterior Cingulate Cortex

In major depression, *decreased* ACC activation relative to control subjects has been repeatedly reported. In single photon emission computed tomography (SPECT) studies, decreased regional CBF in the left (Curran et al 1993; Mayberg et al 1994) or right (Ito et al 1996) ACC has been found in medicated depressed unipolar patients compared to control subjects. Decreased ACC activation has been recently replicated with PET (Bench et al 1992; Drevets et al 1997; George et al 1997a; Kumar et al 1993) and functional MRI (Beauregard et al 1998) techniques. Interestingly, the region of the ACC found to be hypoactive in major depression (dorsal ACC: dorsal region of area 32; areas 24′, 32′) appears to be different from the one found to be *hyper*active in eventual treatment responders (ventral and rostral ACC, including pregenual areas 24 and 32). Whereas the state of being depressed is associated with reduced dorsal ACC activity (see above), remission has been characterized by increased activity in the same region (Bench et al 1995; Buchsbaum et al 1997; Mayberg et al 1999). Similarly, the increased activity in the rostral ACC characteristic of treatment responders (Mayberg et al 1997; Ebert et al 1991; Pizzagalli et al 2001; Wu et al 1992) has been shown to normalize (i.e., decrease) in the same subjects after sleep deprivation (Wu et al 1999, Smith et al 1999). Based on these findings, recent neurobiological models of depression have highlighted the role of the ACC in the pathogenesis of depression and in the manifestation of its symptomatology (Drevets 2001; Ebert and Ebmeier 1996; Mayberg et al 1997).

The interplay between the affective and cognitive subdivisions of the ACC is presently unknown. From a theoretical perspective, several authors have suggested that the affective subdivision of the ACC may integrate salient affective and cognitive information (such as that derived from environmental stimuli or task demands), and subsequently modulate attentional processes within the cognitive subdivision accordingly (Drevets and Raichle 1998; Mayberg et al 1997, 1999; Mega et al 1997; Pizzagalli et al 2001). In agreement with this hypothesis, dorsal anterior and posterior cingulate pathways devoted to attentional processes and amygdalar pathways devoted to affective processing converge within area 24 (Mega et al 1997). These mechanisms may be especially important for understanding the repeatedly demonstrated finding that increased *pre*-treatment activity in the rostral ACC is associated with eventual better treatment response (Ebert et al 1991; Mayberg et al 1997; Pizzagalli et al 2001; Wu et al 1992). In an influential paper, Mayberg et al (1997) reported that unipolar depressed patients who responded to treatment after 6 weeks showed higher pretreatment glucose metabolism in a rostral region of the ACC (BA 24a/b) compared to both nonresponders and nonpsychiatric comparison subjects. Recently, Pizzagalli et al (2001) replicated this finding with EEG source localization techniques and demonstrated that even among those patients who respond to treatment, the magnitude of treatment response was predicted by baseline levels of activation in the same region of the ACC as identified by Mayberg et al (1997). In addition, it was suggested that hyperactivation of the rostral ACC in depression might reflect an increased sensitivity to affective conflict, such that the disparity between one's current mood and the responses expected in a particular context activates this region of ACC, which then in turn issues a call for further processing to help resolve the conflict. This call for further processing is hypothesized to aid the treatment response.

One of the major outputs from the ACC is a projection to PFC. This pathway may be the route via which the ACC issues a call to the PFC for further processing to address a conflict that has been detected. Abnormalities in PFC function in depression may thus arise as a consequence of the failure of the normal signals from ACC, or may be intrinsic to the PFC, or both. It is also possible, and even likely, that there are different subtypes of depression that may involve more primary dysfunction in different parts of the circuitry discussed above; however, it is important to underscore the possibility that there may exist a primary ACC-based depression subtype and a primary PFC-based depression subtype. These subtypes might not conform to the phenomenological and descriptive nosologies that are currently prevalent in the psychiatric literature.

The findings reviewed above on PFC and ACC activation and morphologic differences in depressed patients compared to control subjects underscore the considerable specificity within this region of the brain. There are important differences in connectivity between adjacent regions of cortical tissue, and future studies should examine patterns of functional connectivity in addition to activation differences that may distinguish between depressed patients and control subjects.

HIPPOCAMPUS. In their recent review, Davidson et al (2000) noted that various forms of psychopathology involving disorders of affect could be characterized as disorders in context-regulation of affect. That is, patients with mood and anxiety disorders often display normative affective responses but in *inappropriate* contexts. Given the preclinical and functional neuroimaging literature reviewed above, one may hypothesize that patients showing inappropriate context-regulation of affect may be

characterized by hippocampal dysfunction. Consistent with this conjecture, recent morphometric studies using MRI indeed reported hippocampal atrophy in patients with major depression (Bremner et al 2000; Mervaala et al 2000; Sheline et al 1996, 1999; Steffens et al 2000; but see Ashtari et al 1999; Pantel et al 1997; Shah et al 1998; Vakili et al 2000; von Gunten et al 2000), BPD (Noga et al 2001, but see Pearlson et al 1997), posttraumatic stress disorder (Bremner et al 1995, 1997b; Stein et al 1997), and borderline personality disorder (Driessen et al 2000) (for review, see Sapolsky 2000; Sheline 2000). Where hippocampal volume reductions in depression have been found, the magnitude of reduction ranges from 8% to 19%. Recently, functional hippocampal abnormalities in major depression have been also reported at baseline using PET measures of glucose metabolism (Saxena et al 2001). Whether hippocampal dysfunction precedes or follows onset of depressive symptomatology is still unknown.

In depression, inconsistencies across studies may be explained by several methodological considerations. First, as pointed out by Sheline (2000), studies reporting positive findings generally used MRI with higher spatial resolution (~0.5–2 mm) compared to those reporting negative findings (~3–10 mm). Second, it seems that age, severity of depression, and most significantly, duration of recurrent depression may be important moderator variables. Indeed, most studies reporting negative findings either studied younger cohorts (e.g., Vakili et al [2000]: 38 ± 10 years versus Sheline et al [1996]: 69 ± 10 years; von Gunten et al [2000]: 58 ± 9 years; Steffens et al [2000]: 72 ± 8 years) or less severe and less chronic cohorts (Ashtari et al 1999 vs. Bremner et al 2000; Shah et al 1998; Sheline et al 1996). In a recent study (Rusch et al, in press), hippocampal atrophy was not found in a relatively young subject sample (33.2 ± 9.5 years) with moderate depression severity. Notably, in normal early adulthood (18–42 years), decreased bilateral hippocampal volume has been reported with increasing age in male but not female healthy subjects (Pruessner et al 2001). Finally, in women, initial evidence suggests that total lifetime duration of depression, rather than age, is associated with hippocampal atrophy (Sheline et al 1999), inviting the possibility that hippocampal atrophy may be a symptom rather than a cause of depression. Future studies should carefully assess the relative contribution of these possible modulatory variables and of comorbid features, such as alcohol abuse, in the hippocampal pathophysiology and examine hippocampal changes longitudinally in individuals at risk for mood disorders.

Structurally, the hippocampal changes may arise due to neuronal loss through chronic hypercortisolemia, glial cell loss, stress-induced reduction in neurotrophic factors, or stress-induced reduction in neurogenesis (Sheline 2000) or reductions in neuropil due to dendritic reshaping (Drevets 2000, 2001; McEwen 1999). The latter view has particularly been supported by postmortem studies of the hippocampus, which showed abnormal reductions in the mRNAs for synaptic proteins (Eastwood and Harrison 2000) and in the apical dendritic spines of pyramidal cells (Rosoklija et al 2000) largely limited to the subicular subregion in samples with BPD. In depression, the hypothesis of an association between sustained, stress-related elevations of cortisol and hippocampal damage has received considerable attention. This hypothesis is based on the observation that the pathophysiology of depression involves dysfunction in negative feedback of the HPA axis (see Pariante and Miller 2001 for a review), which results in increased levels of cortisol during depressive episodes (e.g., Carroll and Mendels 1976). Higher levels of cortisol may, in turn, lead to neuronal damage in the hippocampus, because this region possesses high levels of glucocorticoid receptors (Reul and De Kloet 1986) and glucocorticoids may be neurotoxic (Sapolsky et al 1986). Because the hippocampus is involved in negative-feedback control of cortisol (Jacobson and Sapolsky 1991), hippocampal dysfunction may result in reduction of the inhibitory regulation of the HPA axis, which could then lead to hypercortisolemia. Consistent with this view, chronic exposure to increased glucocorticoid concentrations has been shown to lower the threshold for hippocampal neuronal degeneration in animals (Gold et al 1988; McEwen 1999; Sapolsky et al 1990) and humans (Lupien et al 1998). At least in nonhuman primates, this association is qualified by the observation that chronically elevated cortisol concentrations in the absence of chronic "psychosocial" stress do not produce hippocampal neuronal loss (Leverenz et al 1999). In depression, hippocampal volume loss has been shown to be associated with lifetime duration of depression (Sheline et al 1999), consistent with the assumption that long-term exposure to high cortisol levels may lead to hippocampal atrophy; however, this conjecture has not been empirically verified in humans.

Although intriguing, these findings cannot inform us about the causality between hippocampal dysfunction, elevated levels of cortisol, and most importantly, inappropriate context-regulation of affect in depression. Unfortunately, none of the structural neuroimaging studies in depression investigating hippocampal volume were prospective and took into account cortisol data in an effort to unravel the causal link between cortisol output and hippocampal dysfunction.

The possibility of plasticity in the hippocampus deserves particular comment. In rodents, recent studies have shown hippocampal neurogenesis as a consequence of antidepressant pharmacological treatment (Chen et al 2000; Malberg et al 2000), electroconvulsive shock

(Madhav et al 2000), and most intriguingly, as a consequence of positive handling, learning, and exposure to an enriched environment (Kempermann et al 1997, see Gould et al 2000 for review). In humans, neurogenesis in the adult human hippocampus has been also reported (Eriksson et al 1998). Further, in patients with Cushing's disease, who are characterized by very high levels of cortisol, slight (3% on average) increases in hippocampal volume were significantly associated with the magnitude of cortisol decrease produced by microadrenomectomy (Starkman et al 1999). As a corpus, these animal and human data clearly suggest that plasticity in the human hippocampus is possible (for reviews, see Duman et al 2000; Gould et al 2000; Jacobs et al 2000), a finding that suggests that structural and functional changes in the hippocampus of depressed patients may be reversible.

In summary, preclinical and clinical studies converge in suggesting an association between major depression and hippocampal dysfunction. Future studies should 1) assess whether hippocampal atrophy precedes or follows increased onset of depression; 2) assess the causal relation between hypercortisolemia and hippocampal volume reduction; 3) directly test a putative link between inappropriate context-dependent affective responding and hippocampal atrophy; and 4) assess putative treatment-mediated plastic changes in the hippocampus.

FUTURE RESEARCH DIRECTIONS AND CHALLENGES. There are several types of studies that critically need to be performed in light of the extant evidence reviewed above. First, studies that relate specific abnormalities in particular brain regions to objective laboratory tasks that are neurally inspired and designed to capture the particular kinds of processing that are hypothesized to be implemented in those brain regions is needed. Relatively few studies of that kind have been conducted. Most studies on depressed patients that examine relations between individual differences in neural activity to behavioral phenomena almost always relate such neural variation to symptom measures that are either self-report or interview-based indices. In the future, it will be important to complement the phenomenological description with laboratory measures that are explicitly designed to highlight the processes implemented in different parts of the circuit that we described.

Such future studies should include measures of both functional and structural connectivity to complement the activation measures. It is clear that interactions among the various components of the circuitry we describe are likely to play a crucial role in determining behavioral output. Moreover, it is possible that connectional abnormalities may exist in the absence of abnormalities in specific structures. This possibility underscored the real necessity of including measures of connectivity in future research.

As noted in several places in this review, longitudinal studies of at-risk samples with the types of imaging measures that are featured in this review are crucial. We do not know if any of the abnormalities discussed above, both of a structural and functional variety, precede the onset of the disorder, co-occur with the onset of the disorder, or follow by some time the expression of the disorder. It is likely that the timing of the abnormalities in relation to the clinical course of the disorder varies for different parts of the circuitry. The data reviewed earlier showing a relation between the number of cumulative days depressed over the course of the lifetime and hippocampal volume suggest that this abnormality may follow the expression of the disorder and represent a consequence rather than a primary cause of the disorder; however, before such a conclusion is accepted, it is important to conduct the requisite longitudinal studies to begin to disentangle these complex causal factors.

Research into the pathophysiological mechanisms operative in psychiatric disorders, and the insights that those findings provide regarding pathogenetic factors and treatment options, has been greatly accelerated in recent years through the increasing temporal, spatial, and biochemical resolution of in vivo neuroimaging techniques. In addition, genetic and behavioral animal models have provided tractable systems for investigating details of plausible pathophysiological mechanisms; however, neither in vivo neuroimaging nor animal models permit the direct investigation of the diseased brain tissue. Clearly, postmortem human brain studies are limited in certain ways by factors such as confounding variables that cannot be directly controlled; however, direct studies of postmortem human brain tissue provide the only vehicle for exploring, at molecular and cellular levels, the alterations in neural circuitry that give rise to the clinical manifestations of mood and other psychiatric disorders (Lewis 2002). In addition, the study of human brain tissue is essential for the harnessing of the recent powerful advances in functional genomics and of the promise of proteomics to our efforts to understand the critical neurobiology of these disorders. Thus, investigations of the postmortem human brain represent a critical component of the programmatic study of mood disorders; however, as in any area of scientific investigation, such studies must be conducted with an astute awareness of their strengths and limitations, and with the inclusion of other types of studies that mitigate these limitations.

In other brain disorders, postmortem studies have proven to be useful by 1) providing the "gold standard" for the diagnosis of a disorder; 2) delineating the pathogenesis of the disorder; 3) producing informative leads for candidate genes in the disorder; and/or 4) revealing the pathophysiology of the disorder or the possible relationship

between brain abnormalities and the clinical symptoms of the illness. In the case of mood disorders (as for most psychiatric disorders), almost no firm data exist in any of these areas. Recent studies from several research groups have produced findings suggesting that MDD and BPD are associated with a reduction in glial cell density in the multiple regions of the prefrontal cortex; however, this abnormality is unlikely to be diagnostic of the disorder, and how (or if) it may relate to disease genetics, pathogenesis, or pathophysiology is unclear at present and certainly represents an important gap in our understanding of this disorder. The effective utilization of postmortem studies to address these types of questions requires consideration of the following types of resources and research strategies.

Clearly, adequate sample sizes of postmortem human tissue specimens must be available for such studies. But beyond numbers, the success of such investigations rests upon the extent to which the samples are well characterized, the studies are well designed and appropriate for the question of interest, and the potential confounds of the study are well considered. These issues are discussed in detail elsewhere (Lewis 2000, 2002; Harrison and Kleinman 2000), but several points specific to the study of mood disorders are worthy of note here. First, in terms of characterization, not only is a full reconstruction of the subject's history required for accurate diagnosis, but the outcome of many studies may also be dependent on knowing the state of the illness at the time of death. For example, published studies typically indicate that subjects met diagnostic criteria for MDD, but fail to specify whether the diagnosis was based on a single episode or recurrent illness and whether the subject was actually depressed at the time of death. Similarly, the phase of BPD at time of death is frequently not indicated. Clearly, such information may prove critical for testing hypotheses that episodes of illness are precipitated by changes in dentate gyrus neurogenesis (Jacobs et al 2000) or that structural changes in the hippocampus reflect total lifetime duration of depression (Sheline et al 1999). In addition, questions regarding heterogeneity within MDD and BPD need to be considered. For example, to what extent is the observation of decreased cortical glial density influenced by the presence of both psychosis and a disturbance in mood disturbance? Could such an interaction explain why diminished glial density appears to be present in both a subset of MDD/BPD subjects and in at least some subjects with schizophrenia, a disorder frequently complicated by abnormalities in mood?

Differentiating the effects of the illness from the consequences of its treatment on the brain structure of interest would ideally be assessed in never-medicated subjects; however, because an adequate sample of postmortem brain specimens from never-medicated subjects with MDD or BPD is unlikely to ever be available, several less direct approaches must be used to address this question. These approaches include 1) the comparison of data from subjects who were on or off medications at the time of death; 2) the examination of subjects with other disorders who also were treated with these medications; and 3) the use of animal models that mimic the clinical treatment of mood disorders (Lewis 2002). Certainly, the first two approaches have obvious, and difficult to control, potential confounds. Long-term exposure to medications, as is typical in the treatment of recurrent MDD and BPD, may have effects on brain morphology, neurochemistry, or gene expression that persist for a substantial period of time after the drug is discontinued. In the case of animal models of drug effects, many studies have been conducted in rodents with dosage and time parameters that do not necessarily reflect the human treatment condition. These limitations can be overcome through studies in nonhuman primates that involve extended periods of treatment with doses that produce serum drug levels shown to be therapeutic in humans; however, one is still left with the problem of potential species differences and the possibility that the medications of interest may have different effects on the brain of an individual with MDD or BPD than on the normal brain. Despite the limitations of each of these three approaches individually, convergent findings across approaches should lead to reasonable, if provisional, conclusions about the influence of medications on the brain measures of interest.

Postmortem human studies may be most informative when conducted within the context of animal investigations that have characterized the neural circuitry of interest. One obvious gap in this regard is the relatively little knowledge that exists (aside from topographic patterns of regional connectivity) about the actual circuitry and functional architecture, in the primate brain, of the cortical regions implicated in mood disorders. Both the design and interpretation of human postmortem studies will be improved by an integration with parallel animal studies of the same systems of interest.

Finally, we regard the evidence presented in this review as offering very strong support for the view that depression refers to a heterogeneous group of disorders. It is possible that depression-spectrum disorders can be produced by abnormalities in many different parts of the circuitry reviewed. The specific subtype, symptom profile, and affective abnormalities should vary systematically with the location and nature of the abnormality. It is likely that some of the heterogeneity that might be produced by deficits in particular components of the circuitry reviewed will not map precisely onto the diagnostic categories we have inherited from descriptive psychiatry. A major chal-

lenge for the future will be to build a more neurobiologically plausible scheme for parsing the heterogeneity of depression based on the location and nature of the abnormality in the circuitry featured in this review. We believe that this ambitious effort will lead to considerably more consistent findings at the biological level and will also enable us to more rigorously characterize different endophenotypes that could then be exploited for genetic studies.

Computational Approaches

Although few efforts have so far been made to model depression computationally, this approach has tremendous potential. Computational models provide mechanistic accounts of psychological processes and have been used to understand both normal cognition and its disorders in neurologic and psychiatric disease. Among the particular strengths of computational models, which would be of great help in research on depression, are the ability to integrate theorizing at different levels of explanation (e.g., neurochemical, psychological) and the ability to capture complex causal pathways by which phenomena "emerge" from multiple interacting factors.

THE CURRENT STATUS OF THE FIELD. Computational modeling has played two roles in cognitive science, each of which can be applied to the study of affective disorders. The first is a very general one, involving theories with computational concepts such as encoding, search, networks, and spreading activation. Examples of the application of these models to affective disorders can be found in the literature on mood and cognition (e.g., Williams et al 1997). This work has shown how models of memory and attention from cognitive psychology can be extended to explain mood effects in normal individuals and in those afflicted with depression.

The other role for computational modeling in cognitive science is more explicit, involving fully implemented running computer simulations. These models are in some ways more powerful than the first type. They can offer explanations of psychological phenomena that are not intuitively obvious, because the number of interacting causal factors or the nature of their interactions exceeds our ability to think precisely about them. For example, behavioral dissociations after brain damage can be modeled without separately lesionable components (e.g., Farah 1994), qualitatively different developmental stages can be modeled with a continuous learning process (Rumelhart and McClelland 1986), and seemingly disparate components of a syndrome or disease can be modeled with a single underlying abnormality (Cohen and Servan-Schreiber 1992).

Connectionist computational models, in which the individual computational units function as simplified neurons, allow us to test hypotheses relating neuronal function at the cellular or neurochemical level to system function at the behavioral level. The best-known example of such a model in psychopathology comes from Cohen and Servan-Schreiber (1992). They simulated the abnormalities in dopamine levels of patients with schizophrenia by altering the activation function of the units in a connectionist network. The resultant effect on network behavior was to impair performance in a number of cognitive tasks that are, in fact, affected by schizophrenia. Analogous work in affective disorders would provide a much-needed link between the multifaceted neurochemical and behavioral abnormalities in these disorders.

A VISION FOR PROGRESS. Despite the success of computational approaches within the study of many aspects of human cognition and in many areas of cognitive neuroscience, there is relatively little work to date that relates explicitly to the modeling of mood, mood regulation, and mood disorders. There have been some important strides taken in models of the processes that lead to reward signals that may be instrumental in influencing positive affect and a positive cognitive outlook, and may provide the motivation that ordinarily serves to promote instrumental behaviors such as problem solving, goal seeking, and the expenditure of effort (Montague et al 1996). Moreover, there is every reason to believe that such an effort can be undertaken, with vast potential for enhancing our understanding of mood disorders, their neural substrates, their developmental antecedents, and their possible amelioration and remediation through retraining and rehabilitation studies.

The time is at hand to launch an effort to apply models to affective/mood issues and their disorders. Models of the sort that have been used to model cognitive processes, their disorders, and their links to the neural substrates provide an excellent starting place for this for several reasons:

1) Many of the processes that have been modeled already are affected by affect and are compromised in mood disorders. For example, as discussed earlier in this report, depression gives rise to impaired performance on tests of cognitive abilities, particularly those that depend on the maintenance of concentration and attention for adequate performance. Depression is also known to affect neuromodulatory systems that have been implicated in existing models of cognitive control (Cohen and Servan-Schreiber 1992). Thus it appears likely that certain aspects of the disordered thought processes observed in depression might be accounted for by fairly straightforward extensions of existing models.

2) It is unlikely that there are sharp boundaries between cognition and affect, and thus good models of mood and affect will necessarily incorporate models of cognition. For example, negative cognitions about outcomes and self-efficacy are known to predispose individuals to depression in response to stressful life events. The development of explicit models of the formation and maintenance of such cognitions will necessarily play a part in any attempt to understand the etiology of those forms of depression that are affected by negative cognitions.

3) The kinds of mechanisms that have been explored in models of other cognitive processes are likely to prove useful in modeling affect. These mechanisms include a) the use of recurrent excitatory and inhibitory interactions among neurons to mediate competition between alternative cognitive states and to support the maintenance of a particular cognitive state in the face of competing inputs; and b) the use of a relatively diffuse signal such as that which may be provided by dopamine and other catecholamines to modulate excitatory and inhibitory interactions among neurons, thus providing a starting place for capturing the effects of such systems on cognitive and affective processes and for capturing the effects of disturbances in such systems on affect and cognition.

4) Models are particularly helpful for understanding the effects of experience on mental processes; this should be as true for affective as it is for cognitive processes. Several aspects of mood disorders are relevant here. For example, models of cognitive processes that address how cognitions arise from experience could be developed to account for some aspects of the impact of negative child-rearing practices, including maladaptive inferential feedback from parents, on the emergence of maladaptive inferential cognitions in children. Experience-sensitive models may also account for kindling effects, whereby an initial depressive episode elicited by a stressful life event could then predispose an individual to future episodes of depression. Finally, experience-sensitive models might also suggest specific ways in which the experience of depressed individuals might be manipulated to help the individual develop more positive thought processes and behavioral coping strategies that might reduce the likelihood that negative life events would trigger a depressive episode and/or increase the likelihood of pulling out of the episode once triggered.

CHALLENGES AND OPPORTUNITIES. The challenges and opportunities are closely interlinked. Modeling proceeds most effectively when individuals who are expert in the phenomena in question join forces with individuals who know and understand available modeling tools. A tremendous opportunity exists for breakthroughs in our understanding of mood disorders comparable to those that have been provided by models in areas such as reading and executive function, if only researchers with expertise in modeling can be brought into the effort to understand mood and affective disorders. This opportunity will be enhanced further if these individuals join forces with others who are experts in affective processes, their disorders, and/or the neural substrates thereof. Such an interdisciplinary effort will be strengthened by training programs that explicitly foster such cross-disciplinary links.

Developmental Approaches

Capacities unique to developmental stages will almost certainly yield correspondingly unique biological correlates of mood states and mood regulation across the life span. Given that a person's interpretations of changes in consciously detected internal tone occurring within particular contexts is a central feature of every human emotional state, these interpretations should be accompanied by new emotions as those interpretations are affected by maturing cognitive competencies and experiential knowledge. Depression, like most affective constructs, is not a unitary state defined by one physiologic profile or one pattern of behavior or self-report, but refers to a family of states, and thus the sadness ascribed to infants and very young children is likely to be different, perhaps qualitatively, from the depression ascribed to adolescents and adults.

Evidence suggests, for example, that important cognitive transitions occur in children between 6 and 12 months, 1 and 4 years, 5 and 8 years, and at puberty (Piaget 1952; Tomasello 1999). The human infant during the first year does not impose interpretations on events, whether external or internal. The apathy often observed in neglected infants is therefore likely to be the product of insufficient variety in experience, malnutrition, illness, or acquired reactions to imposed distress. During the next 2 years, children become aware of the concept of right and wrong actions, conscious of their feeling tone and intentions, able to infer the feelings and thoughts of others, and able to impose symbolic constructions on events. As a result, 3–4-year-olds can appear depressed because of empathy with the distress of another, or because the child categorized the self as one who violates family rules and, therefore, is a "bad" child. By age 4, most children also automatically integrate a present event with the relevant past and, as a result, become vulnerable to a sadness that is derivative of the comparison of a present state with a more desirable state of affairs from the past.

At age 5 or 6, most children from industrialized societies have the capacity to mentally re-run a past behavioral sequence and attribute causality to it. This allows a child to experience guilt for the first time when he causes

distress to another person because he is now able to reflect on the asocial act and realize that he could have suppressed it. Infants feel neither shame nor guilt when they throw food on a clean tablecloth; 2-year-olds will feel shame; 6-year-olds will feel guilt (Lewis 1992; Zahn-Waxler et al 1991).

Children at this age also have the capacity to compare a diverse set of events on the same dimension or property. This competence, which Piaget called seriation, is revealed when children given a set of six sticks of varying length arrange them in a pattern from shortest to longest. This capacity permits children to compare themselves with others on attributes of concern to the child, like strength, size, attractiveness, popularity, and varied skills. The results of that comparison create a new emotional state. If the child judges that she possesses less of a desired characteristic than a sibling or friend, she may experience an emotional state for which there is no consensual name. This state could be called self-doubt, sadness, or low self-esteem. Younger children may be less likely to experience this emotion.

New cognitive abilities emerge during the adolescent years. One is the detection of semantically based, logical inconsistencies among one's beliefs about a theme. Recognition of these inconsistencies renders the adolescent vulnerable to a state some might call dissonance. This capacity can generate new members of the family of depressive affects. For example, an adolescent recognizes the inconsistency between his fantasy that his father is a wonderful man and the fact that the father is a vocational failure. This state differs from the guilt of the 6-year-old, because the adolescent has not violated community or personal standards. Another new intellectual competence is the capacity to be convinced that one has exhausted all possible solutions to a problem. If the problem involves the adolescent's security, safety, or acceptability to others, the conviction that no coping action is possible can lead to an emotion some might call the depression of hopelessness. This state can motivate a suicide attempt. Because the cognitive competence of a young child is vastly different from that of an adult, the state of a 7-year-old who tried to kill himself with a knife should not be compared with the state of a pregnant adolescent who tries to do the same.

Thus, defining cognitive competencies are potentially as significant for nosology as are the verbal descriptions of depressed feelings; however, because the feelings are salient to the patient, and drugs are better able to alter feelings than to change beliefs or living conditions, it is understandable that psychiatrists have made the felt emotion the defining feature of the clinical syndrome. The itch that accompanies a body rash is also salient, but the itching is a sign, not the cause, of an ailment that could be the result of a multitude of causes. Selection of the best therapy for the rash requires understanding its etiology, and the same is likely to be true of depressive conditions. If the central features of depressive disorder—sadness, apathy, low energy level, sleeplessness, and poor appetite—occurred in a middle-class 8-year-old who had failed to meet a high standard on academic achievement promoted by the family, the profile is more properly called a guilt reaction. If a description of the same symptoms came from an adolescent from a poor family who, in addition, was failing in school and was convinced of the futility of improving her life, a more correct label is a depression of hopelessness. Finally, some youths who report the same symptoms may have inherited a biological diathesis for depression, a category that used to be called endogenous depression. These three patients may belong to different categories, even though all report sadness and apathy. The conflation of the causes of these various depressive symptom types across vastly different developmental stages is likely responsible for the dearth of replicable neurobiological findings in studies of depressed children and adolescents and for the failure thus far to develop even a rudimentary neurobiological model of depressive illness in children.

Progress in this field will require several lines of investigation. First, longitudinal studies in different populations are required to gather prospective data on children at risk, to see which combination of pedigree, temperament, experiences, and biological indices are predictive of one of the depressive syndromes. Second, this work will require funding of investigators to develop psychological procedures (tasks and behavioral paradigms), other than interview and questionnaire, to assess the affective state of the child. For example, shy, inhibited children show Stroop interference to words that refer to shy, isolated behavior. Similar procedures should be developed that refer to states of sadness in depression (Kagan 1981, 1998). Third, work should begin on other biological measures (EEG, event-related potentials (ERP), biochemical indices), to work toward profiles of biological measurements that might be sensitive correlates or predictors of one or more categories of depressive illness. Again, previous studies of biochemical measures in children have likely not been successful due to the study of heterogeneous phenotypes. Fourth, translating these advances to the definition of specific and effective prevention and intervention strategies is required.

FUTURE DIRECTIONS AND CHALLENGES. Several kinds of research efforts have high priority. First, the field needs to determine whether some infants inherit a temperamental vulnerability to a state of depression that is preserved from infancy through adolescence. This ques-

tion will require a longitudinal study of a large group of infants, some of whom should be at risk for depression, and the assessments should include behaviors, physiology, cognitive competencies, and reports of feeling states. This research will require developing standard protocols that include all four sources of information to determine the coherence of these measurements in children and adolescents who appear to observers to be apathetic or depressed. Also needed is knowledge of whether the physiologic and psychological profiles that accompany affects in one developmental stage are the same across stages of cognitive development. The gender difference in the prevalence of adolescent depression should be better understood.

One or more longitudinal studies of children at risk for the development of affective illness from a variety of social and ethnic backgrounds has the highest priority. These studies will permit us to determine the contribution of early biological vulnerability and experience to the later development of pathology. It should also allow us to determine which combination of biological vulnerability and experience is related to the different categories of affective illness. These studies should gather not only interview data, but they should also gather psychological and biological measures, including imaging, biochemical, and electrophysiological measures.

Longitudinal studies of high-risk populations are also required to begin identifying which measures that differ between groups are relevant to pathophysiology, which are epiphenomenal, and which are adaptive or compensatory. Sorting out from cross-sectional studies alone which group differences are central to the process being investigated and which are compensatory effects is exceedingly difficult. This is particularly true when studying regulatory processes in the brain, including processes that regulate mood and affect. Some of the activations that are seen may be a function of regulatory processes that are either automatically or voluntarily invoked to attenuate or suppress unwanted negative affect or to sustain positive affect. Moroever, because of important developmental changes in regulatory processes and in prefrontal and anterior cingulate mechanisms that presumably underlie some of these developing competencies, developmental differences in patterns of brain activation may in part reflect maturational changes in regulatory abilities.

Engagement of circuitry that presumably reflects regulatory or suppressor processes is commonly observed in tasks where suppression of an automatic response is required either explicitly or implicitly. For example, activations of anterior cingulate and inferior prefrontal cortex have been reported in Stroop interference and go-no-go tasks (Bush et al 1998; Carter et al 1995; Leung et al 2000; Pardo et al 1990; Peterson et al 1999), and in studies of pain (which require subjects to inhibit withdrawal of the painful extremity) (Craig et al 1996; Derbyshire et al 1997, 1998; Talbot et al 1991) and itch induction (subjects are not allowed to scratch) (Hsieh et al 1994). Clearly, successful pain reduction or antipuretics would reduce both the noxious stimulus and the behavioral response that is intended to remove, alleviate, or adapt to the stimulus, and therefore normalization of these activations with successful treatment would not prove that the activations represented either the neural substrate of perceiving the noxious stimulus or the inhibited attempt to adapt to them. These same difficulties of interpreting cross-sectional findings also plague imaging and neurobiological studies of mood regulation and affective illness (Baxter et al 1985; Bench et al 1992; Drevets et al 1997; George et al 1995; Lane et al 1997; Mayberg et al 1999; Nobler et al 1994; Pardo et al 1993; Schneider et al 1995). Studies of treatment response or symptomatic remission provide little help in sorting out findings that represent the core process of interest (e.g., dysphoric mood or depressive illness) from those that represent either effects intended to compensate for that process or that are its downstream or epiphenomenal effects (Bench et al 1995; Buchsbaum et al 1997; Mayberg et al 1999). Adaptation to the presence dysphoric mood and affect will likely alter broadly distributed adaptive systems throughout the brain. Repeated and chronic activation of these brain regions is likely to induce plastic changes in the underlying neuronal structural and functional architecture. It is therefore imperative that we find ways to study the neural substrate of mood and affective illness before the initiation of chronic compensatory changes. This may mean extending our imaging techniques to progressively younger age groups or to high-risk cohorts to identify trait rather than state markers of central nervous system functioning that predispose individuals to particular patterns or disturbances in regulation of mood or affect. “High risk” may mean the traditional unaffected but genetically vulnerable members of high-density families, or it may mean individuals who have particular characteristics, such as a temperament or cognitive profile, or adverse psychosocial experiences, that place them at an elevated risk for developing disturbances in mood or affect. Identifying trait abnormalities in vulnerable but minimally affected individuals would help to disentangle cause from compensatory effect. Following these individuals prospectively would then allow the study of state disturbances early in their course, before chronic compensatory mechanisms would exert their neurobiological effects. It must also be emphasized that some aspects of mood disorders or certain mood disorder subtypes may themselves reflect failures of regulatory processes and not primary disturbances in the mechanisms of emotion generation. Such a model would predict the expression of

symptoms only during those developmental stages when regulatory processes are known to emerge and not before.

Recommendations for NIMH Priorities

We provide recommendations in five specific areas: 1) the behavioral domain; 2) the neural domain; 3) the domain of behavioral-neural interaction; 4) training; and 5) dissemination.

Behavioral Domain

1. Examine relations among experimental/behavioral measures of mood and cognition, phenomenology, and clinical diagnoses. This is particularly needed for bipolar disorders. This effort would involve research aimed at developing a mechanistic account of the manner in which cognitive and affective vulnerabilities culminate in psychopathology, including the use of computational approaches.
2. Examine the nature of the vulnerability/stress interaction, with stress conceptualized broadly to include medical conditions, major life transitions, as well as more traditional stressors. As part of this effort, we need research designed to develop better measures of the environment, and we need to identify those specific environmental variables most important for the development of mood disorders.
3. Foster connections between experimental studies of mood and emotion in normal individuals with research on patients with mood disorders. These two research traditions have developed remarkably independently and they each have something important to contribute to the other.
4. Study protective mechanisms and resilience. There has been insufficient attention paid to the factors that promote resilience and buffer individuals from the impact of significant environmental stress. Identifying these factors could help in the development of more effective treatment strategies.

Neural Domain

1. Study the human brain to identify the circuits that are relevant to the understanding of mood, the connections among the structures within these circuits, and the developmental changes that occur both anatomically and functionally. This effort should take advantage of new noninvasive imaging methods available to probe human brain function and structure, including measures sensitive to connectivity (e.g., diffusion tensor imaging).
2. Develop a national effort to create the infrastructure for postmortem studies that promote appropriate tissue preparation and clinical characterization. Insufficient use has been made of postmortem studies of mood disorders, in part because of the lack of a systematic effort of this kind. The National Institute on Aging (NIA) funded Alzheimer's Disease Research Centers provide a compelling, and replicable, example of a type of national effort that has resulted in both an increase in the number of brain specimens available for study of this illness, and equally important, of a uniform approach to diagnostic and other procedures. For postmortem studies of psychiatric disorders, the relative merits of national versus local brain banks have been debated; however, the substantial need for more well-characterized brain specimens, especially from subjects with BPDs, suggests that both strategies are needed. It is, of course, obvious that an increase in the number of brain specimens will only produce useful advances in our knowledge of the neural basis of mood disorders if the studies utilizing these specimens are conducted in a rigorous fashion with appropriate attention to the potential confounds of such studies. Toward that end, the development of a consensus statement on the types of information that should be included in experimental design and in the reporting of experimental results from postmortem studies, similar to the Consolidated Standards of Reporting Trials (CONSORT) statement used for randomized clinical trials (Moher et al 2001), is recommended.
3. Continue the development of nonhuman animal models of mood and mood disorders, specifically with the goal of discovering animal homologs of human brain mechanism involved in mood and affect. Foster research designed to elucidate the underlying brain mechanisms through invasive studies, including exploration at the microarray level that can only be carried out in animals. Encourage research that explicitly seeks to examine parallels between mechanisms in humans and nonhuman animals.

Domain of Neural-Behavioral Interaction

1. Distinguish between the neural circuitry associated with emotion/mood on the one hand and the regulation of mood on the other, using experimental probes and imaging methods. This effort is required in both normal individuals and patients with mood disorders to specify where abnormalities reside and to help parse heterogeneity within the disorders.
2. Study pathologic plasticity by examining the impact of negative life events on the circuitry of positive and

negative affect longitudinally. Such longitudinal studies are critically needed to determine whether certain anatomical abnormalities precede or follow the development of symptoms.

3. Develop computational models that allow exploration of the emergent functional properties of hypothesized neural mechanisms underlying mood and mood disorder. Encourage the use of these models to explore the ways in which disorders in the neural mechanisms lead to disorders of affect, cognition, and behavior. Foster development of models that explain how experience alters affect, cognition, and behavior, and encourage efforts to apply such models to the development of novel approaches to prevention, amelioration, and treatment of mood disorders. Encourage integration of modeling with experimental investigation to ensure that each research approach benefits from the insights provided by the other.
4. Develop neurally inspired behavioral methods of affective rehabilitation that utilize brain-based behavioral strategies to train functions that might be impaired and use imaging to track changes in the hypothesized neural substrate. It is likely that any such training that might produce beneficial effects will require intensive practice and thus will only be appropriate for certain types of patients.
5. Determine the relationship between cognitive and affective vulnerabilities identified through self-report and behavioral methods and neural vulnerabilities identified through neuroimaging. The study of such vulnerabilities in the behavioral and neural domains has proceeded almost entirely independently and it is critical that these two approaches seek rapprochement.
6. Examine the relationship between emotion, mood, and temperament on the one hand, and phasic and tonic features of brain function on the other. It is important to determine whether the phasic and tonic features identified in affective circuitry are related to the traditional constructs of state and trait affect.
7. Develop behavioral probes of affect and affect regulation that can be used identically across species (particularly with nonhuman primates) along with simultaneous measures of brain function. This will significantly advance the use of nonhuman primate models and will greatly facilitate cross-species comparisons.

Training

1. Foster interdisciplinary training that combines psychology, psychiatry, and neuroscience. This is greatly needed to prepare the next generation of scientists to make significant progress in this arena.

Dissemination

1. Impart new knowledge to clinicians and the lay public. Increase opportunities for scientists to interact with these constituencies.

Great advances have been made in the past decade in the behavioral and neuroscientific study of mood and mood regulation in both normal individuals and in patients with mood disorders. We are beginning to see increasing evidence of interdisciplinary research that takes advantage of behavioral and neuroscientific approaches and gathers data from both realms in the same patients. Such efforts need to be strengthened. A relative paucity of research on mood regulation and mood disorders in children has been performed. Such work needs to include longitudinal studies of developmental changes in both brain function and structure and in the skills of mood regulation. Research progress in this area critically depends on training a new generation of affective neuroscientists who have expertise in behavioral, neuroscientific, and computational approaches. The burgeoning interest in this topic along with the development of new methods and tools to probe human brain function bodes well for important breakthroughs in the future.

This manuscript is one of ten prepared by workgroups under the auspices of the National Institute of Mental Health (NIMH) strategic planning initiative for mood disorders research. Each of the workgroups was given the specific charge to 1) review the state of their assigned area; 2) identify gaps and state a vision of where the field should be going and why; and 3) make general recommendations for NIMH to consider regarding research initiatives that would advance and improve the knowledge and treatment of mood disorders. This document reflects the opinions of the authors and not those of NIMH, but was used in an advisory capacity while the actual strategic plan was developed by NIMH staff. Overall guidance was provided by the National Advisory Mental Health Council.

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