Neuropsychology of Depression and Related Mood Disorders

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Tremendous strides have been made toward understanding the neuropsychological, neuroanatomical, and neuroimaging findings associated with depression. Whereas understanding of the neuroanatomical networks involved in depression and related mood disorders remains in an adolescent phase, neuropsychological findings in depression and related mood disorders are fairly well codified at this point. To be sure, there are a number of clinical and demographic features that substantially impact cognitive performance in the context of a mood disorder, including later age of onset, polypharmacy/substance abuse, medical complications, greater severity, and resistance to traditional treatments. Whereas the “causes” for depression-associated cognitive difficulties are heterogeneous, the co-occurrence of features of depression and cognitive difficulties of specific types suggests a common set of neural networks that may be adversely affected, including medial and ventral frontal, limbic, and basal ganglia structures. The present chapter is intended to provide the reader with a blend of traditional neuropsychological investigations of depression and related mood disorders, hereafter referred to generally as mood disorders, in addition to integrating the latest cognitive and affective neuroscience research. We will review the moderating impact of age of onset, effort, subtypes of depression, and medications on cognitive functioning in mood disorders, as well as research using cognitive measures as predictors of treatment response.

The present chapter follows several previous chapters on depression and depression-related cognitive difficulties by King and Caine (1996) and Caine (1986) in earlier editions of this book. As King and Caine note in the previous edition of this book, study of cognition in mood disorders has moved from being a nuisance when studying late-life dementias, also known as pseudodementia, to a full fledged area of inquiry. The underlying assumptions about mood disorders as being functional and not organic disorders have now been assailed on a number of different fronts (Tucker et al., 1990). In fact, it is now best to consider mood disorders under a category of “potentially reversible cognitive decrements” (Sobow et al., 2006), although the careful reader of this chapter will come to appreciate that for some individuals, the cognitive difficulties that co-occur with depression are in no way reversible. This characterization may sit poorly with many in a field christened in the tradition of degenerative dementias, wherein dysfunction is the inevitable, and currently irreversible, sequelae of neurological disease. However, as studies of disorders such as multiple sclerosis and Huntington’s disease have aptly informed the field, assumptions about “functional” disorders can be largely misplaced (Ghaffar & Feinstein, 2007). This is by no means to associate the frequently present, moderate cognitive inefficiencies observed in depression to those more severe, highly prevalent, and persistent difficulties observed in degenerative conditions. Rather, the purpose is to place the field
and the reader in the proper pose of humility when making inferences about the current state of knowledge in brain–behavior relationships in mood disorders. Mood disorders, like any other psychological phenomena, have the central nervous system (CNS) as the wellspring for their existence, and many of the same tracts and systems implicated in neurological disorders are similarly implicated in mood and other psychiatric disorders (Cummings, 1993).

The burgeoning fields of affective and cognitive neuroscience, as well as the expanding body of knowledge on mood disorders from traditional neuropsychological investigations, together make a chapter on the neuropsychology of mood disorders no small endeavor. There are many allied areas of inquiry that are not seamlessly integrated into one theory, model, or basis for understanding of the brain–behavior relationships most typically observed in mood disorders. Given this challenge, we have attempted to balance specific and important areas of inquiry within mood disorders with the more general purview that one might typically expect from a book chapter. We make no pretense of being exhaustive in breadth or depth, but do hope that the present chapter provides a ample overview of general areas along with very specific subtopics that we feel the reader might most benefit from. We begin with an overview of what might be considered a typical cognitive profile of a depressed patient, based largely on the traditional neuropsychological studies of depression. We move from these to discuss neuroanatomical and neuroimaging evidence currently available in mood disorders research. The neuroimaging data largely rely upon cognitive and affective neuroscience research. We then delve into critical mediating factors in understanding brain–behavior relationships in mood disorders. This is a necessary and, we believe, very valuable overview of factors that directly relate to what extent cognitive difficulties might be expected to occur in mood disorders. We will also highlight some specific subtypes of mood disorders that illustrate potential brain–behavior relationships, or where greater prevalence or severity of cognitive difficulties might be expected. We review potential medication effects in depression, as this is likely a frequent question that arises in the neuropsychological assessment of mood disorders. The chapter closes with several compelling studies that have used neuropsychological and cognitive/affective neuroscience measures to predict treatment response, a summary, and some recommendations for what a “core” battery might be comprised of when assessing a patient with a mood disorder.

Traditional Studies and Cognitive Profile

Major depressive disorder (MDD) is associated with inefficiencies in various cognitive domains (Austin et al., 2001, p. 57; Miller, 1973; for reviews see Elliott, 1998; Rogers et al., 2004) including attention (Cornblatt et al., 1989; Porter et al., 2003; Weiland-Fiedler et al., 2004), psychomotor speed (Sobin & Sackeim, 1997), executive function (Grant et al., 2001; Paelecke-Habermann et al., 2005), and memory (Austin et al., 1992; Brown et al., 1994; Burt et al., 1995; Elliott et al., 1996). It is well known that intragroup heterogeneity of cognitive decrements exist, though the reasons are still not completely clear. Possible mediating factors, some of which are addressed later in this chapter, include the age of onset, age of participants, premorbid level of cognitive function, symptom severity, number of previous depressive episodes, effort and motivation, medication status, patient status (inpatient or outpatient), state of the individual (i.e., remitted or depressed), and history of hospitalization (Elliott, 1998; Fossati et al., 2002; Gualtieri et al., 2006). As such, drawing conclusions regarding cognitive decrements in MDD is challenging because studies often utilize a depressed group of heterogeneous individuals varying in aforementioned characteristics. Furthermore, many such studies are powered only to detect large and very large effect sizes and also typically use tasks designed to assess for obvious brain injury or neurodegenerative conditions.

In this section, we review cognitive decrements in adults who are under the age of 65 as other neurological factors often contribute in the disease process in geriatric or late-onset depression. The specific topic of late-onset depression is discussed in the Age of Onset section in this chapter. Readers can also find several excellent articles on neuropsychological
dysfunction in geriatric depression (Bieliauskas, 1993; Elderkin-Thompson et al., 2007; Marcos et al., 2005; Sheline et al., 2006; Wright & Persad, 2007). We focus on domains of attention, psychomotor speed, executive function, and memory, which are the areas that have been most researched and found to be pertinent to MDD (Bulmash et al., 2006; Gualtieri et al., 2006; Landro et al., 2001; Porter et al., 2003). We also understand that sorting neuropsychological measures into different constructs may be arbitrary as one measure usually taps more than one cognitive domain. Furthermore, attention, working memory, processing speed, and executive function mainly involve the common structures in the frontal–subcortical neural networks (Cummings, 1995; Mega & Cummings, 1994).

Attention
Research on attention in MDD suggests that although simpler attentional processes may not be affected in adult depressed patients (Harvey et al., 2004; Ravnkilde et al., 2003), more complex attentional processes such as working memory or sustained attention are often compromised in patients with MDD (Porter et al., 2003; Rose & Ebmeier, 2006) and even in remitted individuals in some cases (Weiland-Fiedler et al., 2004). Hartlage et al. (1993) noted that depressed individuals have more difficulty on tasks that require effortful processing compared to tasks that are simpler or require automatic processing. Indeed, some studies of attentional processing in MDD have shown that short-term attention such as the forward digit span is generally unaffected compared to more difficult working memory tasks (Harvey et al., 2004; Ravnkilde et al., 2003). For example, Harvey et al. (2004) found that short-term attention on forward and backward digit span and forward spatial span did not differ between 22 young inpatients with MDD and 22 normal controls, while poorer performance was found in the patient group on a backward spatial span task and a verbal n-back task. However, their results did not fully support an automatic versus effortful processing hypothesis as they failed to find a group and complexity interaction (i.e., the patient group did not do disproportionately worse as the task became more difficult). By way of background, the automatic effortful hypothesis states that depressed individuals should incrementally show poorer performance as the degree of effort required on any given task increases (Hasher & Zacks, 1979). Similarly, Rose and Ebmeier (2006) examined working memory in 20 patients with MDD (in or outpatients, most of who were on antidepressant medications) and 20 healthy controls by using a different version of n-back task. The researchers found slower reaction times and reduced accuracy in the MDD group compared to the control group in a linear fashion, again, with no disproportionately slower reaction time and decreased accuracy with increasing cognitive load, suggesting a more uniform pattern of weakness rather than an automatic/effortful continuum.

In tasks of sustained attention, individuals with MDD were shown to make more omission errors (Langenecker et al., 2007a, 2007b; Porter et al., 2003; Sevigny et al., 2003) and commission errors (Farrin et al., 2003; Porter et al., 2003) on continuous performance tests (CPTs). In addition, individuals who were in euthymic or remitted states were also shown to demonstrate persistent difficulty with sustained attention. Recently, Weiland-Fiedler et al. (2004) found decrements in 28 fully remitted, unmedicated individuals with a history of MDD compared to 23 healthy controls on the Rapid Visual Information Processing Task of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Paelecke-Habermann et al. (2005) also found continued attention difficulty in remitted individuals with MDD. Although the aforementioned studies demonstrated attentional inefficiencies in euthymic and depressed states, Grant et al. (2001) did not find differences on the digit span task and a CPT in 123 nonchronic, MDD outpatients and 36 healthy controls. The dependent measures reported by Grant and colleagues were different from the measures reported by other researchers (Harvey et al., 2004; Porter et al., 2003; Sevigny et al., 2003).

Psychomotor Speed
Research on psychomotor speed in mood disorders has shown inconsistent findings. Some
Executive Functioning

Research has shown that individuals with MDD demonstrate decrements on tasks that are presumed to measure executive function (Grant et al. 2001; Langenecker et al., 2005; Paecke-Habermann et al., 2005; Porter et al. 2003). Executive function tasks in neuropsychological assessments involve various functions including concept formation, set-shifting, planning, inhibition, working memory, and fluency (Brown et al., 1994; Miyake et al., 2000). Some of the commonly used tests to assess executive dysfunction both in research and clinical settings include the Wisconsin Card Sorting Test (WCST; Channon, 1996; Grant et al., 2001), tests of verbal fluency (for a review see Henry & Crawford, 2005), the Stroop interference test (Harvey et al., 2004; Markela-Lerenc et al., 2006), Trail-Making Test Part B (Grant et al., 2001; Harvey et al., 2004), the Tower of London test (Naismith et al., 2006; Porter et al., 2003), and the Halstead–Reitan Category test (Grant et al., 2001).

Individuals with depressive symptoms have been shown to complete fewer categories and make more perseverative responses on the WCST (Channon, 1996; Grant et al., 2001), although inconsistently (Fossati et al., 2001; Ravnikilde et al., 2003), Grant et al. (2001) compared 123 outpatients with MDD to 36 healthy controls on the WCST and found that the MDD group completed a fewer number of categories, made more perseverative responses and errors, and more often failed to maintain set and learn. No difference was found, however, on the other measures of executive functioning including the Halstead–Reitan Categories Test, letter fluency, and Trail-Making Test Part B. Ravnikilde et al. (2003) found no difference on the WCST between 40 inpatients with MDD and a group of 49 controls. The researchers did find that Stroop word reading, color naming, and interference were all poorer in the MDD group compared to the healthy control group. Harvey et al. (2004) reported that the depressed group did not differ from the control group on the word reading condition of the Stroop test while they performed worse on the color naming and interference conditions. The researchers also found slower completion times on the Trail-Making Test Part B. Fossati et al. (2001) did not find a significant difference between 22 depressed inpatients and 22 healthy controls on the modified WCST but found a difference on the spontaneous condition of the California Card Sorting Test (Delis et al., 1992). Individuals with MDD were found to generate fewer words on verbal fluency tasks (i.e., a lexical fluency test and on the ‘exclude letter’ fluency test) in some studies (Porter et al.,...
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2003) but not in others (Harvey et al., 2004; Naismith et al., 2006). No difference was found between the MDD and normal controls on the Tower of London test (Naismith et al., 2006; Porter et al., 2003).

Memory

Although many studies have shown decreased memory function in patients with MDD (Austin et al., 1992; Bornstein et al., 1991; Brown et al., 1994; Burt et al., 1995; Elliott et al., 1996), the findings again do not show consistent patterns or severity of memory impairment (Basso & Bornstein, 1999; Brand et al., 1992; Fossati et al., 2002). In addition, the initial acquisition process seems to be more affected than retrieval in depressed individuals, as evidenced by decreased initial recall as well as decreased delayed recall and recognition (Austin et al., 1992; Basso & Bornstein, 1999; Ravnkilde et al., 2003). This is likely associated with the affected attentional processes that are interfering with the encoding process. Austin et al. (1992) indicated poorer performance on initial acquisition and delayed recall and recognition portions of the Rey Auditory Verbal Learning Test (RAVLT) in two depressed patient groups (“endogeneous” and “neurotic”) compared to controls. In contrast, Grant et al. (2001) failed to find differences in memory function in 123 MDD outpatients compared to controls on the Hopkins Verbal Learning Test (HVLT) and on the Visual Reproduction subtest of the WAIS-R. Hasher and Zacks (1979) proposed that memory dysfunction in depression is likely demonstrated with more complex tasks that require effortful encoding rather than less effortful or automatic encoding processes. Rohling and Scogin (1993) examined 30 depressed patients (21 outpatients and 9 inpatients), 20 psychiatric controls, and 30 normal controls on measures that appeared to be more challenging such as paired-associate learning or free recall tasks versus measures that were presumed to be easier such as memory for frequency of occurrence or spatial locations. The researchers noted that as there were no significant correlations between the measures of depression severity and the measures of effortful memory, their results failed to support Hasher and Zacks’ hypothesis. Porter et al. (2003) utilized recall versus recognition memory tasks (presuming that the recall tasks are more difficult than recognition tasks) to examine Hasher and Zacks’ hypothesis. The researchers found that the only difference between the medication-free MDD group and the normal group on the RAVLT was the distractor list recall without any evidence of proactive interference. In contrast, the researchers found that the MDD group performed poorer on measures of recognition memory (memory for visual information such as patterns and spatial locations on the CANTAB compared to the control group).

As mentioned, the number of recurrent depressive episodes and inpatient status may be associated with poorer memory function. Basso and Bornstein (1999) studied 20 single-episode depressed inpatients and 46 recurrent depressed inpatients and found a greater memory dysfunction in the recurrent group compared to single-episode patients on the California Verbal Learning Test—Second Edition (CVLT-II) measures including total initial recall, learning curve, short-delay cued recall, long-delay free and cued recall, and recognition discrimination. Ravnkilde et al. (2003) did not find a difference in learning and memory on the Luria Verbal Learning Test but found a difference on the immediate recall of the Logical Memory Test of the WAIS and immediate and delayed recall on the Visual Reproduction Test of the WMR-R between 40 medicated depressive inpatients and 49 normal controls. More positively, memory decrements appear to subside in remitted individuals. Weiland-Fiedler et al. (2004) did not find any difference in memory acquisition on the CVLT-II between a group that consisted of 28 fully remitted, unmedicated individuals with a history of MDD and a group of 23 healthy participants.

Neuroanatomy of Mood Disorders

Limbic, frontal, and subcortical areas have been strongly implicated in depression and related mood disorders (Alexopoulos, 2002; Carroll et al., 1976; Drevets & Raichle, 1992; Goldapple et al., 2004; Mayberg et al., 1994; Videbech, 2000), although it should be noted that these areas are implicated in a number of disorders for which dysfunctions in mood and affect are not always present (Nilsson et al., 2002; Owen, 2004;
Van Praag et al., 1975). The relationship of mood and cognitive disturbance to neuroanatomical abnormalities remains somewhat tenuous, as few studies have examined these relationships with sufficient sample size and measurement specificity. This section will review several structures shown to be affected in mood disorders but will not exhaustively review the many studies that have been completed of morphometry in mood disorders. There is specific focus on studies with larger samples, better clinical characterization, and attempts to look at the relationship between cognitive or affective variables and brain morphometry when possible. Functional imaging studies are reviewed in a subsequent section below. Figure 22.1 illustrates brain regions referenced throughout this section, whereas Brodmann areas can be found elsewhere (Kolb & Whishaw, 1996). (See also the color version in the color insert section.) By and large, these areas are all part of a ventral cingulate–medial prefrontal circuit, as described by Cummings (1993) and further subdivided by Rolls (Rolls, 1999) in lateral and medial orbital-frontal circuits. There is also a dorso-lateral prefrontal circuit that is implicated in some of the research described below. We further note that subcortical structures are incorporated within these circuits and are consistent with what was previously described in this book by King and Caine (1996).

**Structural Imaging**

Structural imaging studies of MDD and related mood disorders, like most morphologic studies, are limited primarily by region of interest (ROI) approaches. For example, many studies only examine one ROI within total brain volume, or a subsection of total brain volume. This approach can provide for a single disassociation, but does not address the possibility of entire systems being disrupted in mood disorders. It does not enable one to understand other parts of the limbic and frontal networks that may be implicated in depression, nor does it address whether there is a global problem or if other systems are unaffected. More recently, voxel-based approaches have been used to do full brain comparisons, but these are limited by heterogeneity in anatomy across subjects and limitations in strategies for anatomical warping to address the heterogeneity. There are a number of brain regions implicated in the neuroanatomy of mood disorders, illustrated in Figure 22.1.

**Regions of Interest in Mood Disorders**

1. Insula
2. Dorsolateral Prefrontal
3. Anterior Temporal
4. Orbital Frontal
5. Putamen
6. Hippocampal Formation
7. Amygdaloid Complex
8. Posterior Cingulate
9. Dorsal Anterior Cingulate
10. Caudate
11. Medial Prefrontal
12. Nucleus Accumbens
13. Thalamus & Hypothalamus
14. Raphe
15. Subgenual Anterior Cingulate

**Figure 22-1.** Frequent Regions of Interest Reported in Structural and Imaging Studies Relevant to Understanding Depression and Related Psychiatric Disorders. Numbers indicate center of foci, although some foci are collapsed across the left-right axis to reduce the number of images necessary to display these foci.
The importance of the hippocampus in mood disorders is now accepted, though the specificity and reliability of this relationship has yet to be fully explicated (Caetano et al., 2004; Campbell & MacQueen, 2004; Lee et al., 2002; Lopez et al., 1998; Mervaala et al., 2000; Sapolsky, 2001; Stockmeier et al., 2004). There are several reviews of studies of hippocampal (and amygdalar—see below) volume and depression available and we refer the reader to these (Sheline, 2003; Videbech & Ravenkilde, 2004). A voxel-based morphometry study of 20 patients with treatment resistant depression (TRD), compared to 20 remitted and 20 control subjects revealed atrophy in bilateral hippocampal structures, as well as other areas described in subsequent sections (Shah et al., 2002). Their TRD group had a significantly greater number of hospitalizations compared to the remitted depressives and all had received at least six sessions of electroconvulsive therapy (ECT). An earlier study by this group demonstrated reduced Auditory Verbal Learning performance in treatment resistant depression patients compared to remitted patients (Shah et al., 1998) and a positive correlation between left hippocampal volume and AVLT performance. A study by Vythilingam and colleagues failed to demonstrate differences in hippocampal volume between 38 depressed and 33 control subjects, but the study did show trend level correlations between hippocampal volume and visual immediate and visual delayed recall on the Selective Reminding Test (Vythilingam et al., 2004). In 37 moderate to severe traumatic brain injury (TBI) patients with co-occurring depression, smaller hippocampal volume was associated both with development of mood disorders and poorer vocational outcome at 1 year, suggesting a strong link between hippocampal integrity and affective and cognitive functioning (Pournajafi-Nazarloo et al., 2007). A study of 34 inpatients with depression and 34 control subjects reported reduced hippocampal volume in MDD and a relationship between lower hippocampal volume and poorer performance on the WCST, but not the AVLT (Frodl et al., 2006). Furthermore, there was no association of cognitive measures with frontal volumes. A longitudinal study of 61 depressed patients over the age of 60, compared with 40 age and education matched controls indicated a relationship between right hippocampal volume and persisting memory difficulty 6 months after the initial assessment (O’Brien et al., 2004). Of course, it is unknown if smaller hippocampi placed one at greater risk for mood disorders and reduced cognition due to increased vulnerability, or if these are the result of length and severity of illness.

There is continued debate about whether the amygdala is involved in mood disorders, whereas it is well-established that the amygdala is critical in anxiety disorders. There is a mixture of studies reporting increased compared to decreased amygdala volume (Sheline, 2003). A study of 30 first-episode patients with MDD demonstrated increased bilateral hippocampal volume compared to the match control group of 30 patients and 27 recurrent depressed patients and was stable over 1 year (Frodl et al., 2003). A larger study of 47 female twins pairs exploring amygdala volumes suggested that there were no differences between those with MDD, those at high risk for MDD, and the control subjects, although there was a significant relationship between twin amygdala volumes suggesting a genetic influence (Munn et al., 2007). Reductions in amygdala volumes have been associated with the short form of the 5-HTTLPR polymorphism in one large study of 114 subjects using voxel-based morphometry (Pezawas et al., 2005), but with the long form in another study of 247 young adult female twins (Chorbov et al., 2007). The data available on relationships between amygdala volume, cognition, and affect measures is limited in morphology data and may be further complicated by comorbidity between depressed and anxiety subjects in some studies. Whereas there are animal and theoretical models of mood disorders that would suggest an important role for the amygdala in the etiology and maintenance of the mood disorders, the present state of knowledge using morphological techniques is equivocal in this regard. Importantly, there is now some suggestion that amygdala volumes may be enlarged in first onset of mood disorder, yet smaller or not different in size with recurrence of depression and/or treatment with medication.

The frontal lobes have long been implicated in mood disorders (Harlow, 1868; Moniz, 1954).
However, notes of caution for the reader include the following: first, the frontal lobes encompass 33% of the cortical surface, second, there are five, possibly six, frontosubcortical circuits regulating everything from eye movements to emotional functioning, and third, the zeitgeist remains focused on frontal pathology as a cause, or result, of mood disorders. As such, one cannot conclude that the frontal lobes are uniquely involved in mood disorders. Methodological challenges in measuring specific frontal regions are formidable, whether by Brodmann area or by specific landmarks. The subgenual anterior cingulate has been demonstrated to be smaller in several studies (Botteron et al., 2002; Drevets et al., 1997; Ongur et al., 1998, also Coryell et al., 2005) with one of the negative studies showing a functional abnormality in the same region (Pizzagalli et al., 2004). One other group studied both anterior and posterior cingulate volume in 21 unremitting and 10 remitted patients with unipolar depression compared to 31 control subjects, showing reduced volumes in all four (right, left by anterior, posterior) ROIs in those with unremitting depression, but only in the left anterior cingulate in the subset with remitted depression, both compared to the control group (Caetano et al., 2006). The remitted and unremitting groups did not differ in ROI volumes, suggesting that reduced power in the subset analysis may have masked differences between the patient groups, as well as between the remitted patient and control groups. A study of 44 elderly patients with depression showed larger lateral ventricles in those depressed patients with prior ECT compared to those without ECT (Simpson et al., 2001). Furthermore, there were multiple correlations of neuropsychological measures with frontal (reverse digit span), temporal (Trial 1 of the RAVLT, perseverative errors on the WCST, copy of the Rey–Osterrieth Complex Figure Test, and memory for the Rey–Osterrieth Complex Figure Test), and parietal (Digit Symbol Substitution Test, Trial 1 of the RAVLT, and reverse digit span) lobe volumes but not volume of the lateral ventricle. Another study compared 30 elderly depressives and 40 controls, demonstrating a negative relationship between perseverative errors and a positive relationship with total correct on the Benton Visual Memory Test with left orbital frontal cortical volume (Steffens et al., 2003). These studies suggest that the frontal lobes are indeed relevant when understanding the pathophysiology of depression and the potential for concurrent neuropsychological decrements.

Other brain regions, and related affect and cognitive measures, have received very little research focus thus far in mood disorders. Studies of the basal ganglia are mixed, and there appears to be a distinction in volume between simply depressed (reduced) and bipolar (increased) patients with mood disorders (Anand & Shekhar, 2003; Krishnan et al., 1992). One study of the thalamus with 25 bipolar and 17 unipolar patients showed no differences in thalamic volume from 39 control subjects (Caetano et al., 2001). The insula has also been implicated in mood disorders, although variability in measurement boundaries likely have precluded obtaining strong reliability in morphologic measurements, thus reducing reports in the literature about this region (Nagai et al., 2007). Voxel-based morphometry studies, which are limited in structural specificity, have shown more structural abnormalities in the insula in schizophrenia, and not in mood disorders (Nagai et al., 2007).

Of course, the relevance of subcortical and periventricular hyperintensities in mood disorders is of increasing interest, particularly in elderly or middle-age onset mood disorders, and these patients are more likely to exhibit cognitive difficulties (Bhalla et al., 2006; King et al., 1998; O’Brien et al., 2004; Sobow et al., 2006). One large study of 48 depressed patients and 73 depressed inpatients demonstrated an increasing odds ratio of 5.32 for subcortical hyperintensities in those with depression (Coffey et al., 1993). Another of 37 patients found that white matter hyperintensities were predictors of conversion to dementia syndromes and/or persisting cognitive difficulties (Hickie et al., 1997). A more recent study of 41 MDD patients and 41 control subjects reported inverse relationships between bilateral orbital frontal volumes and subcortical gray matter lesions severity, but not deep white matter lesion severity (Lee et al., 2003). One very large study of 2546 subjects between age 60 and 64 did not find an association between cognitive measures and hippocampal or amygdalar volume, APOE4, or white
matter hyperintensities, but rather found these decrements to be associated with psychiatric symptoms, poor physical health, and personality factors (Jorm et al., 2004). A subset analysis of this sample suggested that degree of white matter hyperintensities in 475 elders was related to depressive symptoms, potentially mediated by smoking and physical disability (Jorm et al., 2005). The disruption of networks important for cognitive and affective processing is the likely consequence of white matter hyperintensities, even if the underlying pathology behind white matter hyperintensities remains under debate (Cummings & Benson, 1984; Lamberty & Bieliauskas, 1993).

**Functional Neuroimaging and Cognitive and Affective Neuroscience Research**

Tremendous progress has been achieved in functional imaging studies of mood disorders in the last decade. Indeed, the field has progressed to the point of trials for deep brain stimulation with subgenual cingulate, ventral striatal and left inferior frontal targets for treatment resistant depression (Mayberg et al., 2005; Schlaepfer et al., 2007), as well as in use of repetitive transcranial magnetic stimulation (rTMS) (McLoughlin et al., 2007). In addition, imaging data are being used to prospectively predict treatment response, highlighting both the heterogeneity in mood disorders and the specificity of actual brain function to illness and treatment parameters (Brody et al., 1999; Langenecker et al., 2007b; Mayberg et al., 1997; Pizzigalli et al., 2001). Herein, we will review very briefly functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) studies of mood disorders, again with specific focus on those studies using larger sample sizes and directly assessing relationships of activation with clinical and cognitive variables. We note that the time and spatial sensitivity for PET/SPECT and fMRI differ, as well as the cognitive/affective/rest paradigms used, which might easily explain the apparent discrepancy between PET/SPECT and fMRI results. In addition, artifact and signal voids in orbital and medial temporal regions in fMRI make imaging these areas more challenging. Finally, due to current funding structures, recruitment difficulties given restrictive exclusion criteria for imaging protocols, and the expense of imaging technology, most, if not all, imaging studies are underpowered, limiting convergence across functional imaging studies, particularly in a biologically heterogeneous set of mood disorders. This section is subdivided into a brief review of neurotransmitter studies, resting glucose/blood flow studies, affective challenges, and cognitive challenges.

Before beginning to review functional imaging studies in mood disorders, it is valuable to review the affective neuroscience literature, as much of this data was the genesis for imaging paradigms described below. In fact, in future chapters on mood disorders, emotion processing may more appropriately be placed under the “traditional” neuropsychological profile of mood disorders. Herein, we differentiate between emotion perception and processing as they might differ from emotional experience. The former denotes a cognitive process in the same vein as visual perception and processing, whereby, the latter refers more broadly to a gestalt of experience. Behavioral studies of emotion processing abnormalities in mood disorders have often focused on aspects of behavior such as mood-congruent memory biases (Gotlib et al., 2004, 2005; Rude et al., 2002), negative processing biases (Danion et al., 1991, 1995; Watkins et al., 1992, 1996; White et al., 1992), memory priming (Bradley et al., 1995; Mogg et al., 1993), and interference effects. These studies indicate a proclivity for processing and remembering negative stimuli, and better delayed memory for such stimuli, in those with mood disorders. Facial emotion stimuli have also been used to determine whether depressed individuals experience difficulty with processing and classifying the emotion expressed in these faces. A majority of these studies indicates that depressed individuals have difficulty in correctly classifying emotions in facial stimuli (Bouhuys et al., 1996, 1999; Gur et al., 1992; Langenecker et al., 2005; Mikhailova et al., 1996; Nandi et al., 1982, Persad & Polivy, 1993). These data have formed a basis for exploring the functional underpinnings of affective irregularities in mood disorders, primarily in fMRI (below), but also in PET and SPECT studies.
Imaging with transmitter-specific ligands using SPECT and PET suggests decreased 5HT1-A and 2-A binding in medial temporal structures in mood disorders, although the data are not consistent, with affects of gender, age of onset, current age, and illness severity all playing a potential role in these discrepancies (Kennedy & Zubieta, 2004). Studies with dopamine ligands, such as DR2, and endogenous opioids, have received relatively less research focus in mood disorders (Kennedy et al., 2006; Larish et al., 1997), but these studies also suggest relatively decreased binding in mood disorders. There is some suggestion that dopamine binding may differ by mood disorder subtype. In one small study, those with psychomotor retardation and anhedonia associated with decreased DR2 binding, whereas those with impulsivity showed normal binding in left caudate (Martinot et al., 2001). A more recent study of a mixed group of 12 suicide attempters, most with mood disorders, suggested higher impulsivity was related to lower serotonin (5HTT) and dopamine (DAT) binding potential, with relationships most strongly located in the basal ganglia, and extending into insula for serotonin. Unfortunately, there is mixed evidence related to whether treatment of depression results in a significant change in dopamine and serotonin concentrations (Argyelan et al., 2005; Moses-Kolko et al., 2007). Important for the purposes of this chapter, these neurotransmitters are represented quite densely in the same anatomical areas discussed up to this point: frontal, anterior and medial temporal, insular, and subcortical areas.

Fluorodeoxyglucose (FDG), H2(15)O, and resting cerebral blood flow (rCBF) PET studies in depression implicate a network of frontal and limbic areas involved, much like that reported in the section on ‘Neuroanatomy of Mood Disorders’. Subgenual anterior cingulate abnormalities in rest and affective paradigms have been reported, with hypometabolism in MDD and in the depressed phase of bipolar disorder (Drevets et al., 1997; Kennedy et al., 1997; Kegeles et al., 2003; Mayberg et al., 1994). The abnormalities in subgenual anterior cingulate resolve with effective treatment (Brody et al., 2001; Kennedy et al., 2007). The same brain regions implicated in anatomical studies of MDD, prefrontal cortex, basal ganglia, and medial temporal areas are perhaps more consistently shown to deviate from controls using blood flow and glucose studies with PET (Liotti et al., 2000; Milak et al., 2005; Videbech, 2000). One PET study of 40 patients with depression showed diminished rCBF-to-cognitive measures relationships when compared to similar relationships in 49 healthy controls (Ravnkilde et al., 2003). One unique study used acute tryptophan (precursor to serotonin) depletion in eight remitted men, showing diminished ventral anterior cingulate and orbital frontal cortex H2(15)O PET after depletion associated with increased depression symptoms (Smith et al., 1999). Those who exhibited related slowing in verbal fluency had diminished anterior cingulate activity.

Functional imaging studies with cognitive and affective challenges in mood disorders have exploded, particularly within the last 5 years. In addition, increasing sophistication in measure design, combined with tighter recruitment protocols and relatively larger sample sizes, has resulted in exciting new findings within the field. As before, we will highlight studies, with larger sample sizes and attempts to relate functional abnormalities in mood disorders with clinical and cognitive variables, with the goal of increasing confidence about brain regions and systems that are affected in mood disorders.

Affective neuroscience studies in mood disorders using fMRI focused heavily on experiential aspects of emotion processing, for example, passive viewing and resting activation studies (Bench et al., 1993; Dolan et al., 1994; Kalin et al., 1997; Sheline et al., 2001; Whalen, 1998; Wright et al., 2001). Stimuli have included faces, complex visual scenes, and more recently semantic stimuli, some of which are rated as to personal relevance (Canli et al., 2004; Fossati et al., 2003; George et al., 1993, 1994, 1996; Gilboa-Schechtman et al., 2002; Gorno-Tempini et al., 2001; lidaka et al., 2001; Kensinger & Corkin, 2004; Maddock et al., 2003; Ochsner et al., 2004; Phan et al., 2003; Siegle et al., 2002, see Figure 22.2 for an example from our own work, see also the color version in the color insert section). Physiological reactivity to emotional stimuli and emotion induction is distinctly different in depressed compared to control groups.
(Kalin et al., 1997; Ketter et al., 1996; Kumari et al., 2003; Paradiso et al., 1999; Phillips et al., 2001; Thomas et al., 2001). This disruption in neurophysiological reactions to emotion stimuli is reversible with successful treatment (Brody et al., 2001; Davidson et al., 1999; Davidson et al., 2003; Fu et al., 2004; Kalin et al., 1997; Sheline et al., 2001; see example of our own work in Figure 22.2 below). Although compelling, these studies have just begun to explore the nature of emotion processing difficulties in depression.

Cognitive neuroscience studies of mood disorders in fMRI are perhaps the most intriguing in recent years, with several recent studies indicating increased frontal activation in mood disorders relative to comparison groups. One study of interference resolution reported increased activation for MDD patients (e.g., left DLPFC, AC) compared to the control group (Wagner et al., 2006). Studies utilizing working memory and verbal fluency tasks have generally reported more prominent activation in the control groups in frontal, basal ganglia, and parietal areas compared to MDD patients (Audenaert et al., 2002; Barch et al., 2003; Elliott et al., 1997; Holmes et al., 2005; Hugdahl et al., 2003, 2004; Matsuo et al., 2002; Okada et al., 2003), while three other studies (examining working memory, attention, and interference control, respectively) have noted greater activation in frontal areas for the MDD groups compared to the control groups in the context of preserved behavioral performance (Harvey et al., 2005; Holmes et al., 2005; Wagner et al., 2006). In this same vein, our group has used a parametric Go/No-Go test in 20 patients with MDD compared to 22 control subjects (Langenecker et al., 2007b). The MDD patients exhibited decreased attention and increased inhibitory control accuracy performance in a significant interaction, relative to the control group. The MDD group also exhibited greater subgenual cingulate and bilateral ventral frontal activation compared to the control group during correct rejections of No-Go stimuli (inhibition).

More recently, resting functional connectivity and ROI-linked functional connectivity studies are now on the forefront of studies of mood disorders. There appears to be a disruption in the core, low-frequency “cross-talk” between what has been termed the default network (including medial, rostral, and posterior cingulate) and more task-oriented structures in depression (lateral prefrontal and parietal, Anand et al., 2005; Greicius et al., 2007), although the specificity and clinical meaning of these findings remain to be seen.

In summary, morphological and functional imaging are strongly suggesting that limbic, frontal, and subcortical regions are involved in mood disorders (see Figure 22.1), converging nicely with the traditional neuropsychological profile described earlier in the chapter. At present, the nature of the relationship is largely correlational—it is unclear if these abnormalities precede onset of the mood disorder and may place individuals at higher risk for development of a mood disorder, or if they are the result of neurobiological changes concurrent with, or resulting from, experience of the mood disorder. Nonetheless, imaging studies of frontal, medial temporal, and subcortical regions will likely continue in mood disorders. There is currently debate about relative increases and decreases in lateral activation bias (right over left), or cortical/subcortical (under activation of cortical, overactivation of subcortical/limbic), but the body of research has not yet converged on a consistently replicable pattern of findings (Davidson et al., 2002; Northoff et al., 2000; Phillips et al., 2003). We strongly urge researchers to more routinely include analysis of structure/function to affective/cognitive relationships, particularly with neuropsychological variables. These can provide better grounding of the significance of any differences between those with mood disorders and control groups.

**Critical Mediating Factors in Cognitive Dysfunction related to Depression**

**Age of Onset**

There does not appear to be a gold standard for determining age of onset for depression due to difficulties with individual patient memories, inconsistency of report from one query to the next, and variability in depressive symptoms (Knauper et al., 1999). Authors have reported that early-onset major depression has a mean age
of 13.7 (SD = 5.0) and late-onset depression has a mean age of 33.5 (SD = 9.5) (Klein et al., 1999). Early-onset depression is considered more malignant, persistent, and resistant to treatment.

The cognitive changes associated with this adult onset depression are felt to include decreased attention on tasks that require increased effort, decreased initial acquisition of stimuli, and decreased retrieval of information that is encoded (Caine, 1986). Caine (1981) describes these changes as being similar to a subcortical dementia. Interestingly, in their description of the syndrome of subcortical dementia, Cummings and Benson (1994) note depression to be a prominent feature. The cognitive changes, however, are coincident with the severity of the depression and many are lessened if the severity of depressive symptoms is therapeutically ameliorated (Bieliauskas, 1993).

When symptoms of depression occur for the first time in older adults, they are more likely to indicate underlying neurological change than to be manifestations of primary depression (Bieliauskas, 1993). In their review of the literature, Lambert and Bieliauskas (1993) report that most late-onset depressive symptoms are accompanied by abnormal findings when neuroimaging is employed. In 1992, the NIH Consensus Conference on Diagnosis and Treatment of Depression in Late Life stated:

There is some evidence to suggest that late-onset depression is associated with a lower frequency of family history of depression but a higher frequency of cognitive impairment, cerebral atrophy, deep white matter changes, recurrences, medical comorbidity, and mortality (NIH Consensus Development Panel on Depression in Late Life, 1992, p. 1019).

Multiple later studies have confirmed the same. Kumar et al. (2000) report that atrophy and high-intensity lesions represent independent pathways to late-life depression, with patients with major depression having larger whole brain lesion volumes than controls and smaller frontal lobe volumes.

As a corollary, depression in the elderly also appears to be predictive of subsequent cognitive decline. Nussbaum et al. (1995) report that 23% of a sample of depressed patients showed cognitive decline over a 25-month period, along with increased white matter MRI, CAT, and EEG abnormalities. This finding was subsequently confirmed in a large longitudinal (Paterniti et al., 2002) and neuropathologic study (Sweet et al., 2004). Similarly, depression in old age is associated with generalized atherosclerosis (Vinkers et al., 2005) and with increased cardiovascular and noncardiovascular mortality (Vinkers et al., 2004).

In sum, while primary depression, generally first occurring in young adulthood, is associated with cognitive dysfunction related to attention, learning, and recall, the initial occurrence of depressive symptoms in the elderly is very likely an indicator of an underlying degenerative or cerebrovascular neurological process. For each depressive symptom observed in the elderly, the rate of cognitive decline has been observed to increase by about 5% predicting cognitive decline in old age (Wilson et al., 2004), though depressive symptoms are not necessarily increased during the prodromal phase of Alzheimer’s disease itself (Wilson et al., 2008). From a quality-of-life perspective, late-life depression is treatable by conventional pharmacotherapies, though careful dosing must be observed (Sadavoy, 2004). The positive change in cognitive efficiency that is observed when primary depression is treated, however, is not likely to be seen in the treatment of late-life-onset depressive symptoms (Bieliauskas, 1993).

**Severity**

It is currently unclear whether severity, as defined by clinician rating or self-report obtained, has any relation to the extent of neuropsychological decrements. There is a suggestion that being seen on an inpatient psychiatry ward is an index of disease severity that would portend greater cognitive difficulties (Burt et al., 1995), as would recurrence of depressive episodes. This section will review studies prototypic of those examining severity according to objective psychometric measures and/or location of treatment service/recruitment. We acknowledge that depression severity gradations assume a dimensional distribution of cognitive decrements, related in a linear fashion. A categorical perspective, such as that used between treatment responders and treatment nonresponders, also provides an index of severity and is reviewed below in a later
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section. Further, there are some mood disorders (e.g., bipolar disorder) that are often viewed as greater in severity relative to others (MDD). These sorts of subtype gradations, such as comparing MDD to Bipolar disorder or comparing melancholic and nonmelancholic depression, are also conducted in a separate section below.

One large study of elderly patients with minor (N = 32) and major depression (N = 63) indicated poorer performance compared to a matched control group of 71 participants in initial learning on trial 1 of the CVLT and on List B, as well as in number of correct categories for WCST (minor depression only), and Letter–Number Sequencing (major only (Elderkin-Thompson et al., 2007)). There were no significant effects of severity using this classification. A very large study of 385 elderly patients showed an increase in disruption on the Stroop test between mild and moderate depression, but not with severe depression (Baune et al., 2006).

A smaller study of 26 severely depressed patients demonstrated a significant positive relationship between severity of depression and measures of simple and complex reaction time, or processing speed (Egeland et al., 2005) and one measure of memory, with a surprising number of significant negative correlations between 8:00 a.m. cortisol levels and memory and executive functioning measures.

As is probably well known, those with severe depression have poorer long-term treatment prognosis (Elkin et al., 1995; Saghaei et al., 2007), which may in fact be mediated by extent of neuropsychological decrements in performance. There have been attempts to use chronicity as a measure of severity, including structured interviews to code number of days ill. However, it should be noted that recall bias may significantly affect patient reports of length of illness and number of episodes (Riso et al., 2002). One interesting study used retrospective recall of days of untreated depression to predict hippocampal volume loss in women with recurrent depression (Sheline et al., 2003). It is important to conduct longitudinal studies to determine whether severity of symptoms is related to cognitive performance in a meaningful way (e.g., reflective of permanent underlying disruption of neural networks as an etiological risk factor), or whether depression itself results in significant cognitive decrements and underlying neurological dysfunction (as a chronological sequel of depression).

A history of inpatient hospitalization and/or the number of previous depressive episodes appear to be associated with the executive and memory decrements in some studies, both different indices of clinical severity. Purcell et al. (1997) examined 20 depressed patients (19 outpatients and 1 inpatient; 12 medicated) and 20 age and education matched normal controls on the CANTAB and found attentional set-shifting decrements in the depressed group. On closer examination, the researchers found that a history of inpatient hospitalization was associated with poorer performance on the set-shifting task. Paelecke-Habermann et al. (2005) studied 40 euthymic patients with a history of MDD diagnosis (20 individuals with one to two episodes and 20 individuals with three or more episodes) and 20 healthy controls on tasks of executive function (Behavioral Assessment of the Dysexecutive Syndrome, word fluency, and backward visuospatial span) and found worse performance in the MDD group. Furthermore, the severe MDD group performed worse than the mild group, suggesting that individuals with recurrent episodes demonstrate greater decrements than those with one or two episodes.

Studies of the impact of severity of illness as they relate to significance of cognitive decrements are limited in many respects due to nonuniformity in neuropsychological measures employed, clinical measures of severity utilized, and the broader issue of heterogeneity in mood disorders by subtype. Future studies will likely have to further subdivide into different cognitive domains, different depression subtypes, with unique mediating factors.

Effort

Effort, motivation, and abulia continue to be key concepts in understanding mood disorders and related cognitive decrements (King & Caine, 1996). Indeed, the effort-automatic hypothesis of depression had direct roots in beliefs about how depression might affect motivation and effort. For example, early studies indicated that memory tasks that were more automatic (recognition) tended to be performed
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just fine by depressed patients, whereas more
effortful, difficult tasks (recall) tended to be
tasks that were more difficult for those with
mood disorders (Cohen et al., 1982; Roy-Byrne
et al., 1986; Weingartner et al., 1981). As noted
in chapter 9 by King and Caine (1996) in the
previous edition of this book, there are other
theories accounting for cognitive decrements in
mood disorders, including decreased resource
availability, increased distraction through ineffi-
cient inhibitory process, and mood congruent
memory biases, though we will not go into these
in detail herein.

More recently, there has been a strong and
healthy debate about the genesis of cognitive
decrements in patients with depression, largely
revolving around the old concepts of “func-
tional” and “organic” brain-based cognitive
difficulties, particularly within legal contexts
(Rohling et al., 2002). In a recent study of pri-
marily legal cases, over 40% of subjects recruited
were excluded because of documented poor
effort using standardized measures (Rohling
et al., 2002). Interestingly, the excluded group
had significantly higher depression scores on
the Hamilton Depression Rating Scale (HDRS)
compared to the group that was not excluded,
and performed significantly worse on multi-
ple cognitive measures including learning and
memory. A smaller percentage (15%, 8%) of
patients filing for workers compensation with
depressive symptoms failed formal effort mea-
sures in a study of 233 patients (Sumanti et al.,
2006). Because anergia and amotivation are
key symptoms of depression and these symp-
toms can adversely affect effort, it is reason-
able to assume that for a minority of depressed
patients, “amotivation” may result in a failed
effort test. One possible interpretation of this
finding is that significant primary depression
may not result in permanent brain dysfunction,
but rather that insufficient engagement of moti-
vational drive (evident in depression) can mimic
cognitive decrements on challenging tasks.
However, two recent studies have not shown
any difficulty in depressed patients or those
with anxiety, in passing formal effort measures,
suggesting that depression symptoms may
have very different etiologies and purposes in
legal as opposed to clinical settings (Ashendorf
et al., 2004; Egeland et al., 2005). We have also

recently found that depression, as measured by
DSM-IV criteria and Geriatric Depression Scale
(GDS; Yesavage), was not related to very basic
measures of effort such as the Rey 15-Item Test
(Lee et al., 1992; Rey, 1964) or the Kaufman
Hand Movements Test (Bowen & Littell, 1997;
Kaufman & Kaufman, 1983) in a population of
elderly medical inpatients (Vadnal, 2005).

These differences in failed versus passed
effort tests in “depressed” samples highlight
the importance of using formal or informal,
but validated, effort measures when assessing those
with mood disorders, especially when the pos-
sibility of primary and secondary gain becomes
crucially important in interpreting the relevance
of poor test performance. When no primary or
secondary gain can be found, the clinician can
correlate self-reported energy levels, depres-
sion severity, psychomotor retardation, and so
on with observed inefficiencies in performance
(everyday functioning), but estimates of opti-
mal functioning levels or inference of underly-
ing neuronal dysfunction in these contexts need
to be carefully interpreted.

Subtypes of Mood Disorders

There are a number of different subtypes of
depression, wherein cognitive function may be
greater (e.g., cerebrovascular, bipolar disorder).
Furthermore, there are certain subtype-by-
cognitive function distinctions, most nota-
bly the prevalence of psychomotor retardation
in melancholic but not in atypical depression.
A rapidly emerging set of data is in cognitive
decrements with co-occurring depression and
medical conditions. Cushing’s disease is a rare
disease with high prevalence of depression,
thought to be mediated by hypercortisolism
and epitomizing the glucocorticoid cascade
hypothesis of depression. Review of these select
subtypes exemplifies the variability of cognitive
dysfunction in mood disorders.

Cerebrovascular

The increased prevalence of depression among
patients with cerebrovascular accidents (CVAs)
has long been established, with between 50% and
68% manifesting symptoms of depres-
sion (Eastwood et al., 1989). These estimates
rendered the occurrence of “melancholia in up to 25% of patients,” with minor or masked depression in 75%–95% of cases (Wiart, 1997). A more recent study has demonstrated that patients with ischemic stroke have double the risk of depression compared with those without stroke (11.2% versus 5.2%) with a greater incidence of depression corresponding to more severe CVAs, particularly in vascular territories supplying limbic structures (Desmond et al., 2003). Though there has been speculation that the distribution of CVAs, especially as related to syndromes of aphasia, may specifically relate to depressive symptoms, more recent evidence suggests that screening for aphasia across studies is highly inconsistent and that conclusions as to relationships between aphasia subtypes and depression are not justified (Townend et al., 2007). Laska et al. (2007) alternatively suggest that depression diagnosis and severity can be reliably made during the acute phases of aphasia and suggest that depression can be identified in at least 24% of such patients.

Nevertheless, there remains little doubt that depression is common following CVA. There has been the suggestion of a vascular depression hypothesis, that is, that cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes. It is hypothesized that prefrontal systems are disrupted with associated executive dysfunction (Alexopoulos et al., 1997), mechanisms discussed in the section on ‘Neuroanatomy of Mood Disorders’.

Secondary to Medical Condition

Depression is a common comorbid condition in medical illnesses including cancer (Chochinov, 2001; McDaniel et al., 1995; Spiegel, 2001), diabetes (Anderson et al., 2001; Ciechanowski et al., 2003), heart disease (Ruo et al., 2003), asthma (Eisner et al., 2005), chronic obstructive pulmonary disease (Yohannes et al., 2000), obesity (Thomsen et al., 2006), migraine headaches (Molga & Patten, 2005), chronic fatigue syndrome (Patten et al., 2005), fibromyalgia (Ahles et al., 1991; Patten et al., 2005), and chronic pain (McWilliams et al., 2003). A bidirectional relation between depression and medical illnesses appears to exist, with each possibly altering the normal course of illness of the other. In the past, depression associated with a medical illness was considered to be a psychological reaction to having a medical illness and thought to have a less severe course (Boland et al., 2006). However, it is now clear that depression in the medically ill may be more difficult to treat compared to depression in individuals without a comorbid medical condition (Boland et al., 2006). These individuals generally report more medical symptoms even when the severity of the medical disorder is taken into account (for a review, see Katon et al., 2007). Depression can be detrimental in the medically ill in that these individuals are three times less likely to adhere to medical treatment recommendations compared to nondepressed medically ill individuals (Dimatteo et al., 2000). In addition, when the depression is not properly treated, it could negatively impact the morbidity and mortality of the medical illness, especially in older adults (Boland, 2006; Covinsky et al., 1999; Frasure-Smith et al., 1993; Ganzini et al., 1997; Katon, 2003; Lesperance & Frasure-Smith, 1996). For example, Frasure-Smith et al. followed 222 patients who were hospitalized for myocardial infarction for 6 months and found that MDD was an independent risk factor for mortality. Overall, MDD can be identified in 7–17% of patients with chronic medical conditions (Egede, 2007). In contrast, when depression is treated, medical symptoms decrease regardless of the improvement in the medical disease status (Borson et al., 1992).

The cognitive profile of the medically ill individuals with depression should not differ from the traditional profile described above. However, additional physical symptoms including pain and increased fatigue, which are more common in certain medical populations including cancer, chronic pain, and fibromyalgia need to be taken into consideration when interpreting test results. Neuropsychological investigations in the non-neurological, medically ill individuals with depression are scarce with only a few that have focused on fibromyalgia and chronic fatigue syndrome (Johnson et al., 1997; Landro et al., 1997; Suhr, 2003). Nonetheless, it appears that cognitive inefficiencies are generally associated with the individual’s presenting symptoms such as fatigue or depression. For example, Suhr investigated 28 individuals with fibromyalgia,
27 individuals with chronic pain, and 21 healthy controls on measures of intellect, memory, executive functioning, attention, and psychomotor speed, as well as on self-reported measures of depression, pain, fatigue, and cognitive complaints. The fibromyalgia group reported more memory complaints, fatigue, pain, and depression than the other groups. Although no difference in performance was found on cognitive measures when fatigue, pain, and depression were taken into account, the severity of depression was associated with memory performance and fatigue was associated with psychomotor speed.

Cushing’s Disease and Hypercortisolemic Mood Disorders

One very well-understood model for describing the neurobiological sequelae of mood disorders is the glucocorticoid cascade hypothesis (Sapolsky, 2000). In this model, the increased stress often observed in mood disorders results in excessive release of CRF, signaling release of ACTH, resulting in subsequent release of cortisol. In 33% of individuals with MDD, an abnormal ACTH response to the steroid dexamethasone is indicative of failed feedback mechanism, putatively a result of chronic excessive glucocorticoids (Sonino & Fava, 1996; Young et al., 1991). Cushing’s disease is a rare disorder often thought to typify the glucocorticoid model, as there is sustained, elevated cortisol levels for as long as several years before the condition is diagnosed and treated (1961). The excess cortisol levels have been associated with a 60% prevalence of mood irregularities, typically depression. Further, treatment of Cushing’s disease typically results in alleviation of depressive symptoms (Sonino et al., 1993; Starkman et al., 1981, 1986). The remission of cognitive difficulties thought to be secondary to Cushing’s disease is more equivocal in nature, with some studies showing no improvement, and others showing improvement in memory and executive functioning (Dorn & Cerrone, 2000; Dorn et al., 1997; Forget et al., 2002; Heald et al., 2004; Hook et al., 2007; Mauri et al., 1993; Starkman et al., 2001). One study reported that improvements in memory are positively associated with posttreatment volume increases in the hippocampus, whereas improvements in mood are associated with increases in the caudate (Starkman et al., 1999, 2003, 2007). Cushing’s disease provides a model for how excessive stress hormones can have potentially reversible cognitive and affective sequelae, highlighting the deleterious affects of stress hormones, the link between brain morphometry and cognitive and affective symptoms, and the potential for plasticity in brain and neuropsychological functioning in mood disorders (McEwen, 2002). Although focus has been primarily on amygdala, hippocampus, and caudate thus far, future studies by our group are targeted toward effects of hypercortisolism on the entire medial frontal–subcortical circuit.

Studies of hypercortisolemia in other mood disorders have also helped build the connection between cortisol/ACTH levels and cognitive dysfunction. This may be in part due to the heterogeneity in depressive samples and relative variability of neuroendocrine measurements across subjects. Hypercortisolemia occurs in approximately 50% of individuals with depression, and treatment with agents to reduce cortisol levels can result in improved cognitive performance (Golomb et al., 1993; Young et al., 1994, 2001, 2004). One study of 23 severely depressed patients found significant negative correlations between executive and memory functions and 8 a.m. cortisol levels (Egeland et al., 2005). In a study of 102 female outpatients with remitted MDD, those with recurrent depression had higher cortisol levels than the nonrecurrent women (Bos et al., 2005). Elevated cortisol but not ACTH levels have also been reported in a study of 29 participants with psychotic major depression compared to 26 healthy controls and to 24 participants with nonpsychotic major depression (Gomez et al., 2006). Some modest correlations were reported between measures of executive functioning, processing speed, and memory with cortisol levels. Furthermore, in a study of 17 patients with bipolar disorder, euthymic phase, and 16 matched control subjects, post-dexamethasone cortisol was positively correlated with number of errors on a working memory task (Watson et al., 2006). It is unclear whether hypercortisolemia mediates cognitive decrements in mood disorders, and the relationships between HPA axis measures
and cognition are not always evident (Caine et al., 1984). As noted before, underlying neural networks that control stress responses and assist in certain aspects of cognition are negatively affected in mood disorders, but variability in presence and degree of disruption, when combined with small sample sizes and variability in clinical characterization and classification, might explain inconsistencies within the literature.

**Melancholic Depression**

Apart from the studies of psychotic major depression in the context of hypercortisolism, there are also a subset of studies comparing melancholic and nonmelancholic depression (Cornell et al., 1984). One study demonstrated difficulty in digit symbol and perseverative errors on the WCST on a group of specifically defined patients with melancholic depression, and not on the nonmelancholic group (Austin et al., 1999). A more recent study comparing 11 melancholic with 11 nonmelancholic depressed patients matched on HDRS symptoms, age, age of onset, and education reported poorer performance in intra/extradimensional set-shifting from the CANTAB battery, but not in paired associates learning or stockings of Cambridge (Michopoulos et al., 2006). A smaller study of seven melancholic, eight nonmelancholic, and nine control participants demonstrated slowing on several attention, executive functioning, and processing speed tasks in the patients with melancholic depression but not in the nonmelancholic group (Rogers et al., 2004). It has been hypothesized that frontal dysfunction is greater in melancholic depression (Austin et al., 1999), but no imaging studies to date have tested this hypothesis. Recent neuroimaging studies focusing on anhedonia more specifically have reported decreased ventral striatal/nucleus accumbens response to positive stimuli in depression (Epstein et al., 2006; Knedell et al., 2005; Knutson et al., 2008).

**Bipolar**

Individuals with bipolar disorder (BD) often demonstrate worse performance than healthy individuals on measures of learning and memory, executive function, and psychomotor speed (Ferrier et al., 1999; Martinez-Aran et al., 2004; Rubinsztein et al., 2000; Zubieta et al., 2001). Research on individuals with BD often indicates a similar pattern of cognitive inefficiencies that is found in individuals with MDD, with more decrements in general (Borkowska & Rybakowski, 2001; for reviews see Olley et al., 2005; Quraishi & Frangou, 2002). For example, a study examining unmedicated individuals with MDD or BD during acute depressive episodes indicated worse performance in the BD group on the Performance IQ portion of the WAIS-R and on tests of executive function (Borkowska & Rybakowski, 2001). Specifically, the BD group performed worse on the Stroop test (word reading and color–word interference parts), the letter fluency test, and the WCST (more perseverative errors and fewer completed categories). However, contradicting evidence also exists, indicating no difference between MDD and BD patients, at least in depressed states. Fossati et al. (2004) investigated memory performance on a verbal learning task in patients with a first depressive episode, MDD, and BD in depressed states. The researchers found poorer first trial free recall in both MDD and BD groups but not in the first-episode group and concluded that the repetition of depressive episodes affect verbal memory performance in acute depressive phases regardless of the subtype of depression. Similarly, Bearden et al. (2006) did not find any difference in verbal memory performance between the MDD and BD groups although both groups performed worse than the normal control group. The pattern of cognitive decrements in BD patients has also been compared to that of patients with schizophrenia and found to have similarities, although in less severity (Schretlen et al., 2007).

The clinical state or phase of illness in BD appears to affect the neuropsychological function with mixed/manic states showing the greatest decrements and euthymic states displaying the least. Sweeney et al. (2000) examined 35 BD patients (14 in mixed or manic state and 21 in depressed state), 59 MDD patients, and 51 healthy controls on the CANTAB. Decrements in executive function, episodic memory, and spatial span were demonstrated in BD patients in mixed/manic states but only episodic
memory decrement was shown in BD patients in depressed states and patients with MDD. A recent meta-analysis of BD individuals in euthymic states (Robinson et al., 2006) revealed greater decrements on measures of executive function and memory compared to measures of attention and processing speed. Specifically, large effect sizes were found for category fluency, backward digit span, and total learning score on the RAVLT and the CVLT; medium effect sizes were found for Stroop Color–Word Inference Test, Trail-Making Test B, WCST (perseverative errors and categories), and short-and long-delay free recall of the memory tests; and a small effect size was found for letter fluency and forward digit span. In a recent review, Robinson and Ferrier (2006) indicated that factors influencing the severity of neuropsychological inefficiencies in euthymic bipolar patients include the number of previous manic episodes, hospitalizations, and length of illness. A consistent finding was the negative relation between the number of manic episodes and performance on tasks of verbal memory and executive function. Specifically, regarding memory function, although encoding is more commonly impaired than retention in euthymic BD individuals, the increasing number of manic episodes was associated with poorer retention. A recent study by Malhi et al. (2007) followed 25 patients with BD over 30 months and assessed them in hypomanic, depressed, and euthymic phases of illness. Decrements in executive functioning, memory, and attention were seen in both hypomanic and depressed states with additional fine motor deficit in the depressed state. In the euthymic phase, mild attention and memory decrements were found. Taken together, although euthymic BD patients show relatively less cognitive inefficiency, persisting decrements, albeit mild, appear to be in components of executive function and memory.

It is worth mentioning that the type of BD also has an effect on cognitive function with BD type I being associated with worse cognitive outcome than compared to BD type II. Relatively few studies have specified the type of BD and a fewer studies have examined the differences between the two types (Malhi et al., 2007; Zubieta et al., 2001). However, recently Torrent et al. (2006) examined 38 individuals with BD I in euthymic states, 33 individuals with bipolar II in euthymic states, and 35 healthy controls. The two BD groups showed worse performance on tasks of attention and working memory, executive function, and verbal memory compared to the control group, but the type II group was less impaired on tasks of verbal memory and executive function. Future studies need to carefully consider subtype of bipolar disorder, as well as a consideration of mediating factors such as phase of illness and history of substance abuse and suicide attempts.

**Medication Effects**

The understanding of medication effects in mood disorders poses several challenges in the assessment and interpretation of cognitive and affective data above and beyond the effects of the mood disorder itself. As there is considerable variability in cognitive functioning in mood disorders, and considerable severity of illness in these disorders, understanding any affects of medication becomes quite complex. For example, those with more severe illness may be more likely to receive medications that will affect cognitive functioning, and perhaps even higher doses of these medications than those with less severe illness. As medications are not randomly assigned to patients, there is a potential for medication by severity interactions that may confound interpretation of either one of these alone. As such, the clinician should balance knowledge of the potential cognitive side effects of medication with those that could be a result of the disorder itself. In some cases, it may be advisable to use medication washouts to better determine medication as opposed to illness effects on cognition, while also being aware of greater potential for relapse and/or complications in such instances.

**Anticholinergics**

Medications with anticholinergic effects are frequently prescribed for depression, particularly tricyclic antidepressants, though this class also includes selective serotonin reuptake inhibitors (SSRIs) such as Paroxetine and atypical antidepressants such as Venlafaxine. Caution is urged about use of drugs with anticholinergic
properties, especially in the elderly, due to potentially exaggerated side effects such as confusion, and memory and concentration decrements (Sadavoy, 2004). Use of SSRIs may result in subjective memory difficulties, at least in those with significant psychopathology (Wadsworth et al., 2005). Particular attention to dosing in older patients is recommended, with some ranges based on ¼–½ of the general adult dose. We recently found that when careful dosing with drugs with anticholinergic properties in elderly inpatients is followed, significant cognitive side effects do not appear to be of major concern (Harik et al., 2008). Indeed, by and large successful treatment may in fact increase memory, psychomotor, and attentional functioning (Brooks & Hoblyn, 2007).

Benzodiazepines

Patients with mood disorders, perhaps more often those with significant anxiety or insomnia, are frequently prescribed a benzodiazepine in addition to a primary mood medication. The impact of benzodiazepines on cognitive functioning is fairly well understood and is one of the reasons why they are typically used at night or as needed. For example, on-drug driving performance on a simulator in a double-blind, crossover study of 18 healthy volunteers was significantly poorer than nondrug performance with both extended and immediate release alprazolam (Leufkens et al., 2007). There were also effects of immediate release alprazolam on divided attention reaction time at 1-, 2.5-, and 5-hours postadministration, for Stop RT on a stop signal task at the same intervals, and for delayed recall on a word-learning task at 1 hour. Effects for extended release were present on cognitive tests at 1- and 2.5-hour intervals compared to placebo. Lorazepam, and not chlorpromazine, administration to 72 healthy adults resulted in impaired free recall and word-completion in an earlier study (Danion et al., 1992). Furthermore, in a comparison of 328, 65–80 year olds, 57 of whom were chronic benzodiazepine users, chronic benzodiazepine use resulted in higher rates of postoperative confusion (26% compared to 13%), even though measures of anxiety and depression did not differ between the two groups (Kudoh et al., 2004). A comprehensive review of benzodiazepine effects is available, with expected effects of sedation and cognitive decrements in attention, executive functioning, and memory to be expected (Buffet-Jerrott & Stewart, 2002). The effects of benzodiazepines, by way of increasing sleepiness, have been linked to thalamic glucose metabolism in nine healthy control subjects (Volkow et al., 1995). Further, tolerance to detrimental memory effects of benzodiazepines does not appear to occur with long-term use whereas some tolerance to psychomotor effects of diazepam was present (Gorenstein et al., 1994). This was demonstrated using 10-mg diazepam administration on memory in 28 long-term diazepam users with anxiety. Thus, benzodiazepines can affect attention, executive functioning, and memory, while increasing sedation, perhaps further effecting cognitive functioning in those with mood disorders.

Opiates

Given the high rate of mood disorders in individuals with chronic pain or cancer, the evaluation of opioid medications, which are commonly used in these medical populations, on cognitive functioning is necessary (Haythornthwaite et al., 1998; Turk & Brody, 1992). The concern for possible adverse effects of opioid use has been associated with the presence of opiate receptors in the neural structures that are involved in attention, learning, and memory (Payne, 1990). The complexities of research in medical populations using opioids including varying types of opioid medication and doses, interactions with other medications, and participant variables make drawing any firm conclusions regarding the effects of opioids on cognition difficult. However, there is evidence that short-term use of opioid medication in healthy individuals can affect psychomotor performance on tasks such as Digit Symbol Substitution Test, reaction time, and finger tapping (Kerr et al., 1991; Zacny et al., 1994). Some studies suggest that when individuals with chronic pain and healthy individuals are compared on cognitive tasks after taking opioids, the drug has a less deleterious effect on cognition in individuals with chronic pain, likely due to pain relief and/or the pain possibly counteracting the possible effects of opioids in
the CNS (Haythornthwaite et al., 1998; Lorenz et al., 1997; Sjogren et al., 2000; Twycross, 1994; Vainio et al., 1995). In patients who take opioid medications on a long-term basis, cognitive inefficiencies are suggested to occur during the first few hours after a dose is given and during the first few days of use (for reviews, see Chapman et al., 2002; Zacny, 1995). A recent study (Byas-Smith et al., 2005) evaluated driving ability in a predetermined route in a community; performance on the Test of Variables of Attention and on the Digit Symbol Substitution Test in 21 patients with chronic pain with stable regimens of opioid analgesics, 11 patients with chronic pain without opioid use, and 50 healthy controls were evaluated. No significant difference in driving ability, sustained attention, or psychomotor speed were found, suggesting that at least some individuals with chronic pain who regularly use opioids do not display significantly diminished cognitive abilities.

**Predicting Treatment Response in Mood Disorders**

There is an emerging corpus of data suggesting that neuropsychological and cognitive/affective neuroscience techniques may be valuable in prospectively predicting treatment response in mood disorders. There is, however, an uneasy and nonproductive tension between insurance companies mindful of increasing health-care costs, a relative paucity of treatment studies examining alternative treatment predictive models in mood disorders, and a general unwillingness to integrate neuropsychological techniques into psychiatric clinics. This is perhaps a left-over of the remaining stigma toward mental illnesses, as opposed to the “hard” neurological syndromes where permanent, irreversible, and far more severe cognitive sequelae are more frequently observed. It should not be lost on the reader that perhaps one of the greatest areas for impact and improvement in health care could be the timely and judicious application of neuropsychological evaluations in psychiatry clinics. The current trial and error, “cheapest or newest drug first” treatment model for mood disorders can likely be improved with large clinical trials using demographic, clinical, and neuropsychological measures to predict treatment response, followed up by studies to initiate alternative treatment strategies for those with poor prognosis for positive response to traditional treatments. Screening instruments for use in psychiatry and family medicine clinics are available and can be readily integrated into clinical care settings (Gualtieri et al., 2006; Gur et al., 2001a, 2001b; Langenecker et al., 2007a).

A significant limitation of this section is that most studies of treatment response predictors are much too small in sample size to rule out predictors as being irrelevant in estimating potential for treatment response. This would suggest, however, that any convergence across these small studies is worthy of further and more detailed consideration and study. A study of 53 inpatients with depression who were treated with combined pharmacological and psychotherapeutic treatments used cognitive styles (e.g., dysfunctional attitude and extreme thinking) to predict treatment response at 6 months, noting that less changes in both measures predicted a more rapid return of depressive symptoms (Beevers et al., 2007). In a relatively larger study of 55 depressed patients, better verbal fluency, and poorer Rey–Osterrieth Complex Figure Test, Benton Visual Retention Test, WAIS-R arithmetic, Block Design, and Similarities, as well as poorer Hooper Visual Organization Test performance, were significant predictors of depression remission in HDRS symptoms to SSRIs at 6 weeks of treatment (Kampf-Sherf et al., 2004). Another study of open label SSRI treatment in 35 patients with MDD demonstrated that better verbal fluency performance was a significant, positive prognostic indicator of eventual treatment response (Taylor et al., 2006); this study was supported by a smaller study of 14 middle-aged patients with depression (Dunkin et al., 2000). In the study by Dunkin et al., an omnibus measure of executive functioning including verbal fluency was poorer in the non-responders (n = 6) compared to the responders (n = 8). Another study of 45 depressed elderly patients failed to show any differences between responders and nonresponders on the Mattis Dementia Rating Scale (Butters et al., 2000), although this instrument may not be sensitive enough to difficulties observed in mood disorders. A larger study of 112 elderly patients with depression showed poorer Stroop interference
and Initiation/Perseveration scores from the Dementia Rating Scale in the nonresponder group \((n = 44)\) compared to the responders (Alexopoulos et al., 2005).

Brain imaging studies, including morphologic, EEG, PET, and fMRI have also demonstrated promise in predicting treatment response in mood disorders, most commonly depression. For example, a study comparing 20 subjects with a lengthy depressive episode (greater than 2 years) demonstrated reduced verbal memory performance and decreased left temporal and hippocampal volume when compared to 20 remitted and 20 control subjects (Shah et al., 1998). In a larger PET study of 39 outpatients with MDD, decreasing ventral anterior cingulate and anterior insula activity was associated with improvement in anxiety and tension symptoms, increasing dorsal anterior cingulate activity was associated with improvement in psychomotor retardation, and increasing dorsolateral prefrontal activation was associated with improvement in cognitive symptoms, all from the HDRS and Profile of Mood States (Brody et al., 2001). In our own study of 20 patients with MDD using parametric Go/No-Go task during fMRI, activation during correct rejections of No-Go stimuli at pretreatment in bilateral inferior frontal, right middle frontal, left amygdala and nucleus accumbens, and subgenual anterior cingulate was highly predictive of eventual response to s-citalopram in 15 completers (Langenecker et al., 2007b). An fMRI study using an emotion processing probe also demonstrated that amygdala activation was predictive of treatment response to cognitive behavioral therapy (Siegle et al., 2006). One other PET and an EEG study demonstrated that subgenual and rostral anterior cingulate activity, respectively, were positive predictors of treatment response to SSRIs (Mayberg et al., 1997; Pizzagalli et al., 2004).

The neuropsychological and brain imaging studies predicting treatment response strongly confirm several recurrent themes within this chapter. Disruptions in frontal and limbic activation and in tasks thought to be dependent on these brain circuits are prospectively, as well as retrospectively, valuable in predicting and understanding treatment response in mood disorders. Herein, the correlation between structural, functional, and behavioral abnormalities in mood disorders is extended to some extent to include real outcome variables. Future studies can look at correlation of these different dependent variables as they relate to changes with treatment, in order to assess static (trait) versus phasic (state) abnormalities and decrements in function. There is great hope that these measures can be used within clinical settings to inform clinicians about prognosis for treatment response to standard pharmacotherapies, hastening alternative treatments, and aiding in the development of novel treatments.

**Conclusions**

Neuropsychology, along with cognitive and affective neuroscience research, has taken part in a dramatic transformation in the appreciation for, and understanding of, the neurobiological systems affected in mood disorders. It is increasingly accepted that mood disorders frequently co-occur with cognitive difficulties and further that such difficulties may be reversible in some individuals, but not in others, based on certain characteristics outlined herein (e.g., age of onset, co-occurring medical conditions). Further, genetic and biological risks for developing mood disorders may co-occur with cognitive weaknesses that are evident long before evidence of an affective disorder emerges and are even present to some extent in relatives of those affected with mood disorders.

In the present chapter, we have demonstrated a neuroanatomical network that is affected in a majority of individuals with mood disorders, including amygdala, hippocampus, basal ganglia, thalamus, anterior temporal, insular, ventral, medial, and dorsal prefrontal areas. It should not be lost on the reader that most of these areas are all part of a ventral cingulate–medial prefrontal circuit, as described by Cummings (1993) and further subdivided by Rolls (Rolls, 1999) in lateral and medial orbital–frontal circuits. The exception is dorsolateral prefrontal cortex, which is a distinct dorsal anterior cingulate–dorsal prefrontal circuit that does interact with the corticolimbic circuit. The cognitive and affective findings in mood disorders overlay nicely onto the idea of disruption of these three frontosubcortical circuits, including disruptions.
in emotion processing, attention, executive functioning, memory, and psychomotor speed. It is also not surprising that measures from these five cognitive/affective domains are implicated in understanding mechanistic issues in mood disorders, such as severity and prognosis for successful treatment response. Medication effects and comorbid medical conditions also play a critical role in understanding the impact of mood disorders on neuropsychological functioning and there are certainly subtypes of mood disorders with greater disease burden and chronicity. In essence, neuropsychological probes can be used to understand disease burden and potential for response to traditional treatments. More importantly, these indexes of disease burden can be ascertained at first episode, thus shifting the treatment plan dependent on risk of recurrence of mood disorders or prognosis of poor response to “front line” treatments.

Neuropsychologists should appreciate that the distinction between “organic” and “functional” disorders is increasingly becoming minimized as our understanding of neurobiological mechanisms of brain function improve. A challenge remains in distinguishing poor effort, decreased goal-directed behavior, decreased efficiency in planning, as secondary to mood disorders, from the same observed phenomena in legal or compensation contexts where primary and secondary gain are highly significant factors. There will be greater expectation that neuropsychologists appreciate the impact of psychiatric and mood symptoms in cognitive functioning. Neuropsychologists can function effectively as consultants in psychiatry and even in primary care clinics, wherein the goal is to understand illness burden and prognosis for treatment success, such that alternative and more effective treatments can be more efficiently and rapidly applied. Finally, neuropsychologists should continue to be mindful of the relevance of, and need for, applied knowledge in clinical, legal, and research settings wherein mood disorders will continue to be prevalent.

**Recommendations**

We also wish to share with the reader the types of assessment strategies and instruments that will be most beneficial in different settings. Given the traditional and more recent findings in mood disorders, at a minimum we recommend that an assessment of depression-related cognitive functioning include the following:

1. Estimate of baseline functioning less dependent on effort and memory retrieval.
2. Direct or validated indirect measures of effort, regardless of the possibility of primary or secondary gain.
3. Memory measures that rely on repeated exposure to the same stimuli such that a learning curve can be established.
4. Measures of executive functioning that tap into processing speed, short-term memory, sustained attention, and problem-solving areas.
5. Fine motor dexterity and speed.
7. Objective measures of mood and psychopathology.

Assessments with younger adults should also be attentive to the higher incidence of mood disorders in those with learning and attention deficit disorders, and will likely benefit from judicious use of achievement tests. Evaluations with older adults may benefit from using remote memory measures and cued recall techniques that can help distinguish between mood and amnestic disorders (Dierckx et al., 2007). Finally, the neuropsychologist should be leery of profiles associated with any given psychiatric condition, as at best there is overlap between many different psychiatric conditions, with no validated stable and unique elements for any given mood disorder.

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Figure 22-2 Example of Disrupted Emotion Processing and Regulation in MDD.