

# Are There Biological Commonalities among Different Psychiatric Disorders?

Christopher Pittenger<sup>1</sup>  
Amit Etkin<sup>2</sup>

<sup>1</sup>Department of Psychiatry, Yale University, New Haven, CT, USA

<sup>2</sup>Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA

## Introduction

Psychiatric diagnosis is in a state of flux (Kupfer et al. 2002, Zachar and Kendler 2007). Recent editions of the standard manual of American psychiatric diagnosis, the *Diagnostic and Statistical Manual (DSM)*, have espoused a neo-Kraepelinian diagnostic framework, wherein disorders are divided into discrete, often mutually exclusive entities on the basis of their symptoms (American Psychiatric Association 1980, 1994). This theory-neutral framework has enhanced the precision of psychiatric diagnosis and thereby accelerated psychiatric research over the past 25 years. Recent data challenge this framework, however, by emphasizing common features among ostensibly discrete disorders.

The National Comorbidity Survey, which examined the epidemiology of psychiatric disease across the population, illustrates the challenges faced by the categorical diagnostic system laid out in DSM-III and DSM-IV-TR. A startling percentage of patients with one disorder were found to have one, two, or more additional diagnoses. Moreover, the number of diagnoses correlated highly with the severity of symptoms (Kessler et al. 1994). This may suggest that the sickest psychiatric patients have an underlying vulnerability or predisposition toward psychopathology, independent of the particular symptoms expressed and of the specific diagnosis they receive under our current system.

This picture of commonality among disorders more closely resembles the schema of Griesinger than that of Kraepelin. Griesinger proposed in the 19th century that there is a single protean psychiatric disorder (*Enheitpsychose*) whose expression in different patients is modulated by continuously variable traits. With the next edition of the DSM planned for 2010, an active debate is underway as to what form psychiatric nosology should take (Kupfer et al.

2002). One important perspective in this debate is that of the neurobiology of psychiatric disorders, which has been advancing at an accelerating rate. This conceptual debate—whether psychiatric disease is best conceptualized in terms of discrete entities or of overlapping continua—therefore motivates the central question of this chapter; namely, are there biological commonalities among different psychiatric disorders?

In this chapter, and by way of introduction to the more focused discussions that follow, we explore evidence for the thesis that disorders that we currently consider to be distinct entities often have overlapping or shared biological underpinnings. In the first section, we briefly explore the general relationship between brain and behavior, and thus between disorders of brain function and psychiatric disease. We then provide examples of epidemiological, clinical, neuropathological, and genetic evidence for biological commonalities among different disorders. Finally, we explore a cognitive neuroscience perspective on this question in more detail. In so doing, we discuss how an understanding of the normal functions of different brain circuits informs hypotheses about the consequences of their disruption in psychiatric disease, and therefore how dysregulation of the same brain circuits across different disorders can shed light on aspects of their overlapping symptomatology. Throughout, we focus largely on three major disorders—schizophrenia, major depressive disorder, and drug addiction—making reference to other conditions where appropriate. While this discussion only scratches the surface of the rich neurobiology of these structures and the larger networks in which they are embedded, it serves to illustrate the contributions of an advancing neurobiological knowledge-base to our understanding of psychiatric neurobiology, of diagnosis and, it is to be hoped, of treatment.

## Diseases of the Mind and Diseases of the Brain

### Mind and Brain in Psychiatric Disease

Hippocrates first proposed a fundamental relationship between disordered behavior and disordered brain function. In the treatise on epilepsy entitled “On the Sacred Disease,” Hippocrates decries those who would ascribe this behavioral malady to an extracorporeal cause: “They who first referred this malady to the gods appear to me to have been just such persons as the conjurors, purificators, mountebanks, and charlatans.” Rather, he wrote that “the brain is the cause of this affliction, as it is of other very great disease” (Hippocrates 1952).

This correspondence has not always seemed obvious. Descartes’ substance dualism formalized the intuitive divide between functions of the body and functions of the mind, a division that continues to color Western thinking about brain and behavior. A dualist perspective persisted in formal psychiatric diagnosis into the latter part of the 20th century in the form of the organic/nonorganic distinction that was present in DSM-III (American Psychiatric Association 1980, Spitzer et al. 1989). Indeed, research into psychiatrists’ diagnostic practices and assignment of personal responsibility for symptoms of psychiatric disease reveals persistent dualist tendencies to this day (Miresco and Kirmayer 2006). However, the organic/nonorganic distinction was abandoned with DSM-IV in 1994 (American Psychiatric Association 1994), and by the end of the 20th century the equation of behavioral disorders with pathological brain states had become a fundamental tenet of psychiatry (Kandel 1998, Kendler 2005).

The simple statement that psychiatric disorders are brain disorders masks enormous complexity. Clear, unitary, causes of symptoms are rare in psychiatry. One example is found in the once common affliction known as *general paresis of the insane*. This condition, which was enormously common in the 19<sup>th</sup> and early 20th century, was a dreaded combination of psychosis, progressive dementia, and paralysis. In 1913 Noguchi and Moore discovered that general paresis results from tertiary syphilis, or chronic infection of the brain by the spirochete *Treponema pallidum*. When penicillin was found to kill the spirochete, general paresis became not only treatable but completely preventable if syphilis was treated early. This became a powerful paradigm of simple causation: a psychiatric entity, characterized by dramatic abnormalities in behavior and cognition, which was found to have a specifiable, straightforward biological cause, permitting a definitive new treatment.

Such single necessary and sufficient etiologic agents are, however, the exception in psychiatry. More often, multiple causal factors, each with a small effect, act in concert to produce disease. Moreover, the effects of causal factors may be described at multiple levels of scientific investigation. For example, in the case of major depressive disorder—an example to which we will return throughout this chapter—alterations have been reported in many different neurobiological processes. Genetic loci with a role in the vulnerability to major depression include regulators of monoaminergic neurotransmission as well as neurotrophic factors (Levinson 2006). Antidepressant drugs primarily act on the serotonergic and noradrenergic systems, but some antidepressant drugs also interact with receptors for the

neuropeptides corticotropin-releasing factor and substance P, glucocorticoids, the NMDA glutamate receptor, and cholinergic receptors (Holtzheimer and Nemeroff 2006). Functional and structural imaging has implicated dysfunction in dorsolateral prefrontal cortex, orbitofrontal cortex, cingulate cortex, and hippocampus. Postmortem studies indicate alterations in the number of glia in multiple brain regions as well as changes in neuronal density and the size of neuronal cell bodies (Rajkowska 2003) and a reduction in subpopulations of interneurons (Rajkowska et al. 2007). The etiology and biology of a disorder in which so many diverse genetic mechanisms, neurochemical systems, brain regions, and cellular abnormalities have been implicated are likely to be complex and multifactorial. The daunting complexity of psychiatric disorders therefore raises this question: how may one meaningfully investigate biological commonalities between disorders?

### Endophenotypes in Psychiatry

One fruitful way to come to terms with this complexity is through the analysis of *endophenotypes*. An endophenotype is a measurable neurobiological or psychological parameter that meaningfully contributes to an aspect of a psychiatric disorder but is simpler, less heterogeneous, and more closely tied to measurable aspects of the underlying biology. The study of working memory as an endophenotype, for example, has contributed greatly to an understanding of cognitive dysfunction in schizophrenia—an example that will be explored in greater detail later in this chapter. Endophenotypes may also be shared across overtly distinct disorders, as illustrated by the presence of working memory impairments in schizophrenia, major depression and attention-deficit hyperactivity disorder (ADHD). Investigations focusing on endophenotypes may therefore help bridge the explanatory gap between ultimate etiologic causes, such as genetic or environmental variables, and resulting psychiatric phenomenology (Gottesman and Gould 2003) and thereby provide a handle on biological commonalities.

In the latter portion of this chapter, we explore psychiatric endophenotypes from a cognitive neuroscience perspective. The premise for our arguments is that certain discrete psychological functions are mediated through consistent, definable neural circuitry. Deficits in these psychological functions (i.e., endophenotypes) are therefore likely to be associated with abnormalities in the associated neural circuits. Furthermore, the presence of similar endophenotypes in otherwise disparate disorders predicts that related alterations may be observable in the same neural circuitry. This approach to understanding different psychiatric disorders provides a powerful framework in which to conceptualize mental illness; namely, as a set of conditions that come about due to different combinations of endophenotypes. Therefore, a larger category of illness, such as schizophrenia or depression, may be better “carved at its joints” along endophenotypic lines.

### Specific Biological Commonalities Among Disorders

As mentioned earlier, evidence for shared biological perturbations across different psychiatric disorders can be sought in many domains. Before exploring a cognitive neuroscience perspective, we first briefly describe other ways in which

different psychiatric disorders can be seen to have overlapping biological underpinnings.

### Genetic Commonalities

Specific alleles of certain genes have been associated with multiple psychiatric disorders. For example, a polymorphism in the promoter region of the serotonin reuptake transporter (SERT) gene, which influences the efficiency of removal of serotonin from synapses, has been associated with numerous psychiatric disorders, including depression, psychosomatic disorders, alcoholism, smoking, eating disorders, ADHD, and autism (reviewed in Serretti et al. 2006). Similarly, polymorphisms in the dopamine beta hydroxylase (DBH) gene, whose product is the last step in the synthesis of norepinephrine from dopamine, have been associated with schizophrenia, cocaine-induced paranoia, depression, ADHD, and alcoholism (reviewed in Cubells and Zabetian 2004). The association of the same genetic polymorphism with several different disorders directly suggests shared neurobiological underpinnings.

Possession of a disease-associated gene variant, however, rarely guarantees development of disease. Rather, the risk of developing disease often derives from interaction of genetic contributors with environmental factors (e.g., Caspi et al. 2003). This fact further complicates an understanding of shared mechanisms across psychiatric disorders, leading to complex causal webs (e.g., Kendler et al. 2002, 2006).

### Environmental Etiologies

Important nongenetic etiological factors can also contribute to different psychiatric conditions. For example, childhood stress, including abuse and parental loss, is an important etiological contributor to major depression (e.g., Kendler et al. 2002, 2006), posttraumatic stress disorder (PTSD) (e.g., Pine and Cohen 2002), and borderline personality disorder (e.g., Lieb et al. 2004). This overlap suggests that the neurobiological consequences of childhood stress may be relevant to all of these disorders. Numerous other examples of etiological factors shared among discrete psychiatric disorders can be found in this textbook, and others will doubtless come to light as our understanding of the etiology of neuropsychiatric disease grows.

### Neurochemical Commonalities

Disruptions in defined neurochemical systems can contribute to a variety of psychiatric disorders. For example, dysregulation of dopaminergic neurotransmission is found in schizophrenia, affective disorders, and substance abuse (e.g., Mann 2003, Frankle et al. 2005). Disruption of noradrenergic neurotransmission is implicated in anxiety disorders, affective disorders, suicide, substance abuse, and PTSD (e.g., Mann 2003). Serotonin dysregulation has been linked to affective disorders, anxiety, PTSD, and many other conditions (e.g., Mann 2003). Dysregulation of glutamatergic neurotransmission has been linked to depression (e.g., Kugaya and Sanacora 2005, Pittenger et al. 2007), obsessive—compulsive disorder (OCD) (Pittenger et al. 2006a), anxiety disorders (e.g., Simon and Gorman 2006), and drug addiction (Kalivas et al. 2005). The fact that dysregulation of these neurochemical systems can contribute to so many different psychiatric disorders points yet again to shared neurobiological substrates.

### Histopathological Similarities

The characterization of histopathological abnormalities in psychiatric disorders is still in its infancy. Gross anatomical abnormalities suggestive of underlying cellular change, such as enlarged ventricles and widened sulci in dementia and schizophrenia, have been well characterized for some time (e.g., Steen et al. 2006), but documentation of more specific pathological changes in the brains of individuals with major psychiatric disorders has been harder to come by. Nonetheless, it is becoming clear that here, too, overlapping histopathological changes can correspond to different neuropsychiatric disorders. For example, reduced numbers of glial cells in regions of cortex have been described in major depression (Rajkowska et al. 1999), bipolar disorder (Rajkowska et al. 2002), alcohol dependence (Miguel-Hidalgo et al. 2002), and schizophrenia (Rajkowska et al. 2002). Functional or structural disruption of GABAergic interneurons has been described in schizophrenia (Lewis et al. 2005), major depression (Rajkowska et al. 2007), and Tourette syndrome (Kalanithi et al. 2005).

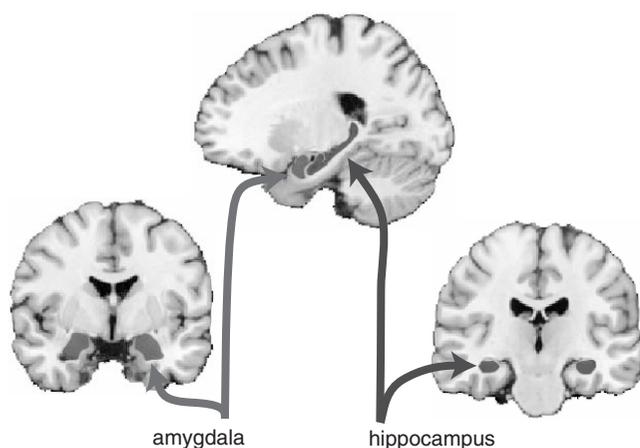
### Gross Anatomical Changes

The involvement of the same neuroanatomical structures can point the way to overlapping biology between disorders. Structural imaging studies have revealed several such examples. For example, reduced hippocampal size has been observed in depression, PTSD, Alzheimer's dementia, and schizophrenia (e.g., Sapolsky 2000, Gilbertson et al. 2002, Steen et al. 2006).

### Beyond Gross Anatomical Similarities: Functional Circuitry in Psychiatric Disease

Mental functioning derives from the operation of large groups of neurons, organized into nuclei, brain regions, and neural circuits. Understanding brain function in terms of functional neural circuitry is the domain of cognitive neuroscience, an approach enabled in part by advances in functional neuroimaging over the past few decades. A cognitive neuroscience perspective allows for integration across other levels of analysis, reflecting the functional consequences of genetic, neurochemical, histopathological and gross anatomical alterations in more psychologically meaningful terms.

The hippocampus provides a useful introductory example (Figure 000–1). As noted above, reduced hippocampal size and other pathological changes have been noted in several neuropsychiatric diseases, including major depression, PTSD, and some forms of dementia. Functional characterization of the hippocampus, in human neuroimaging studies, lesion studies, and animal models, reveals that it contributes critically to the formation of memories for both facts and events (e.g., Scoville and Milner 1957, Tulving 2002, Squire et al. 2004). It would be predicted, then, that memory may be impaired in those disorders in which disruption of hippocampal function has been described. And, indeed, declarative memory is impaired—most obviously in dementias such as Alzheimer's disease, but also in major depression and PTSD (Sapolsky 2000). The hippocampus also has an important role in the regulation of the stress response, as orchestrated in part by the hypothalamus-pituitary—adrenal (HPA) axis. And indeed, HPA axis regulation and the stress response are dysregulated in major depression, PTSD, and some



**Figure 000-1** Location and relationship of the human hippocampus and amygdala. As described in the text, the hippocampus has an important role in memory formation and stress modulation. Hippocampal dysfunction is implicated in numerous psychiatric disorders, including major depressive disorder, PTSD, schizophrenia, and dementia. The amygdala, which we do not treat in detail in this chapter but which is discussed at length elsewhere in this textbook, is involved in both negative and positive emotion, and is implicated clinically in mood and anxiety disorders.

dementias (McEwen 2004). Hippocampal dysfunction represents an endophenotype of multiple disorders.

This neural circuitry perspective on the question posed in this chapter—whether disparate psychiatric disorders have shared neurobiological underpinnings—has particular advantages, beyond its cogency in individual cases, that motivate its further exploration. First, by its nature it is of heuristic value in understanding the relationships between specific brain functions and the phenomenology of psychiatric disease. Second, it motivates the study of brain biology by psychiatric clinicians. Third, it represents a fruitful guide to future research: when seeking neurobiological data on a poorly understood psychiatric disorder, it is useful to examine brain areas whose normal function is known to correspond to domains in which the disorder's symptomatology is expressed.

Finally, examination of circuits that are perturbed in different psychiatric disorders is likely to inform the rational categorization of psychiatric disease, and is therefore likely to contribute to the ongoing debate as to what form DSM-V nosology should take. This is true for either a categorical or dimensional conception of psychiatric disease. If two conditions are shown to correspond to qualitatively different functional perturbations of a defined brain circuit, with minimal overlap, then different categorical diagnoses may be appropriate—even if the conditions are phenomenologically similar. Such a discovery might help differentiate a complex syndrome, such as major depression, into meaningfully different subtypes. Conversely, if two conditions are found to be characterized by qualitatively similar perturbations of a particular underlying brain circuit, they might best be conceptualized as lying along a continuum—even if they present quite differently at the clinical level. This might be the case, for example, in psychotic depression, psychotic mania, and schizophrenia, which could contribute to a dimensional categorization of psychosis that transcends our current diagnostic system.

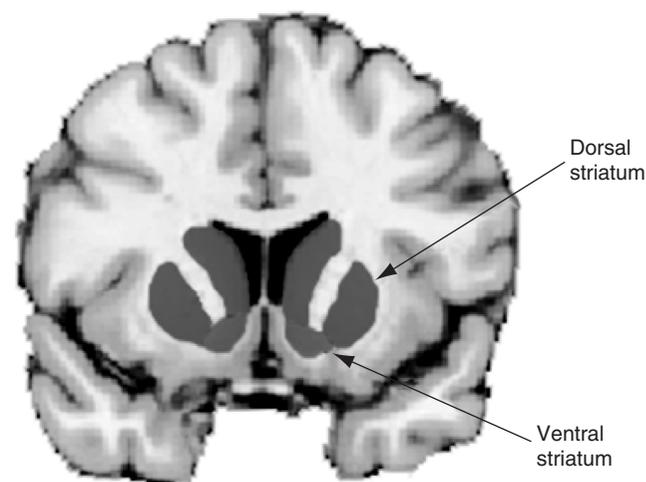
We spend the remainder of this chapter exploring this perspective on the shared biology of distinct psychiatric diseases. We focus on four particular circuits: the ventral striatum, the dorsal striatum, the anterior cingulate cortex, and the dorsolateral prefrontal cortex. While this treatment cannot be exhaustive, it demonstrates the utility of a cognitive neuroscience perspective and exhibits how commonalities between disorders at the level of brain circuitry can reveal relationships that may inform psychiatric diagnosis in the future.

### The Ventral Striatum and Mechanisms of Reward

As Freud famously emphasized, many of our actions are driven, directly or indirectly, by the quest for reward—food, sex, power, affiliation, acclaim. Investigation of the neurobiology of reward has revealed a central role for the ventral striatum, especially the nucleus accumbens, and related structures such as the orbitofrontal cortex and ventral tegmental area (VTA) in reward-driven behavior and reinforcement learning.

The striatum can be divided into at least two functionally distinct regions, the dorsal striatum (the caudate and putamen) and the ventral striatum (Figure 000-2; Haber 2005). The ventral striatum receives input from the orbital and medial frontal cortex, the hippocampus, the amygdala, and the thalamus. It also receives a prominent dopaminergic projection from the VTA, which has profound effects on motivational processing.

The cells of the VTA fire spikes, leading to phasic dopamine release in the nucleus accumbens, when an animal encounters an unexpected reinforcer—precisely the circumstances under which reinforced learning occurs (Schultz 2006). All addictive drugs also result in dopamine release in the nucleus accumbens (Wise and Rompre 1989, Hyman et al. 2006). Perturbations of the nucleus accumbens in experimental animals alter motivated behavior in response



**Figure 000-2** Anatomy of the human dorsal and ventral striatum, which are major input nuclei of the basal ganglia. As described in the text, the ventral striatum is implicated in reward and reinforced learning; dysregulation of ventral striatal function is implicated in addiction, schizophrenia, depression, and other disorders. The dorsal striatum functions both in motor control and in the acquisition and performance of automated learned behaviors, including habits; its dysfunction is implicated in OCD, drug addiction, and other disorders.

to drugs of abuse (e.g., Carlezon et al. 1998) and to naturally occurring reinforcers, including sex (e.g., Barrot et al. 2005), food (Georgescu et al. 2005), and emotional stimuli (Barrot et al. 2002). Similarly, the human ventral striatum, together with its orbitofrontal afferents, is central to the processing of reward expectation and response (McClure et al. 2004, Phan et al. 2002, Kringelbach 2005).

## Dysregulation of Reward in Disorders of the Ventral Striatum

### Drug Addiction

Dopamine release in the nucleus accumbens correlates with the “high” associated with consumption of drugs of abuse. Increased dopamine release in the orbitofrontal cortex, which projects to the accumbens, correlates with drug craving—the motivation to engage in behaviors aimed at procuring more of the abused substance (Volkow et al. 1997). In experimental animals, triggering of drug seeking by stress, drug-associated cues, or drug administration depends on activation of the accumbens by a glutamatergic projection from the prefrontal cortex (e.g., McFarland et al. 2003). Modulation of this circuitry is therefore likely to be important in future therapeutic strategies aimed at reducing relapse into drug use (reviewed by Kalivas and Volkow 2005).

Human and animal studies have demonstrated pathological changes in this prefrontal-accumbens circuitry after extended drug use. In cocaine users, dopamine release is attenuated in the ventral striatum, suggesting a compensatory response to chronic overstimulation (Volkow et al. 1997). Basal prefrontal metabolic activity is also reduced in drug addicts (reviewed in Kalivas and Volkow 2005). In animals, there are a variety of changes in the glutamatergic projection from the prefrontal cortex to the ventral striatum after chronic cocaine exposure (reviewed in Kalivas et al. 2005). Experimental manipulations in the nucleus accumbens can, in turn, alter animals’ behavioral responses to cocaine and other drugs of abuse (e.g., Carlezon et al. 1998). The chronic functional alterations in the reward-regulating circuitry correspond to the profound dysregulation of reward that is one of the core features of the addicted state.

### Mood Disorders

Depression and mania are characterized by opposite abnormalities of motivation and reward. Anhedonia, the blunting of motivation and pleasure, is one of the cardinal symptoms of major depression. Several functional neuroimaging studies have suggested that hypometabolism of the ventral striatum may underlie these symptoms (Dunn et al. 2002). For example, in depressed subjects Epstein et al. (2006) found reduced ventral striatal activation to positively valenced words; this reduction correlated with the intensity of their anhedonia. Studies in animal models of depression likewise implicate ventral striatal function in aspects of a depression-like state (Nestler and Carlezon 2006). Convergent evidence, therefore, implicates dysfunction of the ventral striatum in the anhedonia of depression. This circuit-level understanding of the etiology of anhedonia has recently received a dramatic application and test, when Schlaepfer et al. used direct stimulation of the nucleus accumbens as a treatment for profoundly refractory major depression, with promising initial results (Schlaepfer et al. 2007).

Manic patients display the inverse of anhedonia (Hasler et al. 2006), such that reward-driven behaviors are heightened. Typically, manic patients are driven to pursue the most immediate and potent rewards, namely food, sex, social attention, money, and drugs of abuse. The role of the ventral striatal reward circuitry in bipolar disorder is poorly understood. However, structural and functional imaging studies of bipolar disorder indicate dysfunction in a circuit that includes the ventral striatum (reviewed in Blumberg et al. 2004, Strakowski et al. 2005). For example, reduced gray matter in both ventral striatum and the anterior cingulate cortex have been shown to be associated with genetic risk for bipolar disorder (McDonald et al. 2004). It is plausible that the hyperhedonic state of mania correlates with dysregulated overactivity of the ventral striatum and associated structures involved in reward and reinforcement—the opposite of the effect seen in major depression.

### Schizophrenia

Anhedonia is also a cardinal symptom of schizophrenia. Indeed, this negative symptomatology is often more chronic and more disabling than the more colorful, episodic positive symptoms of psychosis. Perturbation of ventral striatal function may contribute to this aspect of schizophrenia. All effective antipsychotics are antagonists at the D2 subclass of dopamine receptors (reviewed in Kapur et al. 2006), which are prominent throughout the striatum. The ventral striatum of schizophrenics shows a blunted response to rewarding stimuli, which correlates with negative symptoms (Juckel et al. 2006) and appears analogous to anhedonia in major depression (e.g., Epstein et al. 2006). The blunting of ventral striatal reactivity in both schizophrenia and major depression suggests important overlap between the underlying neurobiology of these syndromes.

## The Dorsal Striatum and the Automation of the Routine

Many everyday actions have an automatic character. When driving a new road, attention is fully engaged. We respond flexibly to events and cues; we note associations between them and form explicit memories of the process. This contrasts with the experience of driving an overlearned route, like a daily commute. When driving such a route, it is a common experience to suddenly find oneself at one’s destination, having performed a complex series of behaviors without engaging much attention or forming any explicit memories at all. This automation of the routine is adaptive in that it frees attentional resources for other tasks, but it comes at a cost in behavioral flexibility. When engaged in a habitual pattern of responses, effort is required to deviate from the familiar pattern, as when one drives “on autopilot” to a familiar destination even when today’s goal differs from the norm.

Several lines of evidence implicate a circuit including the dorsal portion of the striatum—the caudate nucleus and putamen—in the automation of routine, overlearned behaviors (Mishkin and Petri 1984, Packard and Knowlton 2002, Yin and Knowlton 2006). The caudate and putamen, which regulate multiple aspects of behavior including motor patterning, oculomotor control, and habit learning, receive projections from virtually the entire neocortex and several subnuclei of the thalamus, along with modulatory input from hippocampus and other structures. They, in

turn, project to other, deeper nuclei of the basal ganglia and, ultimately, back to neocortex via the thalamus (Haber 2005).

Neuroimaging implicates the human caudate in overlearned, automated behaviors. For example, following an overlearned route in virtual reality engages the caudate nucleus, while navigating a novel route engages the dorsal hippocampus (Hartley et al. 2003). The caudate is also engaged by nonspatial “probabilistic classification learning,” a form of subconscious, or implicit, pattern recognition (Knowlton et al. 1996, Poldrack et al. 1999). Dorsal striatal function has also been implicated in implicit sequence-learning (e.g., Rauch et al. 1997) and certain motor-learning tasks (e.g., Gabrieli et al. 1997). Studies in rodents similarly support a role for the dorsal striatum in habit and related forms of procedural learning (e.g., Packard and McGaugh 1996, and Knowlton 2006, Pittenger et al. 2006b). Indeed, the pattern of striatal neuronal firing has been shown to shift during the learning of a striatum-dependent cue-driven simple navigation task (Jog et al. 1999).

### Maladaptive Habits in Disorders of the Dorsal Striatum

#### Obsessive–Compulsive Disorder (OCD)

OCD is characterized by intrusive, anxiety-provoking, irrational thoughts, and compulsive behaviors that attempt to relieve the anxiety that attends them. The stereotyped and automatic character of these thoughts has the appearance of a habitual cognition gone awry, suggesting that dysregulation of the dorsal striatum might contribute to the underlying neurobiology of OCD. Indeed, a circuit consisting of the orbitofrontal cortex, the striatum, and the thalamus has consistently been shown to be hyperactive in patients with OCD, and this pathological activation is moderated in parallel with symptom improvement after treatment with either psychotherapy or pharmacotherapy (reviewed in Jenike 2004). Learning of a striatum-dependent implicit sequence-learning task (Deckersbach et al. 2002) and of an implicit card-learning task (Joel et al. 2005) are disrupted in OCD, suggesting that the function of the striatum in learning new automated behaviors are disrupted by this circuit-level dysregulation. Further work will be needed to investigate whether this disruption contributes to the rigid habit-like structure of some OCD symptomatology.

#### Drug Addiction

Drug seeking is often initially motivated by the desire for pleasure or reward, and then at times by attempts to minimize the dysphoria of craving and withdrawal; as noted above, the ventral striatum and related circuitry play a major role in these phenomena. Later, with the development of true addiction, compulsive, habit-like behaviors develop—drug-associated behaviors that are executed automatically. These drug-associated behaviors, which are likely to derive from a subversion of the mechanisms of normal stimulus-response habit learning, are a particularly pernicious aspect of addiction, as they occur without conscious control and are resistant to extinction (Tiffany 1990, Robbins and Everitt 1999, Everitt and Robbins 2005). Automated drug-associated behaviors are likely to represent an important target in the development of novel treatments for addiction.

These observations predict dysregulation of the dorsal striatum in addicted states. Indeed, observations in animal models link compulsive drug-seeking behaviors to the dorsal striatum (Vanderschuren and Everitt 2004, Vanderschuren et al. 2005). In humans, cocaine dependence is associated with increased volume of the dorsal striatum (Jacobsen et al. 2001). Moreover, the dorsal striatum may have a particularly important role in drug seeking after abstinence in animals (Fuchs et al. 2006) and humans (Sinha et al. 2005).

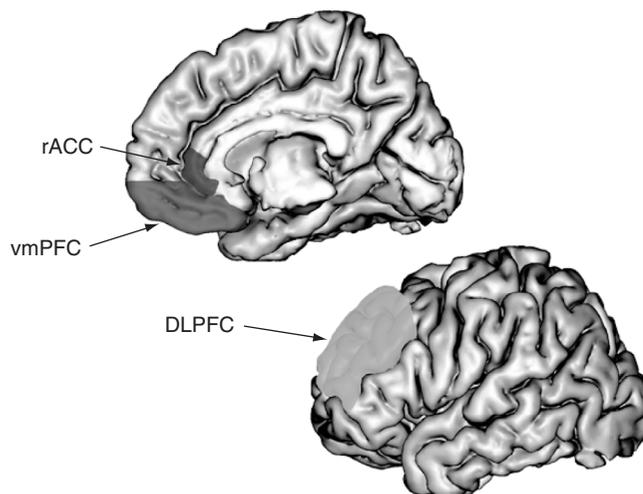
The association of perturbed dorsal striatal function with maladaptive, habit-like behaviors in OCD and drug addiction suggests an important role for the habit-forming circuitry of the dorsal striatum in these and related forms of psychopathology. This points to a commonality between disorders that are widely separated in our current diagnostic system, and may point the way to the development of new therapies specifically aimed at the mechanisms of habit formation.

### Prefrontal Cortex: Attention and Behavioral Flexibility

The capacity for creative, context-responsive flexibility in behavioral responses—termed “top-down” cognitive control or executive functioning—is a function of the frontal lobes. The prefrontal cortex (PFC) is typically not required for the learning or performance of simple tasks. But when task demands change, the PFC is required for proper adjustments in behavior to maintain accuracy. This role for the PFC in cognitive control is seen in humans (Milner 1963), nonhuman primates (Dias et al. 1996), and even in rodents (Birrell and Brown 2000). More broadly, the PFC is responsible for maintaining an internal representation of current goals and modulating activity in brain regions responsible for perception or action in order to flexibly achieve these goals. In order to accomplish this, the PFC must be able to (1) maintain a representation of goals in the face of distraction (working memory), (2) update these representations as new information is received, through multiple sensory modalities, and (3) provide a feedback signal that can select the neural pathways appropriate for the current task context (Miller and Cohen 2001).

In humans, frontal cortical cognitive control mechanisms have been probed using a variety of behavioral tasks. Cognitive control tasks of various sorts recruit a consistent prefrontal network, which includes the dorsolateral PFC (DLPFC) (Duncan and Owen 2000) (see Figure 000–3). In the classic color-word Stroop task (Stroop 1935), for example, subjects have to name the ink color of a word whose meaning is either congruent (e.g., GREEN printed in green ink) or incongruent with the ink color (e.g., GREEN printed in red ink). Naming the ink color in an incongruent trial requires subjects to ignore word meaning. The conflict between the ink color and the incongruent word meaning slows reaction times and increases errors, a phenomenon known as the Stroop effect.

When subjects experience conflict on an incongruent Stroop trial, however, they also reflexively prepare for a subsequent incongruent trial. Consequently, reaction time becomes faster on the second of two consecutive incongruent trials. This anticipatory adjustment in cognitive control for the purpose of performance improvement has been linked to activation of the DLPFC (Kerns et al. 2004).



**Figure 000-3** Neuroanatomy of the frontal cortical structures described in the text. The rostral anterior cingulate cortex (rACC) and ventromedial prefrontal cortex (vmPFC) have roles in emotion regulation, especially in the absence of an explicit attempt to regulate emotional processing. The dorsolateral prefrontal cortex (DLPFC) is critical for working memory and executive function and for deliberate forms of emotion regulation. As described in the text, functional perturbation of these structures and of their functional interrelationships is implicated in numerous psychiatric disorders, including schizophrenia, PTSD, and depression.

Consistent with this, subjects with frontal lobe lesions have difficulty dealing with color-word conflict and make more errors in the Stroop task (Vendrell et al. 1995). The DLPFC achieves this top-down cognitive control in part by enhancing the sensory representation of an object at the focus of attention (Egner and Hirsch 2005).

The capacity for increasing cognitive control to meet task demands, however, is not unlimited. This is illustrated by the *n*-back task, in which subjects must decide on each trial whether the current stimulus matches the one shown 1, 2, or 3 trials back. Doing so requires the sequential updating of working memory content, and maintenance of task goals in the face of increased working memory load. Frontal lobe lesions lead to more errors at greater working memory loads in this task (Muller et al. 2002). Activity in the DLPFC increases as task demands increase through the 0-, 1- and 2-back conditions (Callicott et al. 1999). As subjects' working memory capacities are exceeded at the more difficult 3-back condition, however, both subjects' performance and dorsolateral prefrontal activity decline relative to the 2-back condition.

### Attentional Deficits in Disorders of the Prefrontal Cortex

#### Schizophrenia

Psychosis often dominates the initial presentation of schizophrenia. However, negative symptoms and cognitive dysfunction, including impairments in executive function and working memory, are more chronic, better predict poor outcome, and are not substantially helped by available pharmacotherapies (Harvey et al. 2004). Patients with schizophrenia typically perform worse than control subjects in many neuropsychological tests of frontal lobe function, and this deficit has been linked to greater disorganization of

thought and speech (Kerns and Berenbaum 2002). It is of great interest, therefore, to examine prefrontal cortical function in schizophrenics during tasks that require elements of the cognitive control processes discussed above.

Neuroimaging studies of working memory have indeed found abnormal activation of DLPFC in these patients, but of inconsistent direction: while some studies have found hypoactivation in schizophrenics, others have found hyperactivation. This seeming inconsistency in the data led to debate about the nature of the neuropsychologically suggested “hypofrontality” of patients with schizophrenia.

A solution to this debate arose from the finding that activity in the DLPFC of healthy subjects decreases from its peak as working memory is stressed beyond its maximal capacity (Callicott et al. 1999). If the DLPFC of schizophrenic patients operates less efficiently than that of controls, patients may be found to hyperactivate this region as they strain to keep up with low working memory loads that control subjects can easily handle, and hypoactivate this region at higher working memory loads that exceed patients' working memory capacity, but not that of controls (Callicott et al. 2003b). In other words, whether relative hyper- or hypofrontality is found in imaging studies depends on the presence of performance differences between patients and controls. Unaffected siblings of schizophrenics, who carry some of the genetic load for the disease, were found to hyperactivate the DLPFC relative to performance-matched controls in a working memory task, consistent with reduced processing efficiency in this region (Callicott et al. 2003a).

#### Depression

Patients with major depression also often display neurocognitive deficits consistent with frontal lobe dysfunction, though the deficits are generally not as severe as those seen in schizophrenia (reviewed in Rogers et al. 2004). Imaging studies of resting blood flow or metabolism have supported the view that cognitive control circuitry is perturbed in depression. A number of studies have noted DLPFC hypometabolism in depressed patients (Drevets 1999). These findings support an influential theory of depression, which suggests that hypofunction of the DLPFC and related prefrontal regions accounts for the cognitive symptoms of depression—problems with attention, concentration, and memory (Mayberg 2003). The relationship between these abnormalities and the central mood and motivational symptoms of depression, however, remains unclear.

Neuroimaging studies of activation during cognitive control tasks such as those discussed above have further suggested inefficiency of DLPFC activity in depressed patients. This is true both for the Stroop task (Wagner et al. 2006) and the *n*-back task (Harvey et al. 2005). These studies, however, suggest that while the DLPFC is inefficient in major depression, its capacity for increasing its activity to match task demands is not as easily overwhelmed as that of the DLPFC of schizophrenics.

#### Prefrontal Cortex: “Deliberate” Versus “Implicit” Emotion Regulation Strategies

We are constantly exposed to a larger number of sensory stimuli than our sensory and cognitive resources can process. Representations of individual stimuli therefore compete

for attentional selection to determine which will be further processed, encoded in memory, or used for preparation for action; this is known as the biased competition model of attention. Emotionally salient stimuli are widely believed to have a special advantage in this competition, as evaluation of an emotional stimulus may be critical for predicting threat or reward. Because emotional stimuli nonetheless must compete for further processing, regulation of the effects of emotional stimuli is thought to occur through the same cognitive control process that selects between competing nonemotional stimulus representations.

Gross (2002) has proposed a framework for classifying different emotion regulation strategies. One important distinction is between “antecedent-focused” strategies, which aim to alter emotional responses before they begin, and “response-focused” strategies, which suppress emotional responses after they have been initiated. Antecedent-focused strategies include willful detachment, distraction, and cognitive reappraisal; response-focused strategies include voluntary suppression of positive or negative emotional reactions. Unstated within this framework is that an emotion regulation strategy may be “deliberate,” requiring conscious top-down intentionality, or “implicit,” engaging top-down regulation of emotional processes without requiring conscious intentionality.

Several recent neuroimaging studies of the neural circuitry associated with deliberate efforts at emotion regulation (Beauregard et al. 2001, Kalisch et al. 2005, Kalisch et al. 2006, Levesque et al. 2003, Ochsner et al. 2004) find that deliberate emotion regulation involves the DLPFC, which is associated with top-down cognitive control, regardless of whether an antecedent-focused or a response-focused strategy is being employed. This view of emotion regulation, moreover, suggests that in any disorder in which the DLPFC is dysfunctional, such as in schizophrenia and depression, one might expect deficits in deliberative forms of emotional regulation. Difficulty regulating emotion in this manner would be a specific instance of a more general cognitive control deficit.

A different picture emerges when one considers implicit forms of emotion regulation. Implicit emotion regulation is based on an individual’s expectation or anticipation of emotional stimuli, but without the explicit goal of emotion regulation, and appears to be mediated by top-down regulation of limbic structures by the rostral (pregenual) portion of the anterior cingulate cortex (rACC) and adjacent ventromedial PFC (vmPFC) (see Figure 000–3). These regions have direct projections to regions involved in emotion, such as the amygdala and brain stem. Studies in the likely rodent homologs of these areas also suggest that these projections are inhibitory in nature (Quirk et al. 2003). Importantly, abnormalities in circuitry mediating implicit emotional regulation can be seen in emotional dysregulation disorders in which no dorsolateral prefrontal deficits are observed (Etkin and Wager 2007).

To frame implicit emotional regulation more clearly in the experimental methods employed by the cognitive control literature, Etkin et al. (2006) recently developed an emotional analog to the color-word Stroop task. They showed subjects images of fearful or happy facial expressions and asked them to identify the affect. Written across the faces were the words “fear” or “happy,” which were either of the

same affect (congruent) or of a different affect (incongruent) as the facial expression. As in the color-word Stroop task, subjects were to ignore the text but were unable to avoid involuntarily reading the word and extracting its meaning. The emotional meaning of the words thus led to direct conflict with interpretation of the facial affect. As a result, incongruent stimuli interfered with affect identification in all subjects.

Resolution of emotional conflict in this task activated the rACC, rather than the DLPFC. Rostral anterior cingulate activation was accompanied by a simultaneous and correlated reduction in amygdala activity. These results are consistent with a recent study of the extinction of conditioned fear responses, in which subjects evaluate and override expectations for aversive stimuli. Fear extinction involved increased activity in the rACC and vmPFC and decreased activity in the amygdala (Phelps et al. 2004). Likewise, rostral anterior cingulate activation has also been observed during placebo anxiety reduction, a process in which control over an emotional stimulus (an aversive picture) is recruited to diminish the effect of the emotional stimulus (Petrovic et al. 2005).

## Dysfunctional Emotion Regulation in Disorders of the Prefrontal Cortex

### Posttraumatic Stress Disorder (PTSD)

PTSD is characterized by prominent emotional dysregulation. Patients experience disproportionate arousal—often to stimuli processed outside of conscious awareness—and have exaggerated startle responses, vivid intrusive thoughts, and unbidden images in the form of flashbacks and nightmares related to past trauma (Ehlers and Clark 2000). Patients may go to great lengths to avoid physical or psychological trauma reminders, and may experience dissociative symptoms or emotional numbing. It has been suggested that PTSD is a disorder of excessive conditioned fear, triggered by a severe and often discrete traumatic event (Ehlers and Clark 2000). This view, however, appears to explain only some PTSD symptoms; in particular, it leaves out the symptoms of emotional dysregulation, such as dissociation, emotional numbing, and intrusive thoughts and images.

Neuroimaging studies have searched for markers of abnormal fear responses and abnormal emotion regulation. Amygdala hyperactivity in patients has been noted in a number of these studies (reviewed in Bremner 2004) and has been used to support an excessive fear conditioning model of PTSD. Significant inconsistencies exist in the neuroimaging literature, however, as a number of similar studies have reported no abnormality, or even hypoactivation, in the amygdala of patients with PTSD (Etkin and Wager 2007).

More consistently observed is hypoactivation within the rACC and vmPFC in patients with PTSD (Bremner et al. 2004). DLPFC deficits, in contrast, have not been reported. Moreover, data from other anxiety disorders in which excessive conditioned fear has been proposed to be an important mechanism—social anxiety disorder and specific phobia—suggest that rACC and ventromedial prefrontal hypoactivity is specific for PTSD (Rauch et al. 2003, Bremner et al. 2004, Shin et al. 2006, Etkin and Wager 2007). Thus, these data suggest that emotional dysregulation in PTSD is related to abnormalities in implicit forms of emotion regulation, which

involve the rACC and vmPFC, and spares more deliberate forms of emotion regulation that rely on DLPFC cognitive control mechanisms.

### Depression

Helen Mayberg has developed a model of depression (Mayberg 2003) in which the rACC serves as a regulator region, linking dorsal cognitive/attentional circuitry (dorsal anterior cingulate and DLPFC) with ventral emotional/vegetative circuitry (subgenual anterior cingulate, amygdala, brain stem, and hypothalamus). A number of studies have noted a positive correlation between the outcome of antidepressant treatment and pretreatment levels of rACC activity. A landmark PET study of the pharmacological treatment of unipolar depression, for example, found that resting activity in the rACC uniquely differentiated treatment responders from nonresponders (Mayberg et al. 1997); responders were hypermetabolic prior to treatment with respect to controls, while nonresponders were hypometabolic. Subsequent studies have found similar positive correlations between pretreatment rACC activity and outcome in response to paroxetine (Saxena et al. 2003), nortriptyline (Pizzagalli et al. 2001), venlafaxine (Davidson et al. 2003), and partial sleep deprivation (Wu et al. 1999). Importantly, these results generalize across widely varying neuroimaging methods, including resting FDG-PET (Mayberg et al. 1997, Saxena et al. 2003, Wu et al. 1999), fMRI activation to emotional stimuli (Davidson et al. 2003) and resting EEG (Pizzagalli et al. 2001). Consistent with the outcome-based studies above, an fMRI study of treatment-resistant depression found hypoactivity in the rostral rACC of patients in response to both positive and negative affective pictures (Kumari et al. 2003).

Together, these data suggest that certain treatment-resistant subtypes of depression involve hypofunction of the rACC. If the rostral anterior cingulate is critical for implicit emotional regulation, as suggested above, then its hypofunction may indicate poor capacity to modulate negative emotion. It is furthermore interesting to note that while consistent findings have been observed in the rACC, a comparable relationship between DLPFC activity and clinical outcome has not been observed. Thus, hypofunction of the rACC in patients who are less likely to respond to treatment may represent a neural marker of poor emotional coping resources. Patients who cannot draw on their implicit emotion regulatory reserves may benefit less from treatment.

### Conclusion

Our understanding of the neurobiological abnormalities underlying many psychiatric disorders is rudimentary. Nevertheless, it is becoming clear that the pathophysiology of different psychiatric syndromes results from overlapping perturbations in specific brain systems. This observation challenges current psychiatric diagnostic practices, based as they are on discrete categorical constructs.

We have explored one perspective on the shared neurobiological substrates of disparate psychiatric disorders in detail: that of cognitive neuroscience. Examination of the normal function of various brain regions and circuits, through human lesion and neuroimaging studies and in animal models, produces a progressively refined understanding of regional brain function under normal circumstances. Functional abnormalities in these brain regions or circuits

across distinct psychiatric disorders demonstrate how perturbation of normal brain function relates to specific domains of psychiatric phenomenology and endophenotypes. Such a circuit-level understanding of a disorder can have dramatic implications, as illustrated by the recent interest in invasive neurosurgical techniques for directly modulating brain function—such as by deep brain stimulation—for otherwise refractory psychiatric disease (Mayberg et al. 2005, Greenberg et al. 2006, Schlaepfer et al. 2007).

We have illustrated these principles with several well-characterized neural circuits, and shown how dysfunction of individual functional circuits can contribute to aspects of multiple different psychiatric disorders. This is hardly a complete catalog of brain regions and functions with which such a cognitive neuroscience perspective could be illustrated, nor is our treatment of the circuits and functions that we have described in any way comprehensive. Our purpose has rather been illustrative—to give examples of the utility of a cognitive neuroscience perspective and how it supports the idea that distinct neuropsychiatric conditions have biological commonalities.

This fact has important implications. It reinforces the now obvious truth that psychiatry must, as it advances, be informed by neuroscience, and that an understanding of the normal function of the brain is essential to comprehending how its perturbation can lead to disease. This perspective also illustrates how understanding the underlying biological substrates of psychiatric conditions can inform how we classify psychiatric symptomatology. Likewise, a biological understanding impacts how we view the relationship, both etiological and phenomenological, between disorders that we have previously considered distinct under the symptom-based, categorical nosology of DSM-III and DSM-IV-TR.

Ultimately, the exploration of biological commonalities among different psychiatric disorders, and of endophenotypes that are shared by different disorders, may present a major challenge to our current categorical diagnostic system. When the same neural systems are perturbed in two disorders, what is it that makes them distinct? Conversely, when symptomatically different conditions share underlying etiological factors, whence derives the difference in symptomatic presentation? Future diagnostic systems will have to reflect both the degree of biological relatedness across disorders and the biological and phenomenological differences between syndromes. In the future, we may diagnose psychiatric illnesses on new axes of genetic, environmental, and neural systems levels of analysis, resulting in unexpected groupings of disorders into new categories, spectrums, and dimensions of psychopathology.

### References

- American Psychiatric Association (1980) *Diagnostic and Statistical Manual of Mental Disorders*, 3<sup>rd</sup> edition. American Psychiatric Publishing, Washington, DC, USA.
- American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*, 4<sup>th</sup> edition. American Psychiatric Publishing, Washington, DC, USA.
- Barrot M, Olivier JD, Perrotti LI, et al. (2002) CREB activity in the nucleus accumbens shell controls gating of behavioral responses to emotional stimuli. *Proceedings of the National Academy of Sciences of the USA* 99, 11435–11440.
- Barrot M, Wallace DL, Bolanos CA, et al. (2005) Regulation of anxiety and initiation of sexual behavior by CREB in the nucleus accumbens. *Proceedings of the National Academy of Sciences of the USA* 102, 8357–8362.

- Beauregard M, Levesque J, and Bourgouin P (2001) Neural correlates of conscious self-regulation of emotion. *Journal of Neuroscience* 21, RC165.
- Birrell JM and Brown VJ (2000) Medial frontal cortex mediates perceptual attentional set shifting in the rat. *Journal of Neuroscience* 20, 4320–4324.
- Blumberg HP, Kaufman J, Martin A, et al. (2004) Significance of adolescent neurodevelopment for the neural circuitry of bipolar disorder. *Annals of the New York Academy of Sciences* 1021, 376–383.
- Bremner JD (2004) Brain imaging in anxiety disorders. *Expert Review of Neurotherapeutics* 4, 275–284.
- Bremner JD, Vermetten E, Vythilingam M, et al. (2004) Neural correlates of the classic color and emotional Stroop in women with abuse-related post-traumatic stress disorder. *Biological Psychiatry* 55, 612–620.
- Callicott JH, Egan MF, Mattay VS, et al. (2003a) Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *American Journal of Psychiatry* 160, 709–719.
- Callicott JH, Mattay VS, Bertolino A, et al. (1999) Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cerebral Cortex* 9, 20–26.
- Callicott JH, Mattay VS, Verchinski BA, et al. (2003b) Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *American Journal of Psychiatry* 160, 2209–2215.
- Carlezon WA Jr., Thome J, Olson VG, et al. (1998) Regulation of cocaine reward by CREB. *Science* 282, 2272–2275.
- Caspi A, Sugden K, Moffitt TE, et al. (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301, 386–389.
- Cubells JF and Zabetian CP (2004) Human genetics of plasma dopamine beta-hydroxylase activity: applications to research in psychiatry and neurology. *Psychopharmacology* 174, 463–476.
- Davidson RJ, Irwin W, Anderle MJ, et al. (2003). The neural substrates of affective processing in depressed patients treated with venlafaxine. *American Journal of Psychiatry* 160, 64–75.
- Deckersbach T, Savage CR, Curran T, et al. (2002) A study of parallel implicit and explicit information processing in patients with obsessive-compulsive disorder. *American Journal of Psychiatry* 159, 1780–1782.
- Dias R, Robbins TW, and Roberts AC (1996) Dissociation in prefrontal cortex of affective and attentional shifts. *Nature* 380, 69–72.
- Duncan J and Owen AM (2000) Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences* 23, 475–483.
- Dunn RT, Kimbrell TA, Ketter TA, et al. (2002) Principal components of the Beck Depression Inventory and regional cerebral metabolism in unipolar and bipolar depression. *Biological Psychiatry* 51, 387–399.
- Drevets WC (1999) Prefrontal cortical-amygdalar metabolism in major depression. *Annals of the New York Academy of Sciences* 877, 614–637.
- Ehlers A and Clark DM (2000) A cognitive model of posttraumatic stress disorder. *Behaviour Research and Therapy* 38, 319–345.
- Egner T and Hirsch J (2005) Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nature Neuroscience* 8, 1784–1790.
- Epstein J, Pan H, Kocsis JH, et al. (2006) Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. *American Journal of Psychiatry* 163, 1784–1790.
- Etkin A, Egner T, Peraza DM, et al. (2006) Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron* 51, 871–882.
- Etkin A and Wager TD (2007) Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry* 164, 1476–1488.
- Everitt BJ and Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature Neuroscience* 8, 1481–1489.
- Frankle WG, Slifstein M, Talbot PS, et al. (2005) Neuroreceptor imaging in psychiatry: theory and applications. *International Journal of Neurobiology* 67, 385–440.
- Fuchs RA, Branham RK, and See RE (2006). Different neural substrates mediate cocaine seeking after abstinence versus extinction training: a critical role for the dorsolateral caudate-putamen. *Journal of Neuroscience* 26, 3584–3588.
- Gabrieli JD, Stebbens GT, Singh J, et al. (1997) Intact mirror-tracing and impaired rotary-pursuit skill learning in patients with Huntington's disease: evidence for dissociable memory systems in skill learning. *Neuropsychologia* 1, 272–281.
- Georgescu D, Sears RM, Hommel JD, et al. (2005) The hypothalamic neuropeptide melanin-concentrating hormone acts in the nucleus accumbens to modulate feeding behavior and forced-swim performance. *Journal of Neuroscience* 25, 2933–2940.
- Gilbertson MW, Shenton ME, Ciszewski A, et al. (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience* 5, 1242–1247.
- Gottesman II and Gould TD (2003) The endophenotype concept in psychology: etymology and strategic intentions. *American Journal of Psychiatry* 160, 636–645.
- Greenberg BD, Malone DA, Friehs GM, et al. (2006) Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology* 31, 2384–2393.
- Gross JJ (2002) Emotion regulation: affective, cognitive, and social consequences. *Psychophysiology* 39, 281–291.
- Haber S (2005) The basal ganglia. In *The Human Nervous System*, Paxinos G and Mai J (eds). Academic Press, New York, USA.
- Hartley T, Maguire EA, Spiers HJ, et al. (2003) The well-worn route and the path less traveled: distinct neural bases of route following and wayfinding in humans. *Neuron* 37, 877–888.
- Harvey PD, Green MF, Keefe RS, et al. (2004) Cognitive functioning in schizophrenia: a consensus statement on its role in the definition and evaluation of effective treatments for the illness. *Journal of Clinical Psychiatry* 65, 361–372.
- Harvey PO, Fossati P, Pochon JB, et al. (2005) Cognitive control and brain resources in major depression: An fMRI study using the *n*-back task. *Neuroimage* 26, 860–869.
- Hasler G, Drevets WC, Gould TD, et al. (2006) Toward constructing an endophenotype strategy for bipolar disorders. *Biological Psychiatry* 60, 93–105.
- Hippocrates (1952) On the sacred disease. In *Great Books of the Western World*, Vol. 10, Hippocrates and Galen (eds). William Benton, Chicago, USA, pp 154–160.
- Holtzheimer PE 3rd and Nemeroff CB (2006) Advances in the treatment of depression. *NeuroRx* 3, 42–56.
- Hyman SE, Malenka RC, and Nestler RJ (2006) Neural mechanisms of addiction: the role of reward-related learning and memory. *Annual Review of Neuroscience* 29, 565–598.
- Jacobsen LK, Giedd JN, Gottschalk C, et al. (2001) Quantitative morphology of the caudate and putamen in patients with cocaine dependence. *American Journal of Psychiatry* 158, 486–489.
- Jenike MA (2004) Clinical practice: Obsessive-compulsive disorder. *New England Journal of Medicine* 350, 259–265.
- Joel D, Zohar O, Afek M, et al. (2005) Impaired procedural learning in obsessive-compulsive disorder and Parkinson's disease, but not in major depressive disorder. *Behavioural Brain Research* 157, 253–263.
- Jog MS, Kubota Y, Connolly CI, et al. (1999) Building neural representations of habits. *Science* 286, 1745–1749.
- Juckel G, Schlagenhauf F, Koslowski M, et al. (2006) Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage* 29, 409–416.
- Kalanithi PS, Zheng W, Kataoka Y, et al. (2005) Altered parvalbumin-positive neuron distribution in basal ganglia of individuals with Tourette syndrome. *Proceedings of the National Academy of Sciences of the USA* 102, 13307–13312.
- Kalisch R, Wiech K, Critchley HD, et al. (2005) Anxiety reduction through detachment: subjective, physiological, and neural effects. *Journal of Cognitive Neuroscience* 17, 874–883.
- Kalisch R, Wiech K, Herrmann K, et al. (2006) Neural correlates of self-distraction from anxiety and a process model of cognitive emotion regulation. *Journal of Cognitive Neuroscience* 18, 1266–1276.
- Kalivas PW and Volkow ND (2005) The neural basis of addiction: a pathology of motivation and choice. *American Journal of Psychiatry* 162, 1403–1413.
- Kalivas PW, Volkow N, and Seamns J (2005) Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. *Neuron* 45, 647–650.
- Kandel ER (1998) A new intellectual framework for psychiatry. *American Journal of Psychiatry* 155, 457–469.
- Kapur S, Agid O, Mizrahi R, et al. (2006) How antipsychotics work—from receptors to reality. *NeuroRx* 3, 10–21.
- Kendler KS (2005) Toward a philosophical structure for psychiatry. *American Journal of Psychiatry* 162, 433–440.

- Kendler KS, Gardner CO, and Prescott CA (2002) Toward a comprehensive developmental model for major depression in women. *American Journal of Psychiatry* 159, 1133–1145.
- Kendler KS, Gardner CO, and Prescott CA (2006) Toward a comprehensive developmental model for major depression in men. *American Journal of Psychiatry* 163, 115–124.
- Kerns JG and Berenbaum H (2002) Cognitive impairments associated with formal thought disorder in people with schizophrenia. *Journal of Abnormal Psychology* 111, 211–224.
- Kerns JG, Cohen JD, MacDonald AW III, et al. (2004) Anterior cingulate conflict monitoring and adjustments in control. *Science* 303, 1023–1026.
- Kessler RC, McGonagle KA, Zhao S, et al. (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry* 51, 8–19.
- Knowlton BJ, Mangels JA, and Squire LR (1996) A neostriatal learning system in humans. *Science* 273, 1399–1402.
- Kringelbach ML (2005) The human orbitofrontal cortex: linking reward to hedonic experience. *Nature Reviews Neuroscience* 6, 691–702.
- Kugaya A and Sanacora G (2005) Beyond monoamines: glutamatergic function in mood disorders. *CNS Spectrums* 10, 808–819.
- Kumari V, Mitterschiffthaler MT, Teasdale JD, et al. (2003) Neural abnormalities during cognitive generation of affect in treatment-resistant depression. *Biological Psychiatry* 54, 777–791.
- Kupfer DJ, First MB, and Regier DA (eds) (2002) *A Research Agenda for DSM-V*. University of Pittsburgh Press, Pittsburgh, PA, USA.
- Levesque J, Eugene F, Joanette Y, et al. (2003) Neural circuitry underlying voluntary suppression of sadness. *Biological Psychiatry* 53, 502–510.
- Levinson DF (2006) The genetics of depression: a review. *Biological Psychiatry* 60, 84–92.
- Lewis DA, Hashimoto T, and Volk DW (2005) Cortical inhibitory neurons and schizophrenia. *Nature Reviews Neuroscience* 6, 312–324.
- Lieb K, Zanarini MC, Schmahl C, et al. (2004) Borderline personality disorder. *Lancet* 364, 453–461.
- Mann JJ (2003) Neurobiology of suicidal behaviour. *Nature Reviews Neuroscience* 4, 819–828.
- Mayberg HS (2003) Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *British Medical Bulletin* 65, 193–207.
- Mayberg HS, Brannan SK, Mahurin RK, et al. (1997) Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 8, 1057–1061.
- Mayberg HS, Lozano AM, Voon V, et al. (2005) Deep brain stimulation for treatment-resistant depression. *Neuron* 45, 651–60.
- McClure SM, York MK, and Montague PR (2004) The neural substrates of reward processing in humans: the modern role of fMRI. *Neuroscientist* 10, 260–268.
- McDonald C, Bullmore ET, Sham PC, et al. (2004) Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. *Archives of General Psychiatry* 61, 974–984.
- McEwen BS (2004) Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Annals of the New York Academy of Sciences* 1032, 1–7.
- McFarland K, Lapish CC, and Kalivas PW (2003) Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *Journal of Neuroscience* 23, 3531–3537.
- Miguel-Hidalgo JJ, Wei J, Andrew M, et al. (2002) Glia pathology in the prefrontal cortex in alcohol dependence with and without depressive symptoms. *Biological Psychiatry* 52, 1121–1133.
- Miller EK and Cohen JD (2001) An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience* 24, 167–202.
- Milner B (1963) Effects of different brain lesions on card sorting. *Archives of Neurology* 9, 90.
- Miresco MJ and Kirmayer LJ (2006) The persistence of mind-brain dualism in psychiatric reasoning about clinical scenarios. *American Journal of Psychiatry* 163, 913–918.
- Mishkin M and Petri HL (1984) Memories and habits: some implications for the analysis of learning and retention. In *Neuropsychology of Memory*, Squire LR and Butters N (eds). . Guilford, New York, USA, pp 287–296.
- Muller NG, Machado L, and Knight RT (2002) Contributions of subregions of the prefrontal cortex to working memory: evidence from brain lesions in humans. *Journal of Cognitive Neuroscience* 14, 673–686.
- Nestler EJ and Carlezon WA Jr. (2006) The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry* 59, 1151–1159.
- Ochsner KN, Ray RD, Cooper JC, et al. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage* 23, 483–499.
- Packard MG and Knowlton BJ (2002) The learning and memory functions of the basal ganglia. *Annual Review of Neuroscience* 25, 563–593.
- Packard MG and McGaugh JL (1996) Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiology of Learning and Memory* 65, 65–72.
- Petrovic P, Dietrich T, Fransson P, et al. (2005) Placebo in emotional processing—induced expectations of anxiety relief activate a generalized modulatory network. *Neuron* 46, 957–969.
- Phan KL, Wager T, Taylor SF, et al. (2002) Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 16, 331–348.
- Phelps EA, Delgado MR, Nearing KI, et al. (2004) Extinction learning in humans: role of the amygdala and vmPFC. *Neuron* 43, 897–905.
- Pine DS and Cohen JA (2002) Trauma in children and adolescents: risk and treatment of psychiatric sequelae. *Biological Psychiatry* 51, 519–531.
- Pittenger C, Fasano S, Mazzocchi-Jones D, et al. (2006b). Impaired bidirectional synaptic plasticity and procedural memory formation in striatum-specific cAMP response element-binding protein-deficient mice. *Journal of Neuroscience* 26, 2808–2813.
- Pittenger C, Krystal JH, and Coric V (2006a) Glutamate-modulating drugs as novel pharmacotherapeutic agents in the treatment of obsessive-compulsive disorder. *NeuroRx* 3, 69–81.
- Pittenger C, Sanacora G, and Krystal JH (2007) The NMDA receptor as a therapeutic target in major depressive disorder. *CNS and Neurological Disorders—Drug Targets* 6, 101–115.
- Pizzagalli D, Pascual-Marqui RD, Nitschke JB, et al. (2001) Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *American Journal of Psychiatry* 158, 405–415.
- Poldrack RA, Prabhakaran V, Seger C, et al. (1999). Striatal activation during cognitive skill learning. *Neuropsychologia* 13, 564–574.
- Quirk GJ, Likhtik E, Pelletier JG, et al. (2003) Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. *Journal of Neuroscience* 23, 8800–8807.
- Rajkowska G (2003) Depression: what we can learn from postmortem studies? *Progress in Clinical Neuroscience* 9, 273–284.
- Rajkowska G, Miguel-Hidalgo JJ, Makkos Z, et al. (2002) Layer-specific reductions in GFAP-reactive astroglia in the dorsolateral prefrontal cortex in schizophrenia. *Schizophrenia Research* 57, 127–138.
- Rajkowska G, Miguel-Hidalgo JJ, Wei J, et al. (1999) Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biological Psychiatry* 45, 1085–1098.
- Rajkowska G, O'Dwyer G, Teleki Z, et al. (2007) GABAergic neurons immunoreactive for calcium binding proteins are reduced in the prefrontal cortex in major depression. *Neuropsychopharmacology* 32, 471–482.
- Rauch SL, Shin LM, and Wright CI (2003) Neuroimaging studies of amygdala function in anxiety disorders. *Annals of the New York Academy of Sciences* 985, 389–410.
- Rauch SL, Whalen PJ, Savage CR, et al. (1997) Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. *Human Brain Mapping* 5, 124–132.
- Robbins TW and Everitt BJ (1999) Drug addiction: bad habits add up. *Nature* 398, 567–570.
- Rogers MA, Kasai K, Koji M, et al. (2004) Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neuroscience Research* 50, 1–11.
- Sapolsky RM (2000) Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry* 57, 925–935.
- Saxena S, Brody AL, Ho ML, et al. (2003) Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. *American Journal of Psychiatry* 160, 522–532.
- Schlaepfer TE, Cohen MX, Frick C, et al. (2007) Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* (Epub: 17429407.)
- Schultz W (2006) Behavioral theories and the neurophysiology of reward. *Annual Review of Psychology* 57, 87–115.

- Scoville WB and Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry* 20, 11–21.
- Serretti A, Raffaella C, Mandelli L, et al. (2006) Serotonin transporter gene variants and behavior: a comprehensive review. *Current Drug Targets* 7, 1659–1669.
- Shin LM, Rauch SL, and Pitman RK (2006) Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences* 1071, 67–79.
- Simon AB and Gorman JM (2006) Advances in the treatment of anxiety: targeting glutamate. *NeuroRx* 3, 57–68.
- Sinha R, Lacadie C, Skudlarski P, et al. (2005). Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study. *Psychopharmacology* 183, 171–180.
- Spitzer RL, Williams JB, First M, et al. (1989) A proposal for DSM-IV: solving the “organic/nonorganic” problem. *Journal of Neuropsychiatry and Clinical Neurosciences* 1, 126–127.
- Squire LR, Stark CE, and Clark RE (2004) The medial temporal lobe. *Annual Review of Neuroscience* 4, 58–66.
- Steen RG, Mull C, McClure R, et al. (2006) Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *British Journal of Psychiatry* 188, 510–518.
- Strakowski SM, Delbello MP, and Adler CM (2005) The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Molecular Psychiatry* 10, 105–116.
- Stroop JR (1935) Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 18, 643–662.
- Tiffany ST (1990) A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. *Psychological Review* 97, 147–168.
- Tulving E (2002) Episodic memory: From mind to brain. *Annual Review of Psychology* 53, 1–25.
- Vanderschuren LJ, Di Ciano P, and Everitt BJ (2005) Involvement of the dorsal striatum in cue-controlled cocaine seeking. *Journal of Neuroscience* 25, 8665–8670.
- Vanderschuren LJ and Everitt BJ (2004) Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science* 305, 1017–1019.
- Vendrell P, Junque C, Pujol J, et al. (1995) The role of prefrontal regions in the Stroop task. *Neuropsychologia* 33, 341–352.
- Volkow ND, Wang G-J, Fowler JS, et al. (1997) Decreased striatal responsiveness in detoxified cocaine abusers. *Nature* 386, 830–833.
- Wagner G, Sinsel E, Sobanski T, et al. (2006) Cortical inefficiency in patients with unipolar depression: an event-related fMRI study with the Stroop task. *Biological Psychiatry* 59, 958–965.
- Wise RA and Rompre PP (1989) Brain dopamine and reward. *Annual Review of Psychology* 40, 191–225.
- Wu J, Buchsbaum MS, Gillin JC, et al. (1999) Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. *American Journal of Psychiatry* 156, 1149–1158.
- Yin HH and Knowlton BJ (2006) The role of the basal ganglia in habit formation. *Nature Reviews Neuroscience* 7, 464–476.
- Zachar P and Kendler KS (2007) Psychiatric disorders: a conceptual taxonomy. *American Journal of Psychiatry* 164, 557–565.

**Abstract:** Mental and somatic illnesses have historically been treated as separate domains. It is increasingly apparent, however, that disorders of the mind arise directly from disorders of the brain. This insight raises the difficult problem of identifying the biological mechanisms of psychiatric disease and of using this knowledge to develop better diagnostic frameworks and treatments. In this chapter, we explore evidence that psychiatric disorders considered distinct in our current diagnostic scheme derive from shared or overlapping underlying biological abnormalities. To illustrate biological commonalities among different disorders, we describe data from cognitive neuroscience, which

has produced evidence for similar brain systems involved in multiple, often disparate, psychiatric conditions. We primarily explore four neural systems in illustrating these points—ventral striatum, dorsal striatum, dorsolateral prefrontal cortex, and anterior cingulate cortex. In each case, considering a region's normal functions helps better make sense of its dysfunction in particular psychiatric conditions. Such an appreciation contributes to an understanding of which clinical aspects of particular disorders reflect shared neurobiological underpinnings.

**Keywords:** cognitive neuroscience, biological psychiatry, nucleus accumbens, basal ganglia, prefrontal cortex