SECTION

III

Jay Gingrich
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Neuroscientific Foundations of Psychiatry

CHAPTER

15

Are There Biological Commonalities Among Different Psychiatric Disorders?

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Introduction

Psychiatric diagnosis is in a state of flux (Kupfer et al., 2002; Zachar & Kendler, 2007; Insel et al., 2010). Recent editions of the standard manual of American psychiatric diagnosis, the *Diagnostic and Statistical Manual* (DSM), have espoused a neo-Kraeplinnean diagnostic framework, wherein disorders are divided into discrete, often mutually exclusive entities on the basis of their symptoms (American Psychiatric Association, 1980, 1994, 2013). This theory-neutral framework has enhanced the precision of psychiatric diagnosis and thereby accelerated psychiatric research over the past 30 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 the DSM. 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, 2005). 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 Kraeplin. Griesinger proposed in the nineteenth century that there is a single protean psychiatric disorder (*Enheitpsychose*) whose expression in different patients is modulated by continuously variable traits. With the recent release of DSM-5 (American Psychiatric Association, 2013), as well as parallel efforts by the National Insitute of Mental Health (NIMH) to establish a theoretical structure for transdiagnostic research (Insel et al., 2010), an active debate is under way 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, by way of introduction to the more focused discussions that follow in subsequent ones, 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

Psychiatry, Fourth Edition. Edited by Allan Tasman, Jerald Kay, Jeffrey A. Lieberman, Michael B. First, and Michelle B. Riba.

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 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 the implicated brain structures and the larger networks in which they are embedded, we hope 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, "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 twentieth 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 & Kirmayer, 2006). However, the organic/nonorganic distinction was abandoned with DSM-IV in 1994 (American Psychiatric Association, 1994), and by the end of the twentieth 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 nineteeth and early twentieth centuries, 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 also 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 implicated in the vulnerability to major depression include regulators of monoaminergic neurotransmission as well as neurotrophic factors (Heim & Binder, 2012; Sullivan et al., 2012). 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 (Sen & Sanacora, 2008). 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 pathophysiology of a disorder in which so many diverse genetic mechanisms, neurochemical systems, brain regions, and cellular abnormalities have been implicated is 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 directly tied to 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 & 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. Our premise is that certain discrete psychological functions are associated with the activity of 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 disparate disorders suggests that related alterations may be observable in

the same neural circuitry. This approach to understanding different psychiatric disorders provides a powerful framework within which to conceptualize mental illness; namely, as a set of conditions that come about due to different combinations of endophenotypes. Heterogeneous syndromes, such as schizophrenia or depression, may be better "carved at their joints" along endophenotypic lines.

Specific Biological Commonalities Among Disorders

As mentioned earlier, evidence for shared biological perturbations across different psychiatric disorders can be seen in many domains. Before exploring a cognitive neuroscience perspective, we very 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 β-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 & Zabetian, 2004). More recently, a genome-wide analysis of genetic polymorphism data across five disorders (autism, ADHD, schizophrenia, depression, and bipolar disorder) revealed several risk loci that are shared across these disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). The association of a single 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 & 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., Sanacora et al., 2012), obsessive–compulsive disorder (OCD) (Pittenger et al., 2011), anxiety disorders (e.g., Simon & Gorman, 2006), and drug addiction (Kalivas, 2009). 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 (Gonzalez-Burgos et al., 2011), major depression (Rajkowska et al., 2007), and Tourette syndrome (Kataoka et al., 2010).

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

Thought, emotion, and behavior derive 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

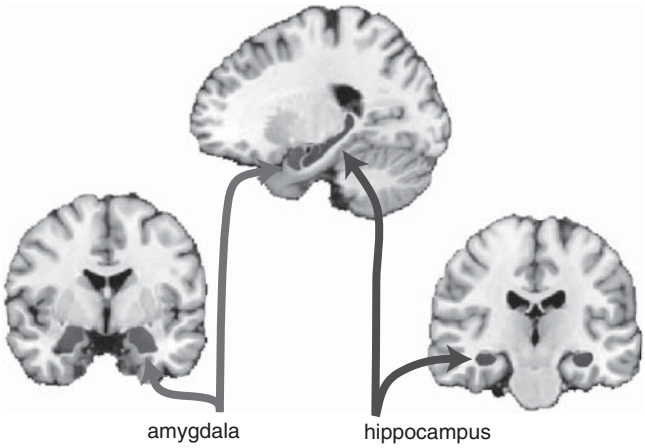

Figure 15–1 *Location and relationship of the human hippocampus and amygdala. As described in the text, the hippocampus has an important role in memory formation and stress modulation. Hippocampal dysfunction is implicated in numerous psychiatric disorders, including major depressive disorder, PTSD, 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. (See color plate section II)*

gross anatomical alterations in more psychologically meaningful terms.

The hippocampus provides a useful introductory example (Figure 15–1). 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 & 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 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, which 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 future versions of DSM should take. This is true for both categorical and dimensional conceptions 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, and 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 15–2; 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 (Richardson & Gratton, 1996; Schultz, 2006). All addictive drugs also result in dopamine release in the nucleus accumbens (Wise & Rompre, 1989; Hyman et al., 2006). Perturbations of the nucleus accumbens in experimental animals alter motivated behavior in response to drugs of abuse (e.g., Carlezon et al.,

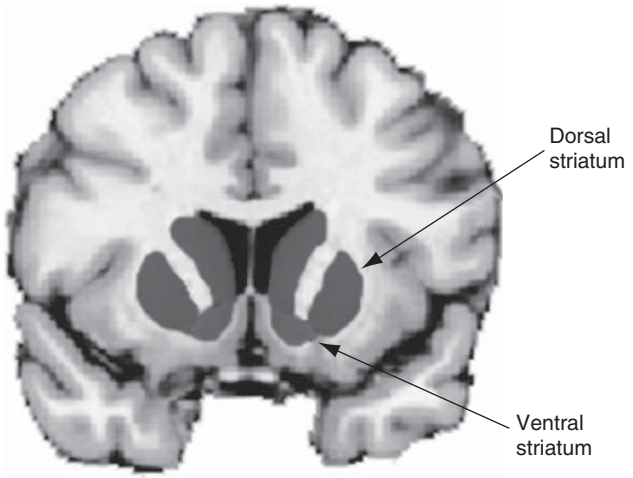

Figure 15–2 *Anatomy of the human dorsal and ventral striatum, which are major input nuclei of the basal ganglia. As described in the text, the ventral striatum is implicated in reward and reinforced learning; dysregulation of ventral striatal function is implicated in addiction, schizophrenia, depression, 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. (See color plate section II)*

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 (Phan et al., 2002; McClure et al., 2004; 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 & 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 & 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, 2009). 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 & 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. (2008) used direct stimulation of the nucleus accumbens as a treatment for profoundly refractory major depression, with promising initial results (Bewernick et al., 2010).

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 has been shown to be associated with genetic risk for bipolar disorder (McDonald et al., 2004). It is plausible, though unproven, 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 ventral striatal dysregulation accompanying 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 & Petri, 1984; Packard & Knowlton, 2002; Yin & 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 & McGaugh, 1996; Pittenger et al., 2006; Yin & Knowlton, 2006). 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 is disrupted by this circuit-level dysregulation. In contrast, recent work suggests that the acquisition of certain habit-like associations is enhanced in individuals with OCD (Gillan et al., 2011). Further work will be needed to investigate whether disruption in the normal habit-learning circuitry contributes to the rigid habit-like structure of some OCD symptomatology.

Drug Addiction

Drug seeking is typically 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 & Everitt, 1999; Everitt & Robbins, 2013). 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 & 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 & 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 & 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 & Owen, 2000) (see Figure 15–3). 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 (e.g., GREEN printed in red ink) with the ink color. 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). 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 & 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.

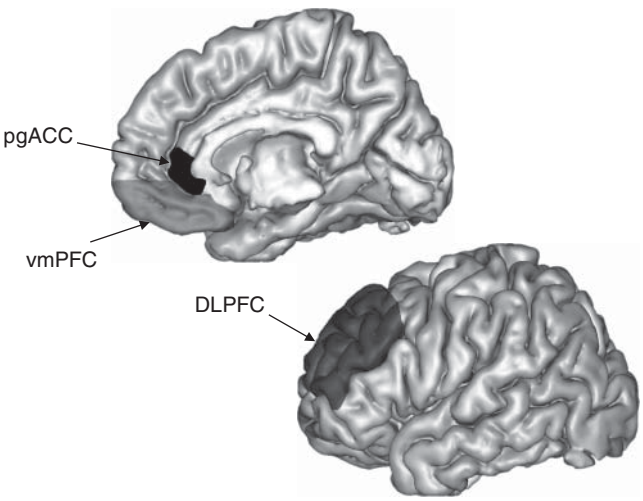

Figure 15–3 *Neuroanatomy of the frontal cortical structures described in the text. The pregenual anterior cingulate cortex (pgACC) and ventromedial prefrontal cortex (vmPFC) have roles in emotion regulation, especially in the absence of an explicit attempt to regulate emotional processing. The dorsolateral 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. (See color plate section III)*

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 & 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.

Neuroimaging studies of the neural circuitry associated with deliberate efforts at emotion regulation (Beauregard et al., 2001; Levesque et al., 2003; Ochsner et al., 2004; Kalisch et al., 2005, 2006) 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. Consistent with this expectation, neuroimaging studies of deliberate emotion regulation have found similar deficits in the DLPFC in depression, PTSD, generalized anxiety disorder, panic disorder, and social anxiety disorder disorder (Johnstone et al., 2007; Goldin et al., 2009; New et al., 2009; Ball et al., 2013).

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 pregenual portion of the anterior cingulate cortex (pgACC) and adjacent ventromedial PFC (vmPFC) (see Figure 15–3). 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 suggest that these projections are inhibitory (Quirk et al., 2003). Abnormalities in circuitry mediating implicit emotional regulation can be seen in emotional dysregulation disorders (Etkin & 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.

Regulation of emotional conflict in this task activated the pgACC, rather than the DLPFC (Egner et al., 2008). pgACC activation was accompanied by a simultaneous and correlated reduction in amygdala activity. These results are consistent with neuroimaging studies of the extinction of conditioned fear responses, in which subjects evaluate and override expectations for aversive stimuli. Fear extinction involved increased activity in the pgACC and vmPFC and decreased activity in the amygdala (Etkin et al., 2011). Likewise, pgACC 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). Finally, individuals with lesions to the pgACC are impaired in the regulation of emotional conflict in this task but have intact DLPFC-based nonemotional conflict regulation (Maier & di Pellegrino, 2012), demonstrating the causal role of the pgACC in implicit emotion

regulation and the dissociability of these two regulatory processes.

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 & 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 & 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 and emotional numbing.

Neuroimaging studies have searched for markers of abnormal fear responses and abnormal emotion regulation in individuals with PTSD. 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 & Wager, 2007). More consistently observed is hypoactivation within the pgACC and vmPFC in patients with PTSD (Bremner et al., 2004). 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 pgACC and ventromedial prefrontal hypoactivity may be relatively more specific for PTSD, or to trauma-related distress disorders more broadly (Rauch et al., 2003; Bremner et al., 2004; Shin et al., 2006; Etkin & Wager, 2007).

Depression and Generalized Anxiety

The emotional conflict task described above reveals deficits in implicit emotion regulation in patients with depression and generalized anxiety disorder (GAD) (Etkin et al., 2010; Etkin & Schatzberg, 2011). Behaviorally, unmedicated patients with GAD, with or without comorbid depression, were completely unable to regulate the effect of emotional conflict on reaction times, as compared to healthy controls. Analysis of fMRI data acquired during the emotional conflict task revealed that patients with GAD or depression both failed to activate the pgACC and to dampen emotional conflict evaluation-related activity in the amygdala. Interestingly, despite deficient pgACC-amygdala function, patients with nonanxious MDD regulated conflict similarly to controls, due to aberrant engagement of a compensatory region in the anterior DLPFC (a region not activated in controls). These data implicate a common substrate of emotion-regulation abnormalities across anxiety and depression (pgACC-amygdala), but they also illustrate the complexity possible when, despite this common deficit, some patients can engage alternative compensatory neural systems.

A number of studies have noted a positive correlation between the outcome of antidepressant treatment and pretreatment levels of pgACC activity (Mayberg, 2003). A landmark PET study of the pharmacological treatment of unipolar depression, for example, found that resting activity in the pgACC 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 pgACC 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; Wu et al., 1999; Saxena et al., 2003), 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 pgACC of patients in response to both positively and negatively valenced affective pictures (Kumari et al., 2003). As the pgACC is implicated in implicit emotional regulation, its hypofunction may indicate a reduced capacity to modulate negative emotion. Thus, hypofunction of the pgACC in patients who are less likely to respond to treatment may represent a neural marker of poor emotional coping resources in general. Patients who cannot draw on their implicit emotion regulatory reserves may benefit less from treatment.

Research Domain Criteria (RDoC) Project: An Organized Transdiagnostic Research Effort

Recognizing how data of this sort challenge the categorical diagnostic framework of the DSM, the NIMH has recently developed a new conceptual framework for human research on psychiatric disorders (Insel et al., 2010). This framework, termed the Research Domain Criteria (RDoC) project, takes objectively measurable endophenotypes, such as those outlined here, as its starting point; its underlying assumption is that specific neural systems underlie specific behavioral phenotypes, and consequently relate to specific clinical abnormalities or symptoms across traditionally discrete disorders. As such, under RDoC, researchers are encouraged to study patients with a range of clinical impairments that cross traditional DSM-based diagnostic boundaries, including those who do not clearly fit into a DSM diagnosis. The expectation is that this will ultimately result in a dimensional brain system-oriented view of mental illness, though this remains a hypothesis to be proven by data as they emerge.

Conclusion

Our understanding of the neurobiological abnormalities underlying many psychiatric disorders remains 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 this general observation 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., 2008).

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 the DSM.

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? The diagnostic system being developed by the RDoC initiative aims to address such questions in an empirical way. However psychiatric diagnostic systems evolve in the coming decades, they 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 find ourselves diagnosing 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.

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