A Research Agenda for DSM-V

Edited by

David J. Kupfer, M.D.
Michael B. First, M.D.
Darrel A. Regier, M.D., M.P.H.

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CHAPTER 2

Neuroscience Research Agenda to Guide Development of a Pathophysiologically Based Classification System

Dennis S. Charney, M.D., David H. Barlow, Ph.D., Kelly Botteron, M.D., Jonathan D. Cohen, M.D., David Goldman, M.D., Raquel E. Gur, M.D., Ph.D., Keh-Ming Lin, M.D., M.P.H., Juan F. López, M.D., James H. Meador-Woodruff, M.D., Steven O. Moldin, Ph.D., Eric J. Nestler, M.D., Ph.D., Stanley J. Watson, M.D., Ph.D., Steven J. Zalcman, M.D.

Psychiatric classifications have historically been organized around each era's prevailing theories about the etiology of mental disorders, reflecting the sense that classifications based on etiology are most likely to be helpful in the clinical management of patients. For example, in the sixteenth century the Swiss physician Paracelsus developed a classification system based on presumed etiology, distinguishing vesania (disorders thought to be caused by poisons), lunacy (a periodic condition believed to be influenced by phases of the moon), and insanity (diseases apparently caused by heredity factors). The obvious problem with such classifications is that their utility is strictly limited by the validity (or lack thereof) of the underlying etiological assumptions. The descriptive approach adopted by the DSM allowed for the development of a classification system that met the field's need for a common language, without being mired in ideological hypotheses about the causes of psychiatric illness. Questions have been raised by many critics (McHugh [2001]) that the DSM's descriptive approach may have outlived its usefulness and is in fact potentially misleading. Although there is a large body of research that indicates a neurobiological basis for

most mental disorders, the DSM definitions are virtually devoid of biology. Instead, DSM-IV definitions are based on clusters of symptoms and characteristics of clinical course.

There has been no shortage of neurobiological theories of causation for psychiatric disorders. The original monoamine hypothesis regarding mood disorders and the dopamine hypotheses regarding schizophrenia have been of substantial heuristic value. For example, the monoamine hypothesis led to more sophisticated examination of monoamine systems, including receptor subtype analysis and the study of brain systems that interact with monoamine system functions (e.g., glutamate, γ-aminobutyric acid [GABA], and substance P). However, these hypotheses were largely derived post hoc from discoveries related to the pharmacologic actions of antidepressant and antipsychotic drug treatments. There have been replicated findings suggesting abnormalities of norepinephrine and serotonin neuronal systems in mood disorders (Garlow et al. 1999) and abnormalities of glutamate and dopamine neuronal systems (Bunney and Bunney 1999; Byne et al. 1999) in schizophrenia. However, none of these findings are sufficiently robust to be of diagnostic value. For example, there is typically a large overlap between diagnostic groups and control subjects. Disturbances in sleep architecture are commonly observed in mood disorders, especially with regard to the onset and duration of rapid eye movement (REM) sleep (Nofzinger et al. 1999). Neuroendocrine abnormalities, particularly involving the hypothalamic-pituitary-adrenal (HPA) system, have been repeatedly identified in depressed patients (Holsboer 1999). Despite initial enthusiasm for the dexamethasone suppression test and REM latency diagnostic tests for depression, neither has turned out to be a reliable and valid diagnostic marker. Test findings may vary from episode to episode in the same individual, and neither is diagnostically specific (i.e., there is substantial overlap in the range of values between depressed patients and nondepressed control subjects). Cerebrospinal fluid levels of corticotropin-releasing hormone (CRH), possibly reflecting extrahypothalamic CRH concentrations, are elevated in at least a subgroup of depressed patients, but this subgroup has not been distinguished clinically, and without the availability of CRH receptor antagonists it has not been possible to identify specific treatment response patterns (Garlow et al. 1999). The situation with anxiety disorders is not any better. There are replicated findings suggesting dysfunction in brain benzodiazepine, norepinephrine, serotonin, cholecystokinin, and CRH systems in the different anxiety disorders (Charney and Bremner 1999). Abnormalities in the regulation of respiration have been well documented, especially by studies investigating responses to inhaled CO_2 . Unfortunately, none of these results have led to the identification of diagnostic markers for anxiety disorders or predictors

of response. As described below, genetic investigations of schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorders have failed to identify vulnerability genes that are useful in predicting current and future risk of disorder. Furthermore, very few studies of the neurobiology of major psychiatric disorders have included ethnically or culturally diverse populations in their designs. This limits the applicability of research results to clinical populations.

At the risk of making an overly broad statement of the status of neurobiological investigations of the major psychiatric disorders noted above, it can be concluded that the field of psychiatry has thus far failed to identify a single neurobiological phenotypic marker or gene that is useful in making a diagnosis of a major psychiatric disorder or for predicting response to psychopharmacologic treatment. A primary purpose of this chapter is to review why progress has been so limited and to offer strategic insights that may lead to a more etiologically based diagnostic system. Such an accomplishment would represent a highly laudable achievement for psychiatry and would help move the specialty into the mainstream of modern medicine, where etiology and pathophysiology have replaced descriptive symptomatology as the fundamental basis for making diagnostic distinctions. For example, before the elucidation of its underlying pathophysiology, diabetes mellitus was classified as a single entity in simple descriptive terms (i.e., abnormally elevated blood glucose) differentiated by typical age at onset (e.g., juvenile vs. adult) and other descriptive features (such as an association with obesity). It was only with the understanding of the underlying pathophysiology that diabetes could be divided into two distinct and clinically meaningful entities, based on insulin deficiency versus insulin receptor sensitivity. Current classification in psychiatry therefore resembles the medicine of 50–100 years ago, before the underlying pathophysiology of many disease processes was understood. Diagnostic distinctions based on etiology (as opposed to descriptive symptomatology) are more likely to lead to rational treatment selection and more valid prognostications.

Despite the importance of this objective, it must be strongly stated at the outset of this discussion that it will be years—and possibly decades—before a fully explicated etiologically and pathophysiologically based classification system for psychiatry exists. Today there is only rudimentary knowledge of the genetic and nongenetic factors that cause the common psychotic, affective, anxiety, and substance use disorders that constitute the large majority of serious psychiatric disturbances. Similarly, very little is known about the molecular and cellular abnormalities that underlie the pathophysiology of psychotic, affective, anxiety, and substance use disorders, and very little specific prognostic information can be given to patients about their disorders. Some very good treatments are available for most

psychotic, affective, and anxiety disorders, and the efficacy of these treatments rivals that seen in many other medical specialties in the treatment of chronic disease. However, virtually all of these treatments were discovered by serendipity a half-century ago, with newer treatments representing refinements of the original mechanism of action of these agents. Thus, the last half-century has seen the development of very few truly new treatments for psychotic, affective, and anxiety disorders, and treatment of most addictions remains highly inadequate for most individuals.

There are many reasons for this relative lack of progress in psychiatry compared with other medical specialties. The brain is far more complex than most other organ systems, and it remains relatively inaccessible, which makes the challenge in psychiatry considerably greater. In the past two decades, more psychiatric research has focused on refining descriptive symptomatology (as embodied in DSM-III, DSM-III-R, and DSM-IV) than on neurobiology and genetics. Furthermore, there has been too strong a reliance on the DSM-defined symptom clusters and too little on biologically based symptoms that may cut across the DSM-IV–defined disorders. This over-reification of the DSM categories has led to a form of closed-mindedness on the part of researchers and funding sources. For example, researchers involved in new drug development tend to focus their efforts on treatment of DSM-IV–defined categories, despite widespread evidence that pharmacologic treatments tend to be effective in treating a relatively wide range of DSM disorders. Furthermore, the erroneous notion that the DSM categories can double as phenotypes may be partly responsibility for the lack of success in discovering robust genetic markers. Although a move to an etiologically and pathophysiologically based diagnostic system for psychiatry will be extraordinarily difficult, it is nevertheless essential, based on the increasing belief that many, and perhaps most, of the current symptom clusters of DSM will ultimately not map onto distinct disease states.

Given the current predicament, then, how can the field develop a pathophysiologically based classification system? Clearly, genetic studies in humans will provide uniquely powerful information. Despite several decades of effort, no bona fide psychiatric disease gene has yet been identified with certainty, although the field is getting closer, and new advances in genetics (including the availability of the human genome sequence) portend rapid progress. Brain imaging studies in humans promise, for the first time, to provide detailed information about molecular and cellular substrates in the brain involved in a psychiatric disorder. Although currently available imaging techniques have thus far failed to provide diagnostic tests for psychotic, affective, or anxiety disorders, it is only a matter of time before such techniques have the spatial and temporal resolution and the chemical specificity to study relevant pathophysiological mechanisms. Finally, studies of

brain samples obtained at autopsy should permit more detailed molecular analysis of the pathophysiology of psychiatric disorders. Over the last decade, the field has greatly increased the sophistication with which it uses postmortem tissue.

There is no question that animal research has vastly expanded the knowledge of normal brain function. It has also been invaluable in identifying the initial protein targets through which most currently used pharmacotherapeutic agents (e.g., antipsychotic, antidepressant, and antianxiety drugs) produce their beneficial clinical effects, as well as the protein targets through which most drugs of abuse cause addiction. It has also been possible to develop several animal models that have outstanding predictive value in developing new medications with the same mechanism of action as, but fewer side effects than, the older agents. The introduction of second-generation antipsychotic agents, the selective serotonin and selective norepinephrine reuptake inhibitor antidepressants, and benzodiazepine-like agents that act on selected subunits of the $GABA_A$ receptor have all derived directly from rational drug-design efforts based on animal models.

In the following sections of this chapter we review the current status of genetic, brain imaging, postmortem, and animal model research relevant to elucidating the pathophysiology of mental disorders. This is followed by a set of recommendations for a research agenda that will allow for the eventual adoption of a etiologically and pathophysiologically based diagnostic system.

Current Status of the Genetics of Psychiatric Disorders

During the past 100 years, there has been considerable interest in examining whether genes play a role in the etiology of mental disorders. If genes play such a role, their identification is expected to have a dramatic effect on improving differential diagnosis, shedding insight into pathophysiology, and developing new treatments. The first step in characterizing the genetic bases of mental disorders has been to demonstrate familial co-aggregation. Family studies of a number of mental disorders—including schizophrenia, bipolar disorder, autism, major depressive disorder, anxiety disorders (including panic disorder and obsessive-compulsive disorder [OCD]), and attention-deficit/hyperactivity disorder (ADHD)—have consistently shown that these disorders are familial and that transmission in families is, at least in part, mediated by genes.

Familial transmission may also occur as a result of environmental factors transmitted from parent to child. Consequently, twin and adoption

studies have been used to disentangle genetic from shared environmental influences. When the monozygotic concordance rate is higher than the dizygotic concordance rate, a genetic basis is the most likely explanation. A measure of the degree of genetic control over a phenotype calculated from twin studies is heritability, the ratio of genetic variance to the total variance in the population.

Adoption study designs also tease apart the effects of genes and environment by studying individuals who have been raised by biologically unrelated adoptive parents and by comparing their adoptive and biological relatives. Adoption studies of schizophrenia, bipolar disorder, alcoholism, and depression support a significant role for genetic factors in their etiologies (Kelsoe 1999; Malhi et al. 2000; Riley and McGuffin 2000; Schuckit 2000; Sullivan et al. 2000).

Starting in the early 1980s, DNA polymorphisms provided a sufficiently numerous set of markers that are spaced throughout the entire genome. Such markers permit the mapping of diseases to specific genomic regions, and their widespread availability ushered in the molecular era of psychiatric genetics. By the late 1980s, promising linkages of schizophrenia to chromosome 5q and bipolar disorder to Xq and 11p were reported, but they were subsequently neither replicated nor confirmed in the original data sets (Moldin 1997b; Risch and Botstein 1996).

Linkages of schizophrenia to numerous chromosomal regions have recently been reported (Baron 2001; Riley and McGuffin 2000). Several have been implicated in multiple data sets and have become the focus of considerable interest: 1q, 5q, 6p, 6q, 8p, 10p, 13q, and 15q. Large genomic regions have been typically implicated, and failures to replicate have been reported for each region. It is difficult to distinguish which of these results (if any) are true guideposts on the path to gene discovery and which are false positives (Moldin 1997b). Weak associations of schizophrenia to several gene loci, including *NOTCH4*, hKCa3/KCNN3 potassium channel, CHRNA7, *NURR1*, SCA1, DRD_3, catechol-*O*-methyltransferase (COMT), and the serotonin (5-hydroxytryptamine) type 2A ($5\text{-}HT_{2A}$) receptor have been reported in candidate gene studies but have not been convincingly replicated (Moldin 1999; Riley and McGuffin 2000).

Linkages of bipolar disorder to numerous chromosomal regions have also been reported (Kelsoe 1999; Moldin 1999). Several have been implicated in multiple data sets: 4p, 12q, 13q, 18p, 18q, 21q, 22q, and Xq. None of the linkage statistics reported in these studies were corrected for the testing of multiple diagnostic and transmission models; other complexities concern the implication of large chromosomal regions and failures to replicate. As in the case of schizophrenia, sufficient ambiguities exist to give pause in considering any of these linkage results as unambiguously repli-

cated. Weak associations of bipolar disorder to several loci involved in the GABAergic, serotoninergic, and dopaminergic systems (e.g., GABRA5, serotonin transporter [5-HTT], tyrosine hydroxylase), genes mediating signal transduction (e.g., phospholipase A2A), and other loci (e.g., CRH, adenosine A, receptor) have been reported, but subsequent studies produced divergent results (V. Nimgaonkar, unpublished data, December 2000).

Researchers have searched for clinical criteria to identify subtypes of depressed patients with familial unipolar illness. Recurrent major depression appears to be the subtype of major depression that most consistently identifies increased familial risk (Sullivan et al. 2000). Childhood or adolescent onset may also be associated with significantly greater risk for recurrence in adulthood (Wickramaratne et al. 2000). Molecular studies have focused on candidate genes. Weak associations have been reported between depression and 5-HTT, but not all studies agree (Malhi et al. 2000). Other candidate loci implicated include dopamine receptor genes, 5-HT receptor genes, tyrosine hydroxylase, and genes in the GABAergic system. Convincing replications of these candidates in multiple data sets have not been forthcoming.

In a genome-wide survey of panic disorder, families with a variety of kidney or bladder problems and other medical conditions were subdivided, and significant 13q linkage evidence was reported (Weissman et al. 2000) (see further discussion below). Most molecular genetic studies of anxiety disorders have focused on candidate genes chosen based on the receptor binding profile of anxiolytic compounds, or in consideration of the molecules in neurotransmitter pathways involved in therapeutic action. Association analyses of OCD patients have implicated several genes—5-HTT, serotoninergic receptors ($5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, $5\text{-}HT_{1}$), DRD_4, and both COMT and MAO (monoamine oxidase) A in males only—but findings typically have not been unambiguously replicated (Moldin 2000; Wolff et al. 2000). Likewise, associations between panic disorder and several genes—5-HTT, α_{2A} adrenergic receptor, A_{2a} adenosine receptor, CCK, CCK-B, DRD_4, COMT, and MAO A—have been reported but not confirmed (Moldin 2000).

Molecular genetic studies of ADHD also have focused on candidate gene studies. A meta-analysis of case-control and family-based association studies of ADHD and the 7-repeat allele of DRD_4 found evidence of a weak association (Faraone et al. 2001). Another meta-analysis of nine studies of a 480–base-pair allele of the dopamine transporter gene found very modest evidence for an association (Curran et al. 2001). Associations to other genes in the dopaminergic system (i.e., DRD1, COMT) have been reported but not confirmed.

There have been numerous reports of aberrations (e.g., deletions,

translocations, and inversions) on nearly every chromosome in autism (Gillberg 1998); however, the rates of these abnormalities vary widely across studies. Most commonly reported are those on the X chromosome, followed by those on chromosome 15. One candidate gene study of 15q identified an association between autism and the $GABA_A$ β_3 receptor subunit gene (Cook et al. 1998), but this result has not been replicated. Studies of other genes in the 15q region (e.g., *UBE3A*), several serotoninergic system genes, neurofibromatosis type 1 gene, and the c-Harvey-Ras gene have failed to consistently reveal an association. A recent report of a substitution variant at HOXA1 on chromosome 7p in a subset of autistic subjects (Ingram et al. 2000) has not been replicated. Although one region—7q—has been identified in five recent genomewide scans (Lamb et al. 2000; Maestrini et al. 2000), no genomic region identified yielded significant or suggestive (Lander and Kruglyak 1995) linkage evidence. All samples comprised fewer than 200 pedigrees; thus, analyses conducted to date likely have had low statistical power to detect true linkages.

In many of the studies described above, diagnostic definitions were broadened to include related, or "spectrum," conditions. Unfortunately, such disorders (e.g., schizotypal personality, bipolar II disorder, broader autism phenotype) are diagnosed less reliably than core phenotypes, and their familial aggregation is less specific to any one disorder (Moldin 1997a). Broadening of the core phenotype has not consistently increased linkage evidence.

Individuals are differentially vulnerable to alcoholism and other substance abuse or dependence, even in societies where disease prevalences are highest and the effects most pernicious. Differential vulnerability could indicate the existence of innate differences, environmental differences, or a combination of both. However, it has been established in twins that about half of the variance in vulnerability to alcoholism is attributable to genes, and other forms of substance dependency are also substantially heritable; for example, opioid addiction is almost 50% heritable. Identification of the alleles responsible for differential vulnerability will lead to new molecular diagnostic markers to improve diagnostic precision and individualize treatment. Better understanding of mechanisms of vulnerability and gene-environment interactions will redefine these disorders in etiologic terms and lead to new molecular targets for intervention.

ADH2 and ALDH2, the two known genes for alcohol vulnerability, are substance-specific vulnerability factors. Because various drugs of addiction elicit common neurochemical responses and behaviors (intoxication, anesthetization) across individuals, it is also likely that general vulnerability factors are present in human populations. Based on evidence from twin and family studies, there are both general and substance-specific inherited fac-

tors for vulnerability to the addictive drugs (Goldman and Bergen 1998). The prediction is that vulnerability genes act in both drug-specific fashion (e.g., the alcohol metabolic gene, ALDH2) and on general vulnerability (e.g., a gene such as 5-HTT, which has been proposed to affect anxiety). Substance-specific genetic factors were particularly important for alcohol and opioids. The conclusion that drug dependence in probands is nonpredictive of alcoholism in relatives is a provocative finding that strongly implies that specific genetic factors are involved in alcoholism. Again, in a study of drug abuse and alcoholism in parents and offspring, parental history of drug abuse was found to be nonpredictive of alcoholism in offspring, and vice versa (Kendler et al. 1997). All of these findings in large and carefully characterized data sets are consistent with previous studies on the familial transmission of alcoholism and other substance abuse (Bierut et al. 1998; Kendler et al. 1997; Merikangas et al. 1998). Only nicotine dependence (True et al. 1999) has shown significant coinheritance with alcoholism. Whole genome scans for loci influencing alcohol dependence have been conducted in a population isolate (Long et al. 1998) and in families from the cosmopolitan population of the United States, with the result that linkages to several regions were detected, including plausible candidate genes such as the dopamine D_4 receptor (chromosome 11p) and a $GABA_A$ receptor complex (chromosome 4p). However, these linkages did not reach significance by the criteria of Lander and Kruglyak (1995), and the only definitive criterion—isolation of the responsible allele—has not been met.

As discussed above, descriptive classifications define diagnostic entities that are undoubtedly heterogeneous from both an etiologic and a genetic perspective. Alternative strategies for increasing diagnostic homogeneity, and thereby increasing the power of genetic analyses, include the identification of genetically distinct diagnostic subtypes. One research team analyzed a periodic catatonia subtype of schizophrenia and found significant evidence of linkage to 15q (Stober et al. 2000). Although the reliability of this phenotype across laboratories has yet to be demonstrated and its theoretical basis has yet to be established, this interesting result demonstrates the potential utility of subdividing and redefining existing diagnostic categories. In a panic disorder study, families were subdivided on the basis of kidney or bladder problems and other medical conditions, and significant evidence of 13q linkage was reported (Weissman et al. 2000). Although replication is essential, this is an intriguing result that may help define a subtype of panic disorder on the basis of pathophysiology, that is, the involvement of CRH and identifiable neural substrates of fear and anxiety in micturition.

All of the genetic studies discussed herein have involved analysis of a binary phenotype, that is, affected or unaffected status. Brzustowicz and

colleagues (1997) performed linkage analysis on quantitative dimensions of psychopathology in schizophrenia and found significant evidence linking positive symptom-scale scores to 6p. Although this result has not been replicated, such an approach represents a potentially fruitful direction for significantly increasing the power of genetic studies.

Another promising approach is the detailed ongoing exploration of behavioral phenotypes and valid and robust dimensional markers that go beyond binary phenotypes. For example, the criteria sets in DSM-IV were often developed and refined by studying disorders in isolation from one another (e.g., the DSM-IV field trials) and without consideration of possible higher-order symptom structures and differential relationships to constructs of temperament or vulnerability. Cross-sectional and longitudinal studies are currently ongoing in which a wide range of clinical indicators cutting across DSM categories are subjected to sophisticated latent variable analyses to determine the first and higher-order structure of these features. Identification of the validity and stability of these behavioral phenotypes would lead to important insights on their clinical validity and would enable more sophisticated genetic and neurobiological studies (e.g., explication of a temporally stable latent dimension that does not co-vary with other dimensions of psychopathology but influences their course). Once these broader models are established, important fine-grained analyses could proceed. For instance, multiple groups latent variable solutions could make possible the evaluation of the degree of invariance of these phenotypes across salient demographic groups (e.g., races, sexes). These analyses could uncover reliable model-based differences in the expressions of psychopathology that would have considerable heuristic value for genetic or neurobiological research (e.g., evidence of ethnic variations in linkage studies). In addition to their superior validity, the use of latent model–based dimensional phenotypes would greatly enhance the statistical power of neurobiological and genetic studies and would foster the ability to detect more complex relationships that would otherwise be masked by use of diagnostic categories alone (e.g., a nonlinear relationship between a neurobiological marker and a dimensional phenotype).

Although it has been grossly underused to date, the latent variable analysis of psychopathology phenotypes could be extended to a set of analytical procedures referred to as latent class modeling (e.g., dimensional or categorical indices of psychopathological features), except that each latent class possesses a different set of parameter values (Muthen 2000). In addition to determining whether various psychopathological phenomena operate in a continuous or a taxonomic manner, these analytical procedures hold substantial promise for establishing empirically derived symptom thresholds between "disordered" and "nondisordered" classes (e.g., iden-

tify symptoms that indicate classes well; determine the number of criteria needed to be fulfilled to meet a diagnostic class) and for determining whether the heterogeneity observed (or unobserved) within a disorder is due to the existence of latent classes (i.e., natural subtypes of disorders) (Nestadt et al. 1994). These modeling possibilities have profound implications for neurobiological and genetic research endeavors, where there is a growing belief that the power to identify markers has often been mitigated (or enhanced) by the failure (or success) to adequately account for or recognize diagnostic heterogeneity. Latent class modeling holds the unrealized potential for explicating classes that represent natural cut points in the expression of psychopathology within and across disorders that would strongly guide the pursuit of the identification of genetic and neurobiological markers.

Researchers have attempted to increase power for genetic analyses by directly incorporating into linkage analyses quantitative information provided by related biological traits presumed to be correlated with underlying disease liability. It is assumed that pleiotropy is present, that is, a gene exerts an effect on both affection status and the ancillary biological trait. Researchers over the last 30 years have searched intensively for such traits, with limited success (Moldin and Erlenmeyer-Kimling 1994). Reported linkages include impaired P50 auditory sensory gating to within 500 kb of CHRNA7 on 15q (Freedman et al. 1997), and a composite biological phenotype of P50 auditory sensory gating and antisaccade ocular motor performance to 22q (Myles-Worsley et al. 1999). Linkage of eye tracking dysfunction was reported to 6p in eight schizophrenia pedigrees (Arolt et al. 1996). Other biological traits posited as vulnerability markers of mental disorders include deficits in sustained attention (Chen and Faraone 2000), eye tracking dysfunction and deficits in the auditory P300 event-related potential (Blackwood et al. 1996), reactivity to a 35% CO_2 challenge (van Beek and Griez 2000), disturbances in sleep architecture (Giles et al. 1998), N4 and P3 components of event-related brain potentials (Almasy et al. 2001), trait anxiety (Mazzanti et al. 1998), response to alcohol (Schuckit et al. 2000) and benzodiazepine drugs (Iwata et al. 1999), and therapeutic response to antipsychotic medication (Arranz et al. 2000a).

Ethnic variations are substantial in the distribution of the genotypes and haplotypes of the majority of the proposed "candidate genes" for psychiatric disorders (Burmeister 1999; Gelernter et al. 1997; McLeod et al. 1998; Palmatier et al. 1999), as well as those of interest in relation to other common medical problems with complex genetics, such as diabetes, asthma, and hypertension (Barroso et al. 1999; Drysdale et al. 2000; Pritchard et al. 2000; Roses 2000). For example, the rate of the short variant of the serotonin transporter promoter region polymorphism may be associated with risks for

mood disorders as well as poor antidepressant response in Caucasians (Pollock et al. 2000; Smeraldi et al. 1998), but the reverse in Koreans (D.K. Kim et al. 2000). However, the frequency of this allele ranges from more than 70% in East Asians to approximately 50% in Caucasians and less than 30% in African Americans (Gelernter et al. 1997). The prevalence of the low-activity COMT, which has been reported to be a risk factor for a number of psychiatric disorders, ranges from 18% in Asians to 50% in Caucasians (McLeod et al. 1998; Palmatier et al. 1999). These emerging data have led to an increased awareness of the importance of "population (ethnic) stratification" and the need to always take ethnicity into consideration in genetic research (Baron 1993; Hamer 2000; Roses 2000).

In summary, considerable evidence from genetic epidemiological studies exists to support the role that genes play in producing vulnerability to mental disorders. These results are among the most robust and replicated in psychiatry. The genetic complexity of these diseases, that is, the involvement of multiple genes in interaction with each other and the environment, has resulted in circuitous pathways from the underlying genotype to the clinical phenotype. Such biological complexities present considerable analytical challenges, and genomic localization and identification of such genes has not yet occurred. These challenges are as daunting in the study of other complex diseases such as multiple sclerosis, hypertension, and diabetes. Powerful new genomic tools and technologies (e.g., high-throughput genotyping via mass spectrometry, draft sequence of the human genome, a comprehensive catalogue of human genetic variation, new statistical genetic methods), in combination with large data sets and innovative study designs in which biological traits and subtypes of existing diagnostic categories are identified, are expected to greatly accelerate gene discovery for mental disorders. Such advances have the potential for revolutionizing psychiatric nosology in subsequent editions of the DSM by providing clinicians with a biological basis for making differential diagnostic decisions.

Current Status of Neuroimaging Studies of Psychiatric Disorders

Structural Neuroimaging

Studies examining potential structural differences associated with psychiatric disorders have been reported for about 25 years. Initial studies used computed tomography (CT), with magnetic resonance imaging (MRI) following about a decade later. Early results were inconsistently replicated, although this may have been related to significant technical and study design limitations. However, differences in brain structure associated with specific dis-

orders such as schizophrenia and bipolar disorder were eventually demonstrated in a replicable fashion. Early demonstrations of relatively global anatomical differences such as increased lateral ventricle volume, third ventricle volume, or basal ganglia changes were often nonspecific and were noted in multiple disorders such as schizophrenia, bipolar disorder, and dementia. However, significant advances in image acquisition technology and image analysis tools have enabled the closer investigation of anatomically relevant regions. Concurrent with these advances, an increasing number of recent studies have reported specific regional differences between patients and control subjects, some of which demonstrate increased diagnostic specificity. For example, decreased superior temporal gyrus volume and decreased thalamus volume are evident in schizophrenia (Shenton et al. 2001). Depression is reported to be associated with changes in amygdala volume and reduction in ventromedial prefrontal cortical regions (Drevets 2000).

Early studies limited their quantification of structural differences to estimates of regional area or volume. However, this only partially characterizes the potential neuromorphometric parameters of specific regions and ignores information such as surface area, thickness, or shape. Shape analysis for imaging has been difficult to realize. However, some newly developed, sophisticated shape analysis methods (M. Miller et al. 1997) have demonstrated increased sensitivity over volume measures in detecting anatomical differences between disorders. For example, in schizophrenia and early dementia, shape changes demonstrated in the hippocampus have had significant power to discriminate affected individuals from healthy control subjects (Csernansky et al. 1998, 2000).

Characterization of regional structure by anatomical MRI methods only is also limiting, and other functional (functional MRI [fMRI] or positron emission tomography [PET]) or chemical (magnetic resonance spectroscopy [MRS]) techniques serve complementary roles in defining pathophysiology associated with specific disorders. A number of studies have demonstrated that structural imaging data are an important adjunct to functional or metabolic imaging. Use of functional or chemical imaging techniques applied without structural data results in the erroneous underlying assumption that there are no differences in tissue composition between patients of interest and healthy control subjects. An example is illustrated in the recent demonstration of decreased gray matter volume in regions of the ventral medial prefrontal cortex in recurrent major depression and bipolar disorder (Drevets et al. 1997; Hirayasu et al. 1998). Early functional studies had reported consistent decreases in blood flow and metabolism in this region, which had been interpreted as decreased activity in the regional neuronal tissue. However, models to estimate the per-unit volume neuronal activity in the context of decreased gray matter volume in

this specific region have suggested that the neuronal activity may in fact be increased on a per-unit basis (Drevets 2000). It is likely that the integration of cross-modality imaging data will result in clearer specification of distinct neuropathophysiologies associated with psychiatric disorders. Structural changes that are secondary to effects of illness via neurodegenerative mechanisms (or via changes in neurodevelopment) not only could have important treatment implications but also would be integral to clarifying current diagnostic heterogeneity. It has been demonstrated that children with ADHD have a reduction in caudate nucleus volume, and they also show a difference in the developmental pattern of change in caudate nucleus volume with increasing age. In comparison to healthy children, who have decreasing caudate nucleus volumes with advancing age, boys with ADHD show no change in volume with age (Castellanos et al. 1996). Another example is the finding that adolescents with prepubertal-onset schizophrenia are noted to have structural differences early in the course of illness, and these changes become accentuated with age as these adolescents demonstrate a clear deviation from normal developmental trends in several regions in comparison to unaffected control subjects (Giedd et al. 1999). Thus these two examples illustrate how the onset of a disorder may affect normal developmental or aging-related brain changes. An increased emphasis on longitudinal neuroimaging studies is important not only for treatment planning but also to further specify diagnostic categorization. For example, two divergent pathophysiologic mechanisms may underlie two different cases, each currently classified as major depressive disorder (MDD). In one case, an adolescent with early-onset depression with high familial loading, and with associated specific prefrontal volumetric differences, has an illness that most likely results from an altered neurodevelopmental process potentially related to specific serotonin-related polymorphisms (Todd and Botteron 2001). In the other case, late-onset MDD that may appear very similar phenotypically and symptomatically may instead be related to subtle cerebrovascular changes that disrupt connections between structures that are essential in affective regulation (Steffens and Krishnan 1998). Although these are extreme examples of divergent mechanisms, they clearly illustrate the types of pathophysiologic heterogeneity that are not well characterized by the current DSM nosology.

Functional Neuroimaging

Functional neuroimaging methods examine brain activity through measures related to energy metabolism, such as rates of glucose and oxygen utilization and cerebral blood flow (CBF). Methods include PET for glucose metabolism and CBF, single photon emission computed tomography

(SPECT) for CBF, and fMRI for changes in signal intensity attributable to CBF.

Imaging studies have examined a wide variety of psychiatric diagnoses, including schizophrenia and other psychotic disorders (Bertolino et al. 2000; Buchsbaum et al. 1996; Farde 1997; Gur et al. 1995; Kapur et al. 2000; J.J. Kim et al. 2000; Laruelle 2000; D.D. Miller et al. 2001; Mitchell et al. 2001; Perlstein et al. 2001; Ragland et al. 2001; J.A. Stanley et al. 2000), mood (Brody et al. 1999; Drevets 1999, 2000; Kennedy et al. 2001; Nobler et al. 1999; Staley et al. 1998; Stoll et al. 2000; Strakowski et al. 2000; Yildiz et al. 2001a, 2001b), anxiety (Liberzon et al. 1999; Osuch et al. 2000; Saxena et al. 1999; Tillfors et al. 2001), substance-related disorders (Childress et al. 1999; Kilts et al. 2001; London et al. 1999; Volkow et al. 1999, 2001), developmental disorders (Filipek 1999; Hashimoto et al. 2000; Hendren et al. 2000; Ohnishi et al. 2000; Rastam et al. 2001; Rumsey and Ernst 2000; Schweitzer et al. 2000; Tuama et al. 1999; Zilbovicius et al. 2000), and dementia (Arnaiz et al. 2001; Bonte et al. 2001; Reiman et al. 2001; Schroder et al. 2001). Early paradigms evaluated resting baseline topography of glucose metabolism and CBF in patients relative to healthy participants. Researchers who conducted studies across clinical populations reported abnormalities in patient groups. Most observed hypometabolism or hypoperfusion in patients with focal areas of relatively increased activity (Buchsbaum et al. 1996; Gur et al. 1995; J.J. Kim et al. 2000). It is difficult to compare findings across studies because regions of interest (ROIs) varied according to the hypothesized pathophysiology of specific disorders. However, the cortico-striato-thalamic-cortical circuitry has been implicated in most disorders, which suggests aberrations in modulation of critical pathways that regulate a wide range of behaviors related to cognition, emotion, and motivation.

Clinical features, including symptoms and treatment status, have been examined to assess relation to underlying neural dysfunction. For example, patients with schizophrenia were subclassified by DSM-IV subtypes, by positive and negative symptoms, and by neuroleptic status (Buchsbaum et al. 1996; Gur et al. 1995; J.J. Kim et al. 2000; D.D. Miller et al. 2001; Mitchell et al. 2001; Perlstein et al. 2001; Ragland et al. 2001). Similarly, resting metabolism and its change in response to pharmacologic and psychotherapeutic intervention has been related to treatment response in depression (Brody et al. 1999, 2001; Kennedy et al. 2001; Yildiz et al. 2001a) and OCD (Baxter et al. 1992; Schwartz et al. 1996).

Nonetheless, heterogeneity within DSM-IV diagnostic groups and individual differences within healthy participants yield appreciable overlap in the distribution of physiologic activity between those with the disorder and unaffected control subjects. Furthermore, the issue of specificity has re-

ceived limited attention, and direct comparison among disorders that share clinical features have been rare.

The field has shifted to activation paradigms with application of specific neurobehavioral probes designed to examine recruitment of circuitry hypothesized to underlie observed abnormalities (Childress et al. 1999; Kilts et al. 2001; J.J. Kim et al. 2000; Liberzon et al. 1999; Mitchell et al. 2001; Ragland et al. 2001; Schweitzer et al. 2000; Tillfors et al. 2001). These probe paradigms rely on multiple measures of physiologic activity obtained during differing conditions such as task performance or sensory stimulation. The activation paradigms are aimed at identifying brain circuits recruited during specific processes and conditions in healthy people and relate abnormalities in patients to the behavioral manifestations of disorders. This approach requires multiple measurements, the number of which has been constrained in isotopic studies because of exposure to ionizing radiation. Because of its temporal and spatial resolution, lack of radiation, and availability, fMRI has become the major tool for this research methodology (Mitchell et al. 2001; Perlstein et al. 2001). The ability to couple CBF changes to specific stimuli using event-related approaches, analogous to event-related potentials (ERPs) used in electrophysiology, afford additional means of tracing the cascade of neural events associated with information processing (Mitchell et al. 2001; Perlstein et al. 2001). Thus, fMRI has helped push neuroscience frontiers to critical examination of fundamental processes underlying memory, emotion, reward, and executive monitoring. Understanding these processes in healthy people is a prerequisite for advancing research in psychiatric disorders where these capacities are affected.

In vivo proton and phosphorus MRS is a noninvasive method for measuring biochemical parameters in ROIs. Qualitative and quantitative spectral analyses provide information on cellular metabolism and molecular structure, such as membrane phospholipids and *N*-acetylaspartate (NAA), a measure of neuronal integrity. Whereas most MRS studies in psychiatry have been conducted in schizophrenia (Bertolino et al. 2000; J.A. Stanley et al. 2000), there is a growing literature on mood (Yildiz et al. 2001b) and developmental disorders. Although there is converging evidence of changes in membrane phospholipid metabolites and reduction in NAA in the dorsolateral prefrontal cortex and temporal lobe in schizophrenia, reports are still inconclusive (Bertolino et al. 2000; J.A. Stanley et al. 2000). Diverse methods have been applied in cross-sectional studies, which have yielded preliminary data that can advance the understanding of the pathophysiology of disorders but do not provide diagnostic specificity or reliability.

Another window for assessing brain function is the understanding of neurotransmitter systems through the application of PET and SPECT.

These efforts are guided by pharmacologic studies and advances in neuroreceptor subtyping. Human neuroreceptor studies have built on progress with in vitro binding measurements of receptor affinity and neuroreceptor autoradiography. Initial investigations have examined antipsychotic agents in patients with schizophrenia. PET studies have suggested that, across antipsychotic agents, the degree of dopamine type 2 receptor (D_2) occupancy relates to clinical response and extrapyramidal signs (Farde 1997; Kapur et al. 2000; Laruelle 2000). The introduction of atypical antipsychotics has been accompanied by PET studies of typical and atypical receptor profiles (D.D. Miller et al. 2001; Soares and Innis 1999). The role of 5-HT_{2A} receptor blockage in the therapeutic effects of atypical antipsychotic drugs is currently scrutinized, as is the role of the D_4 receptor subtype. The role of serotonin in mood regulation has prompted the development of 5-HT_{2A} and 5-HT_{1A} ligands (i.e., radioactively tagged receptors) for PET and SPECT imaging that have been applied in the study of depression (Nobler et al. 1999; Staley et al. 1998). Although reduced binding has been reported for regions implicated in depression, such as the hippocampus and orbitofrontal areas, the field is evolving and correlations with clinical measures are lacking. These efforts are important for advancing the understanding of the pathophysiology of psychiatric disorders and have therapeutic implications. However, the literature on receptor systems is developing, and specificity is yet to be addressed.

Current Status of Postmortem Studies of Psychiatric Disorders

Postmortem studies have been undertaken in psychiatric illnesses for many years. Despite numerous attempts, many of these investigations have resulted in conflicting, often unreplicable findings. These studies have often been important starting points for new lines of investigation and the generation of novel hypotheses. Most postmortem studies have targeted schizophrenia, depression and suicide, and the dementias, although more recently the postmortem brain has been studied in other conditions, including alcoholism and substance abuse. Postmortem studies in alcoholism and substance abuse are difficult to interpret, however, because at present it is not possible to differentiate between neurobiological changes that represent a vulnerability to these illnesses and the effects of the ingested substance on the brain.

Postmortem Studies in Mood Disorders

Historically, the dominant hypotheses regarding the pathophysiology and pathogenesis of mood disorders have centered on the monoamines. Therefore, the majority of postmortem studies in depression have reflected this bias by concentrating on monoamine receptors. Many of the postmortem studies on monoamines have focused on suicide victims without a clear psychiatric diagnosis, and as a consequence these findings do not necessarily apply to mood disorders. The 5-HT_{1A} and 5-HT_2 serotonin receptors and the serotonin transporter (5-HTT) have been the most studied serotonin-related molecules in suicide victims with or without a history of depression, and in depressed patients who died of natural causes. Most, but not all, postmortem studies have reported increased 5-HT_2 receptor binding in frontal cortex in suicide victims irrespective of diagnosis, compared with control subjects (Arango et al. 1990; Arora and Meltzer 1989; Gross-Isseroff et al. 1990; Mann et al. 1986; Owen et al. 1986; M. Stanley and Mann 1983). These findings, however, are less consistent in studies in which a diagnosis of depression has been ascertained (Cheetham et al. 1988; Crow et al. 1984; Hrdina et al. 1993; Lowther et al. 1994; McKeith et al. 1987; Stockmeier et al. 1997; Yates et al. 1990). Postmortem studies of 5-HT_{1A} receptor in subjects with a history of depression have also been inconsistent. Decreased 5-HT_{1A} binding in the temporal pole and lateral orbital cortex (Bowen et al. 1989) and decreases in 5-HT_{1A} mRNA levels in the hippocampus of suicide victims with a history of depression (López et al. 1998) have been reported, but these findings are not universal (Stockmeier et al. 1997). Decreased 5-HT_{1A} binding has also been reported in superficial layers of dorsolateral prefrontal cortex tissue removed neurosurgically from patients with intractable depression (Francis et al. 1993). The decreases in 5-HT_{1A} receptor found in these studies are consistent with findings from PET studies using 5-HT_{1A} ligands (Drevets et al. 1999; Sargent et al. 2000). There also seems to be strong postmortem evidence of presynaptic 5-HT dysregulation, as measured by decreases in 5-HTT binding, in the cortex of depressed subjects (Mann et al. 2000; Perry et al. 1983). Whether these reductions are a trait marker for MDD or represent a compensatory event secondary to impairment in serotoninergic functions remains to be determined.

The noradrenergic system has also been investigated in postmortem studies of MDD, and again the findings are inconsistent. For example, the presynaptic α_2 adrenoreceptor has been reported as increased in the temporal cortex (De Paermentier et al. 1997), hypothalamus (Meana et al. 1992), and frontal cortex (Callado et al. 1998; Gonzalez et al. 1994) of suicide victims with a history of depression, compared with control subjects.

However, these observations have not been replicated in other studies in which diagnoses of depression were made (De Paermentier et al. 1991; Klimek et al. 1999; Little et al. 1993). A carefully executed anatomical study found evidence of reduced norepinephrine transporter binding in the locus coeruleus of depressed subjects who died by suicide (Klimek et al. 1997), a provocative finding that needs replication.

It is not clear if the differences found in postmortem studies of monoamine receptors are due to cause of death, the presence of depressive subtypes, history of medication use before death, postmortem delay in brain tissue processing, or the type of ligand used in some of the studies. The technical difficulties intrinsic in postmortem studies require a large number of subjects as well as a consensus of anatomical regions and standardization of biochemical protocols before clear patterns emerge.

In addition to the monoaminergic systems, the hypothalamic-pituitary-adrenal (HPA) axis has also been implicated in the pathophysiology of MDD. Hypercortisolemia and increased activity of the HPA axis are well-documented phenomena in clinical studies of subjects with depression. Postmortem studies have found evidence of chronic HPA activation in suicide victims, such as adrenal hyperplasia (Dorovini-Zis and Zis 1987), downregulation of CRH receptors, the molecule responsible for adrenocorticotropic hormone (ACTH) release, in frontal cortex (Nemeroff et al. 1988), and increases in proopiomelanocortin mRNA, the precursor for ACTH, in the pituitary (López et al. 1992). It is difficult to determine whether these changes are due to the fact that a significant subset of suicide victims are patients with depressive disorders, are due to the stress surrounding the suicide itself, or are due to a neurobiological abnormality common to all suicides irrespective of diagnosis. The limited information available from studies in which an antemortem diagnosis of depression was made does suggest that evidence of HPA hyperactivity is present in the brains of depressed subjects. Increased CRH immunoreactivity and increased CRH mRNA levels have been reported in the paraventricular nucleus of the hypothalamus of depressed subjects (Raadsheer et al. 1994, 1995). Downregulation of mineralocorticoid receptors has been found in the hippocampus of medication-free suicide victims with a history of MDD (López et al. 1998). This latter observation is consistent with a history of exposure to chronic stress and/or to high peripheral glucocorticoid levels (Herman and Watson 1994; López et al. 1998).

In animal studies, the presence of chronically elevated glucocorticoids has been implicated in neuronal atrophy (Sapolsky 2000), and indeed, recent morphometric studies (Ongur et al. 1998; Rajkowska 2000; Rajkowska et al. 1999) have demonstrated that histopathological changes in neurons and glial cells are present in mood disorder. Significant reductions in glial

cell number and packing density have been reported in postmortem brains of subjects with a history of major depressive disorder and bipolar disorder (Cotter et al. 2001; Ongur et al. 1998; Rajkowska 2000; Rajkowska et al. 1999). These reductions in glia have been described in the anterior cingulate cortex (Cotter et al. 2001), subgenual prefrontal region (Drevets et al. 1997), dorsolateral prefrontal cortex, and orbitofrontal region (Rajkowska 2000; Rajkowska et al. 1999). In addition to glial abnormalities, there is a decrease in neuronal cell body size and a decrease in neuronal packing density in the lateral orbitofrontal cortex and dorsolateral prefrontal cortex in major depressive disorder and bipolar disorder (Rajkowska 2000; Rajkowska et al. 1999). This reduction in cell number may be responsible for the significant reduction in gray matter volume observed in the subgenual region (Cotter et al. 2001) and the reported decrease in cortical thickness in the lateral orbitofrontal cortex (Rajkowska et al. 1999).

It is not clear if depressed patients are genetically predisposed to the cellular histopathological changes observed in these studies, whether these changes are present since birth, or whether these changes are secondary to the pathophysiological process that may occur in mood disorders. It has been proposed that, in individuals with a predisposition to depression, cellular and morphometric changes may be related to stress-induced alterations in neurotrophins, such as brain-derived neurotrophic factor (BDNF) (Duman et al. 1997). Consistent with this view, rodent studies have shown that antidepressants can increase the levels of neurotrophic factors and therefore increase neurogenesis (Duman et al. 1997). Interestingly, glucocorticoids are also capable of modulating many of the monoamine receptors that have been reported to change in suicide and in MDD (López et al. 1999), indicating that there may be a link between the monoamine and HPA alterations seen in mood disorders and the histopathological and volumetric changes observed in this population. It is important to point out, however, that changes in neurotrophic factors have yet to be reported in postmortem studies of mood disorder, although changes in cyclic adenosine monophosphate–responsive DNA-binding protein, a modulator of BDNF, have been reported in the temporal cortex of subjects with MDD (Dowlatshahi et al. 1998). This new avenue of research in postmortem studies may serve as an impetus to forge stronger links between basic and clinical studies and, it is hoped, will increase our understanding of the pathophysiology of mood disorders.

Postmortem Studies in Schizophrenia

The direct study of the brain in schizophrenia has one of the longest histories in postmortem research in psychiatry. Originally these studies took the

form of examination of the brain for gross structural abnormalities, followed by microscopic studies searching for more subtle changes, including alteration of cell density, neuron number, and orientation of cells in structures in which cells are found in patterns of alignment. Numerous attempts were made to find gliosis in the brain, which would be suggestive of an active degenerative process. For the most part, gliosis was never conclusively detected in the brains of individuals with schizophrenia. More recently, well-designed systematic studies of this sort have been undertaken and have yielded more promising results. These studies have tended to find abnormalities in cell number, including reports of decreased neuronal number in the dorsomedial nucleus of the thalamus (Pakkenberg 1990).

In a second type of these studies, instead of changes in cell number, changes in cellular density were found: one of the first of these studies found decreased neurophil in the prefrontal cortex in the face of normal cell numbers, resulting in increased packing density of cells (Selemon et al. 1995). Other studies have focused on cellular morphology: there are reports of abnormal cell size, such as diminished neuron size in the hippocampus (Benes et al. 1991), as well as abnormalities of cytoarchitecture in other medial temporal lobe structures (Krimer et al. 1997). Finally, there have been a few reports of cells being found in abnormal distributions, presumably reflecting altered neuronal migration during development (Akbarian et al. 1993).

Because of pharmacologic evidence implicating D_2 and related dopamine receptors in schizophrenia, there have been a number of postmortem studies focused on the dopaminergic system in the brains of individuals with schizophrenia (Joyce and Meador-Woodruff 1997). The most robust finding in all postmortem studies in schizophrenia is increased striatal D_2 receptor expression in schizophrenia, although this may be secondary to prior neuroleptic treatment. The novel D_2-like receptors (i.e., D_3 and D_4) have recently been the subject of intense study. After some initial excitement around the role of the D_4 receptor in schizophrenia, this receptor is no longer as intensively studied, after clinical trials using D_4 analogs had negative results. On the other hand, several recent studies have found abnormalities in D_3 expression in both cortex (Schmauss et al. 1993) and striatal regions (Gurevich et al. 1997), with abnormalities found both at the level of D_3 transcript expression and at D_3 binding sites.

More recently, abnormalities of glutamatergic transmission have been implicated in schizophrenia. Like the dopamine receptors, the expression of the glutamate receptors has been determined at multiple levels of gene expression in postmortem brain samples from schizophrenic persons; although results have not been entirely consistent from study to study, several generalizations have emerged from this literature (Meador-Woodruff

and Healy 2000). The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate subtypes of glutamate receptor are both abnormal, particularly in the hippocampus of the brains of individuals with schizophrenia. These findings are consistent across transcript, protein, and binding studies. In addition, the *N*-methyl-D-aspartate (NMDA) receptor may be abnormally expressed in some cortical regions in schizophrenia. A current effort for all receptor families is to examine the expression of signal transduction molecules associated with individual receptors in the brains of persons with schizophrenia.

A particularly elegant class of study in postmortem brain involves the use of immunocytochemistry to determine patterns of innervation in specific neurotransmitter systems. The most well-studied examples are abnormal GABAergic innervation (Benes 2000) of limbic cortex, as well as diminished dopaminergic innervation to frontal and temporal cortical areas (Akil et al. 1999). Currently, these types of studies target multiple markers in the service of defining intrinsic cortical circuits that are defective in schizophrenia (Lewis 2000). Finally, recent data suggest that there may be abnormalities in developmentally expressed molecules associated with neuronal migration and cell adhesion (Vawter et al. 1998, 1999), synapse-specific proteins (Vawter et al. 1999), and genes associated with neurotransmitter release (Mirnics et al. 2000).

Blueprint for the Future

How Preclinical Research Can Enhance Knowledge of the Etiology and Pathophysiology of Psychiatric Disorders

Despite the advances in understanding normal brain function and drug mechanisms of action, animal research has not yet yielded clear information about the pathophysiology of human psychotic, affective, or anxiety disorders. The development of better animal models is therefore crucial for laying the groundwork for future discoveries into the pathophysiology of these disorders. More information is available for substance use disorders, probably due to the fact that in this case the drug is a critical etiological agent. It also is not at all clear whether available animal models of psychiatric disorders have predictive value in developing treatments with novel mechanisms of action (e.g., an antidepressant with a non-monoamine-based mechanism). Given these concerns, some have argued that there are inherent limitations in the ability to model psychiatric disease in animals, particularly in rodents, given that many of the features of these diseases involve core human functions (higher cognition, complex emotions, interpretation of reality). Although such limitations must be kept in mind, there remains

a general consensus that animal research will be a vital part of any combined effort to understand psychiatric disorders. Thus, although it may not be possible to generate a "schizophrenic" mouse, it certainly has been possible to generate a mouse that replicates certain key symptoms of schizophrenia, including abnormalities in cognition and motivational state.

We can identify four major areas where animal research will contribute to the formulation of an etiologically and pathophysiologically based DSM-V. The first is the development of better animal models of psychiatric disease. As alluded to above, many extant models are based on currently available medications and lack face validity in replicating the symptoms of specific human disorders. The forced swim test serves as a useful example. In this test, a rodent is placed in a water bath and the amount of time it struggles, before floating without struggle, is quantified. Short-term administration of antidepressant drugs increases the amount of time the animal struggles, and this test has been highly effective at identifying new antidepressants with the same mechanism of action as existing agents. However, there is no reason to believe that placing a normal rodent in a water bath induces a state of depression.

Better animal models of psychiatric disease will come from several sources (Table 2–1). As disease-causing variations in specific genes are identified in humans, these mutations can be placed in rodents with the goal of recreating aspects of the human disease. This approach has proved highly fruitful for many neuropsychiatric disorders, including Alzheimer's disease, Parkinson's disease, and Huntington's disease, to name a few. Such "humanized" rodents are invaluable in understanding how the genetic mutations actually lead to the abnormalities that characterize the disease and in providing in vivo systems for drug discovery efforts. Generation of such mice with psychiatric disease genes will be a major boon for the field.

TABLE 2–1. Blueprint for the future: development of better animal models

Identify disease-specific genes in humans; once this is done, mutations can be placed in rodents, which can facilitate understanding of how the disease process unfolds and can be used in drug discovery efforts
Conduct studies using genetically modified animals (induced targeted, cell-specific genetic mutations in the brain)
Conduct studies in nonmammalian organisms
Identify genes that determine abnormal behavior in animal models (quantitative trait locus, chemical mutagenesis, enhancer trapping)
Functional genomics (microarrays, proteomics, effects of stress, antidepressants, animal models)

An increasingly useful technique is to overexpress or delete a gene of interest from a mouse. Many such genetic mutant mice show interesting behavioral abnormalities that replicate certain symptoms of human psychiatric disorders. Mutations in various genes have led to mice with symptoms of schizophrenia (e.g., abnormalities of working memory), depression, anxiety, or inattention and hyperactivity. Tools for the generation of mutant mice are becoming increasingly sophisticated. It is now possible to target genetic mutations to the brain and even to overexpress or delete a gene of interest in a selected subpopulation of neurons in the brain and to induce such a mutation in the adult animal. Such inducible, cell type–specific mutations avoid the developmental complications of constitutive mutations and will greatly increase the utility of these animals in studies of neural and behavioral plasticity in adults.

Studies in nonmammalian organisms, from yeast to worm to fruit fly to zebra fish, have their place in this endeavor. The more primitive the animal, the less referable any behavioral symptoms will be for a human condition. Nevertheless, the power of genetics in these organisms makes it possible to use them to identify families of genes and biochemical pathways implicated in a particular phenomenon. For example, a mammalian protein involved in cellular adaptations to stress has been studied in model organisms, where it has been possible to identify numerous additional proteins involved in stress responses.

More ethologically based approaches promise improvements in animal models of psychiatric disorders. Abnormal behaviors can be identified in outbred populations of rodents, or abnormal social behavior of rodents can be elicited by a variety of "psychosocial" stimuli. Combinations of such psychosocial stimuli with particular genetic strains or mutants of rodents may be particularly fruitful in identifying the relevant abnormal behaviors. Greater attention should also be given to the study of nonhuman primates, although use of these animals must be confined to carefully defined circumstances, given the cost and ethical concerns involved.

A second major domain for animal research in building a better diagnostic system is to identify genes that help determine abnormal behavior in animal models. Major efforts are now under way, utilizing quantitative trait locus (QTL) analysis, to reveal the precise genetic variations that underlie naturally occurring differences in behavior exhibited among rodent strains, for example, in models of antidepressant action, stress responses, anxiety-like behavior, and addiction. In parallel efforts, investigators are inducing random mutations in mice (as well as in nonmammalian organisms) to identify genes that contribute to normal and abnormal behavior. Chemical mutagenesis and enhancer-trapping approaches are examples of the tools in current use. Finding genes that control behavior in animals will provide

candidate genes to study in human populations and, more importantly, indicate whole biochemical pathways that underlie a particular behavior.

The third area for which animal studies are important is brain imaging. Imaging studies in animals are needed to better understand the nature of imaging signals in humans. For example, fMRI provides a measure of deoxygenation of hemoglobin and thereby reflects oxygen use in the tissue. Yet a majority of oxidative phosphorylation in the brain is thought to be localized to nerve terminals. As a result, brain regions that show an increase in oxygen use as deduced from the fMRI signal presumably contain more active nerve terminals, not necessarily more active neuronal cell bodies, as is often the interpretation. Obtaining fMRI signals in rodents and nonhuman primates, followed by direct histologic and molecular analysis of the brain tissue, will vastly improve the ability to derive neurobiological information from imaging studies in humans. Similarly, PET studies in animals are a necessary concomitant for the development of novel ligands for receptors and other proteins.

Finally, the newly developed tools of functional genomics and proteomics have vastly expanded the ability to study genetic and molecular factors involved in psychiatric disorders. Functional genomics, in the context of psychiatry, generally refers to the identification of genes that are regulated in particular brain regions by a given drug or behavioral state. DNA microarrays are becoming the most widely used tools in functional genomics. Here, literally thousands of DNA samples (derived from mRNAs expressed in tissue) are spotted onto a silicon chip or glass slide. Such microarrays can then be used to simultaneously study the ability of a particular stimulus to regulate the thousands of gene products represented on the arrays. DNA microarrays are being used, for example, to identify genes that are regulated in common by many classes of antidepressant or antipsychotic treatments, or after exposure to various psychosocial stresses. DNA microarrays are also being used in studies of postmortem human brain samples to identify gene products that are present at abnormal levels in specific brain regions of individuals with a particular psychiatric disorder. In addition, different types of DNA microarrays, where sequences of human genes (as opposed to mRNAs) are spotted, are now being used to identify genetic polymorphisms in human populations.

Genes and mRNAs ultimately function through the proteins they encode, hence the power of proteomics, which simultaneously evaluates hundreds or thousands of proteins present in a tissue sample. Proteomic tools are not as well developed as are DNA microarrays, but there is intense research in this area. It is now possible, through mass spectrometry and other protein separation techniques, to identify the thousands of proteins present in a tissue extract or their state of phosphorylation, to name two examples.

Scientists are just now beginning to apply proteomic tools to the study of psychotropic drugs, animal models of psychiatric disorders, and postmortem samples from humans with these disorders.

Ultimately, advances in animal research will contribute critical information toward a new diagnostic system only through an improved integration of preclinical and clinical investigations. Discoveries in animals will define and direct clinical research into the etiology and pathophysiology of human disease, whereas findings in humans will feed back and inform animal studies aimed at identifying the underlying mechanisms involved.

Identification of Disease-Related Genes

The availability of new genetic resources in the domains of information and technology are setting the stage for an exciting new era of molecular psychiatry (Table 2–2). The rough draft of the human genome includes some 3 billion nucleotides of sequence (Venter et al. 2001), a catalog of several million polymorphisms in the genetic code (primarily single-nucleotide polymorphisms, or SNPs) (Chakravarti 2001), and more than 26,000 human genes, most of which were previously unknown and 42% of which remain unknown in function. Comparative sequencing of the fruit fly (Adams et al. 2000) and nematode worm has already defined a list of more than 2,000 genes that are orthologs of human genes, potentially enabling these other species to be used as models for the functions of the orthologous genes. The forthcoming publication of the mouse sequence is likely to have an even greater impact because of the roles of the mouse and rat as model species in neurobiology and because of the very substantial level of structural and functional conservation between the brains and genomes of rodent and human. Advances in technology include faster and cheaper sequencing methods (Tang et al. 1999), high-throughput technologies (including array methods) for genotyping and analysis of gene expression, and full-length cDNA clones containing entire protein coding sequences (Strausberg et al. 1999).

The elucidation of genetic differences among patients with the same clinical diagnosis may lead to identification of new diagnostic subtypes. As noted previously, one research team has identified a subtype of schizophrenia (periodic catatonia) for which there was significant evidence of linkage to 15q (Stober et al. 2000). In a panic disorder study, families were subdivided on the basis of kidney or bladder problems and other medical conditions, and significant 13q linkage evidence was reported (Weissman et al. 2000). Although these results require replication in other samples, this methodology represents a potentially useful strategy for future research by which biologically (and clinically) meaningful subtypes may be delineated.

TABLE 2–2. Blueprint for the future: new tools and technologies in genetics

High-throughout genotyping via mass spectrometry
Draft sequence of the human genome (fruit fly, worm, mouse)
Comprehensive catalog of human genetic variation
New statistical methods
Large data sets
Intermediate phenotypes
Biological traits, disease subtypes, symptom clusters

This in turn may form the basis for a nosology in which fundamental differences in etiology, pathophysiology, course, outcome, symptomatology, and therapeutic response—all of which are of high relevance to clinical psychiatry—are identified and ultimately validated.

Pharmacogenetic factors determine both pharmacokinetics (drug absorption, distribution, biotransformation, and excretion) and pharmacodynamics (tissue response), which in turn determine the clinical effects (both therapeutic and untoward) of medications and are likely to become an important focus in clinical psychiatry. The pharmacodynamic differences may help define new disease subtypes. Across existing diagnostic categories, pharmacogenetic tools could enable psychiatrists to predict which patients would be likely to exhibit a positive therapeutic response, as well as those who would be likely to experience an increase in adverse events (Roses 2000). In a recent study, combinations of multiple SNPs were predictive of bronchodilator response to a β agonist in asthmatics (Drysdale et al. 2000). Association studies in multiple candidate genes have been used to identify the combination of polymorphisms that give the best predictive value of response to clozapine in schizophrenic patients (Arranz et al. 2000b). Such results will not only accelerate the development of a biologically based nosology and subtypes of high relevance for clinical medicine but will also facilitate development of individualized treatment regimens.

A large body of literature demonstrates the existence of substantial cross-ethnic variations in the pharmacokinetics and pharmacodynamics of most pharmaceutical agents. Correspondingly, substantial variations in the genes controlling these processes have also been reported. Research in this area also will serve to further clarify these issues and will render pharmacotherapy increasingly more individually tailored and sensitive to group differences.

Genetic research may be useful in refining clinical phenotypes through the identification and analysis of intermediate (mediating) phenotypes (i.e., biological traits that index genetic liability to mental disorders). Many

complex illnesses (e.g., hypertension, cancer, coronary heart disease, epilepsy, and cutaneous melanoma) can be characterized by multiple intermediate biological traits or risk factors that play a role in producing disease vulnerability. In general, genes will not show a one-to-one relationship to diagnosis because the intermediate phenotypes themselves will be involved in more than one psychopathology. Examples in mental disorders include impaired cognitive executive function, which could be an intermediate phenotype in both substance dependence and schizophrenia. Fear and anxiety as found in several mental disorders may predispose to certain forms of substance abuse. On the other hand, the flushing reaction secondary to deficiency of aldehyde dehydrogenase (ALDH) and/or the "overproduction" of alcohol dehydrogenase (ADH) is an intermediate protective phenotype specific to alcoholism.

The potential benefits of identifying intermediate phenotypes are manifold. Such quantitative correlates of disease liability may be more amenable to genetic analysis than disease status itself (e.g., Almasy et al. 2001). The power to initially map a disease vulnerability locus of small relative effect and to then replicate the result may be enhanced through consideration of the effects of such loci on biological traits correlated with disease, and such complex multivariate phenotypes may be used to judiciously sample families for replicating genetic findings (Moldin 1997a). Genetic research on intermediate phenotypes may directly facilitate identification of new diagnostic categories or disease subtypes of high clinical relevance. Ultimately, incorporation of biological trait data into psychiatric nosology can accelerate research on underlying pathophysiologic mechanisms, increase the accuracy for identifying individuals who fall within a spectrum of illnesses related to a core disease, resolve clinical heterogeneity, and enhance prediction of therapeutic response.

Another challenge for future nosologies will be the integration of both genetic and biological trait information into diagnostic classification. For example, the observation that there is substantial overlap in the information from gene markers (e.g., ALDH2 and ADH2) with information accessible from studies of biological traits (e.g., alcohol-induced flushing, alcohol sensitivity, personality, and electroencephalographic differences) suggests a strong need for continued integrative approaches for clarifying the underlying etiology and pathophysiology of alcohol dependence.

It is very likely that most mental disorders are complex genetic diseases involving structural alterations in the genes in question, and postmortem studies may be very useful in studying many facets of gene function and expression (see below). Anatomical studies can help by indicating which cells express these genes (in the form of mRNA and by using in situ hybridization). Such studies will allow comparison of the normal and illness levels of

expression of these genes. They can also be greatly informative as to which cells and circuits are directly involved. For example, analyses of postmortem tissue from the prefrontal cortex have identified differences in the expression of genes involved in the mechanics of synaptic transmission, which may form the basis for identifying schizophrenia subtypes (Mirnics et al. 2000).

Even in simple genetic diseases caused by single genes, biological defects can and do express themselves in confusing tissue-related fashion. For example, aberrations in the hemoglobin gene are the cause of sickle cell anemia, with many organs being adversely affected. The gene's primary pathological actions are exerted in red blood cells; the pathology in other organs actually reflects red blood cell dysfunction. Hence, the causative gene may have a direct impact in one or a few locations yet indirectly affect many related organs, systems, or circuits. A knowledge of the function of the physiology of such circuits and indications of how these function are altered, perhaps in genetically altered animals using the "same" alteration or mutation, could point to core dysfunctions lying at the heart of a disorder (Tarantino and Bucan 2000). To make matters more complex, the subtle impact of the several variant genes as they affect and interact within core brain circuits and systems must also be considered. The use of these gene variants as a set in animal models can allow studies ranging from pure genetics through human brain anatomy to genetically altered animals in which these gene changes can be directly evaluated.

In summary, future genetic research will yield information highly relevant for an evolving psychiatric nosology. Gene discovery and the resulting molecular characterization of mental disorders will most likely lead to the delineation of new diagnostic subtypes and to the identification of biological traits (intermediate phenotypes) that correlate with disease liability. Postmortem studies and gene expression profiling will provide enormous depth and insight into establishing new diagnostic boundaries. This in turn will accelerate efforts to localize the molecular bases of mental disorders within the brain, and thereby provide starting points for designing new treatments for mental illness. As may be the case throughout clinical medicine of the future, genetic information in psychiatry offers tremendous potential for classifying patients who have a positive therapeutic response and those who experience adverse events. Ultimately, development of a rich multivariate psychiatric nosology may be accelerated, in which complex information on clinical symptomatology, course, outcome, biological traits (intermediate phenotypes), genetic information, and therapeutic response are directly incorporated into the differential diagnostic process and into the development of individualized therapeutic regimens.

Increased Role for Postmortem Research of Psychiatric Disorders in the Future

The direct postmortem study of human brain of individuals with mental illness is likely to have important impacts in several critical areas (Table 2–3). One of these is a follow-up on gene variation studies carried out in families or populations. As noted, it is very likely that most mental illnesses are complex genetic diseases involving structural alterations in the genes in question. Postmortem studies may be very useful in studying many facets of the gene or genes in question. For example, anatomical studies can help by indicating which cells express these genes (in the form of mRNA and by using in situ hybridization). Such studies will allow comparison of the normal and illness levels of expression of these genes. They can also be greatly informative as to which cells and circuits are directly involved.

TABLE 2–3. Blueprint for the future: postmortem investigation

Is the only method to directly study structure and function of brain and gene expression (mRNA)
Can be used to validate gene variant findings from population studies
Can be used to validate neuroimaging findings specifying the impact of disease on neural circuits
Can be used to identify disease subtypes and drug targets
Can provide data for animal models that can be used to assess the impact of gene variants on development of brain circuits and systems

Another type of information obtainable from postmortem studies is in the much broader context of mRNA expression studies. The studies, in many cases, may well cover much of the entire human genome and the expression patterns of this very large set of mRNAs across many critical brain regions. Although this may sound similar to the analysis of altered genes discussed above, it is actually a much larger problem in all respects: the numbers of molecules, regions, and functions studied. In effect, these expression studies actually look at the impact of the illness in all its aspects (genes, behavior, basic brain wiring, experience, etc.). They also detect the impact of the illness on all related co-regulated downstream responsive circuits and genes. Hence, an overall set of relationships is detected. The challenge is to learn how to use this mass of information. In some cases, it might be possible to refine diagnostic systems as a function of the neural systems activated, inhibited, or modified, or even to move to a correlation between these changes and a behavior or illness of interest. Another value found in

these mRNA expression studies can be seen in the nature of altered or affected neurons and circuits. It is likely that medications can be constructed that are not only targeted to repair the effort of key defective genes but are as likely to have an impact on normal genes or pathways affected by the illness. It is probable that most of the medications currently used in psychiatry act on genetically normal neural systems that are only indirectly related to the gene or genes actually involved in the genesis of the illness.

Future of Neuroimaging

Neuroimaging is a burgeoning field, with rapid developments in the methods of acquisition and analysis of data and their application to clinical research. As noted in the previous section, significant strides have already been made, such as the move from simple baseline measures of CBF to activation paradigms that can assess the highly specific regions of brain function. As yet, however, these methods have not produced specific markers for disease states. This may be because of time on task—such studies are laborious and time consuming. It may also be a result of the lack of specificity in the current generation of techniques. However, this is changing. Outlined below are advances that are occurring in the major modalities, as well as some of the new modalities that are appearing.

Positron Emission Tomography

As noted above, new ligands are being developed that have specificity for receptors relevant to psychiatric disorders. To date, these have been used primarily to assess baseline levels of receptor occupancy. However, newer methods have begun to examine displacement, in response to both pharmacologic and sensory and behavioral challenges. Administration of amphetamine has been shown to selectively displace ligand binding at striatal D_2 receptors. Similar approaches are being explored for behaviorally induced displacement. One recent study demonstrated reduced ligand binding, presumably marking increased dopamine release, in the striatum during performance of a goal-directed task that correlated with performance in the task. Such methods should permit receptor-specific assessments of neurotransmitter function in relation to cognitive performance. This has obvious relevance for the understanding, and ultimately for the diagnosis, of psychiatric disorders. When receptor activity is monitored, evaluation of neurobehavioral performance implicated in specific circuitry recruitment will enable direct examination of how neuropharmacologic agents modulate these behaviors. Thus, in addition to elucidating how neurotransmitters modulate behavior, desired effects will have therapeutic implications.

Magnetic Resonance Imaging

Currently, the most rapid advances in noninvasive neuroimaging are occurring in the development of MRI-based methods. MRI can be used for imaging structure as well as function, and dramatic progress is occurring in each area.

One important advance in structural imaging is the development of tensor diffusion imaging (TDI). This method is sensitive to the direction and degree of proton diffusion, and thus can be used to map the structure of different fluid compartments in the brain. This method is currently being developed to diagnose and track structural changes associated with stroke and neoplasm. However, because diffusion is greatest along the axonal axis, this method can also be used to trace neuronal fiber tracts. At present, this can be done at a resolution of 100 μm, providing tract tracing well into regions of gray matter. As these methods are refined and validated against standard anatomical techniques, they promise to offer a quantum level of improvement in the ability to conduct neuroanatomical studies. They will allow us to move from simple volumetric analyses of structure to studies of connectivity. At present, studies of connectivity require elaborate dye tracing methods, which are laborious and cannot be conducted in vivo. The ability to noninvasively image whole brain patterns of structural connectivity is likely to have an impact on anatomical research akin to that of "gene chips" in genomics. This promises to advance not only the basic understanding of neuroanatomy, but also the ability to identify subtle abnormalities of connectivity that may be present in psychiatric disease.

Functional MRI

The fMRI technique currently in widest use is the blood oxygen level determination (BOLD) technique. This technique provides information very similar to PET measurements of CBF. However, because it is noninvasive and nontoxic, measurements can be repeated literally thousands of times in a single scanning session. Thus, even though single measurements are less sensitive than those obtained by PET, extensive signal averaging yields greater overall sensitivity. This provides greater spatial resolution (as high as 1 mm accuracy) and, perhaps more importantly, a temporal resolution that is higher by an order of magnitude or more. Currently it is possible to acquire whole-brain images once per second, and as rapidly as four per second when focusing on particular regions of interest. This approach, like PET, is limited by the fact that it indexes a hemodynamic response rather than neural activity directly. This is problematic for several reasons: 1) the hemodynamic response is significantly slower than the neural response (appearing after about 2 seconds and peaking between 4 and 6 seconds), 2) it

is not yet known, with assurance, that the characteristics of this response are uniform throughout the brain, and 3) it is not yet known whether or how neuropsychiatric disorders and/or psychopharmacologic manipulations influence the coupling between the neural and hemodynamic responses. The evidence to date indicates that the hemodynamic response is "well behaved" (that it is stable across brain regions, pharmacologic manipulations, and neuropsychiatric disease processes). However, a deeper understanding of these factors will be important to (and will presumably help improve) the reliability of fMRI applications in psychiatric research and diagnosis.

Several approaches have begun to appear for improving the temporal resolution of fMRI, by modeling the hemodynamic response and removing ("deconvolving") it from the analysis. So-called event-related designs, coupled with such techniques, have permitted detailed studies of relatively transient cognitive events (e.g., activation of hippocampus during memory encoding). The appearance of higher-field (e.g., 3 and 4 tesla) systems has also helped. By providing greater sensitivity, these systems permit the use of measurement techniques that are sensitized to more local hemodynamic processes, ensuring that the signal is closer to the parenchymal origins of neural activity. The faster scanning that is possible with higher-field systems is also being exploited to overcome signal loss that is characteristic of certain anatomical regions of particular relevance to neuropsychiatric disease, such as the orbital frontal cortex and medial temporal areas (including the amygdala and hippocampus). Finally, ultra-high-field (7 tesla) systems are currently being developed that may permit measurements of the hemodynamic response that are more closely related to neural activity, such as the initial phase of oxygen depletion thought to occur within 500 milliseconds of and more local to the site of neural activity.

Because of the limitations of the BOLD technique discussed above, considerable effort is being devoted to the development of magnetic resonance–based methods that provide more direct measures of neurophysiological function. These include methods for directly quantitating perfusion (e.g., spin tagging); imaging nuclei other than hydrogen (e.g., Na^{2+}, Ca^{2+}, or Mg^{2+}, any of which could be used to directly measure fluxes in ion concentrations associated with neural activity); and using contrast agents that selectively bind to neurotransmitter receptors, akin to the use of radioligands with radiographic techniques. Although current progress on these methods has been slow, a breakthrough along any of these dimensions could provide yet another quantum jump in the level of detail and specificity possible with magnetic resonance–based neuroimaging techniques (Table 2–4).

Another important area of progress is in the combined use of pharma-

TABLE 2–4. Blueprint for the future: neuroimaging

Positron emission tomography
New ligand development
Assessment of neurotransmitter release (drugs, behavior)
Magnetic resonance imaging
Structural tensor diffusion imaging (connectivity)
Functional "event-related" MRI (greater temporal resolution), higher magnetic fields (greater sensitivity)
New contrast agents

cologic manipulations and fMRI. A critical first step in this direction, when used with the BOLD technique, has been to establish that pharmacologic agents do not alter the nature of the coupling of neural activity and the hemodynamic response. Insofar as this can be shown, then the use of fMRI to measure changes in brain activity in response to drug administration holds great promise both as a research tool and, eventually, as a method for assessment of clinical efficacy.

Finally, a critical area of rapid development is in the methods used for statistical analysis of MRI data sets. Increasingly sophisticated methods are permitting precise localization of changes in brain activity associated with individual mental functions, ranging from basic sensory and motor processes to higher-level cognitive and emotional processes such as memory encoding and retrieval, maintenance of information in working memory, reasoning and decision making, and emotional evaluation. Identification of the normal patterns and time course of brain activity associated with such mental functions provide an important reference point for studies that seek to identify abnormalities in these functions associated with psychiatric disorders. However, most studies to date have focused on discrete patterns of activity associated with individual mental functions. In fact, normal brain function involves complex, dynamic, and highly integrated interactions among multiple brain systems and functions. Analysis of such dynamics represents a formidable technical challenge. It would be ideal to correlate the activity of every brain region with every other one and with ongoing measures of behavioral performance throughout the course of a cognitive or emotional task. However, at present this is computationally intractable. Hypothesis-driven methods (such as structural equation modeling) have seen some use, but their validity and reliability have yet to be established. Another approach currently being explored is the use of invertible data compression methods. Sufficient compression, coupled with ongoing improvements in computing power, may soon make it practical to conduct full-scale correlational analyses. The ability to do so, and to fully character-

ize the normal dynamics of brain function, will be particularly important for psychiatric applications, because it is likely that interactions between multiple brain systems, rather than isolated abnormalities in the function of any one system, are what are most relevant to psychiatric disorders. The ability to characterize the dynamics of brain function may be as important an advance over measurements of specific regions of brain activity as activation studies were over simple baseline measurements.

Event-Related Potentials and Magnetoencephalography

Although current MRI-based methods of neuroimaging already provide excellent spatial resolution, temporal resolution (on the order of seconds) still falls well below the time scale of many, if not most, mental operations (on the order of tenths of seconds). These methods are complemented by scalp recording of electrical potentials (event-related potentials; ERPs) and associated magnetic fields (magnetoencephalography; MEG). The primary benefit of these techniques is their high temporal resolution (on the order of milliseconds). This has great value in assessing the dynamics of brain function, as discussed above. Recording of ERPs is the most practical and widely used method and has led to several discoveries, such as the presence of attentional effects at the earliest stages of visual processing, and signals associated with violations of expectation in language and errors in task performance. Several of these signals have been found to be disturbed in psychiatric disorders, such as schizophrenia (e.g., the P300); however, none of these has yet proved to be pathognomic of any disease. The primary problem with these methods is their low spatial resolution. Because the brain is not electrically homogeneous, localizing the source of an electrical potential is problematic (it is like observing a flashbulb in a house of mirrors—the timing can be precisely determined, but it is much harder to know where it came from). One approach has been to develop high-density electrode caps (having as many as 128 electrodes) and quantitative methods to construct current source density maps. Such methods are still somewhat controversial and, at best, provide spatial resolution that remains relatively crude (on the order of centimeters). Because the brain is magnetically homogeneous, MEG permits more precise and reliable source localization. However, the apparatus is relatively expensive (approximately the same cost as an MRI scanner) and the method is primarily limited to cortical structures, where highly structured columns of cells produce magnetic fields that are suitably aligned and sufficiently proximal to be detected by sensors at the scalp. Perhaps the greatest promise of ERPs and MEG are their use in combination with fMRI, as is discussed under the section "Multimodal Approaches" below.

Optical Techniques

Another approach to improving temporal resolution has been the development of optical methods for measuring brain activity. Direct measurements at the cortical surface of animals have established that changes in blood flow (and, some have claimed, in neural activity) produce absorption changes in the visible and near-infrared ranges of the spectrum. Scalp measurements of activity-related changes in blood flow using near-infrared spectroscopy (NIRS) have also been reported. Like MEG, such measurements are limited in depth (a few centimeters) and thus are probably only useful for tracking cortical activity. Because they provide information similar to hemodynamically based methods of fMRI and PET, they are also subject to similar limitations. Nevertheless, they may have some advantages. First, the apparatus is significantly less costly than those for either MRI or PET (about one-tenth the cost) and is also much less expensive to maintain. Perhaps more importantly, like ERP, it involves a mobile head cap and thus can be used in settings (e.g., homes or remote clinics) and with subjects (e.g., infants, very young children, and patients with motor abnormalities) for whom PET or fMRI are not feasible. Furthermore, continued improvements in optical methods offer hope that they will be able to track the oxygen depletion phase of the hemodynamic response, or physiologic changes related more directly to neural activity, that would provide significantly improved temporal resolution.

Other Measures

A variety of other measures of neurophysiologic function have long been in active use, such as eye tracking, pupillometry, and measurements of galvanic skin resistance (GSR). Each of these has already produced some interesting findings (e.g., the abnormalities of smooth pursuit eye movements associated with schizophrenia). The utility of these methods will no doubt be greatly enhanced as they are integrated with more direct measurements of brain activity (see the section "Multimodal Approaches" below).

Transcranial magnetic stimulation. All of the methods discussed above provide passive measures of brain activity. Transcranial magnetic stimulation (TMS) uses focal pulses of magnetic field induction to either stimulate or interfere with brain activity. Thus, this is an interventional rather than an imaging method per se. However, it has potential to be a tremendously important tool, both in research and in clinical intervention. In research, this technique has several potentially valuable applications. First, although imaging can provide information about patterns of brain activity

that are correlated with mental functions, it is difficult to use such information to establish causal relationships (e.g., that a particular brain area is responsible for a particular function). TMS can provide such information: by inducing transient disruptions of function, or exogenously generating activity in a particular brain region, TMS can be used to test whether that region is required for, or is sufficient to produce, a given function. Studies are already being undertaken to examine the effects of pulses in prefrontal cortex on working memory function and the effects of pulses in temporal and parietal areas on attentional performance. Furthermore, used in combination with PET or fMRI, TMS-induced patterns of activity can be used to trace the functional connectivity of different brain regions. Finally, TMS holds the promise of providing a focal means of therapeutic intervention, targeting specific brain areas associated with neuropsychiatric disturbances. For example, recent reports have begun to indicate that TMS in frontal cortical regions may be effective in relieving depression, providing an adjunctive treatment, and perhaps eventually an alternative, to ECT. Similarly, the utility of TMS in temporal areas is being explored for its effectiveness in interfering with auditory hallucinations in schizophrenia. Finally, it is possible to imagine that TMS could be used in conjunction with pharmacologic therapies to increase uptake and/or activity in targeted brain areas to help induce greater selectivity in the sites of drug action.

Multimodal approaches. Although the foregoing list of recent and ongoing techniques illustrates how much progress is being made, perhaps the greatest promise for the field lies in the combined use of the various methods. There are a variety of benefits that can be gained by the integrated use of different modalities, many of which are beginning to be explored. First, methods can be used to complement one another. For example, numerous efforts are under way to combine fMRI with ERP and/or MEG, using fMRI (sometimes together with MEG) to provide spatial information that can constrain efforts to conduct source localization of ERP measurement. Tensor diffusion imaging is also being used to generate better models of the resistance properties of the brain, which can further augment efforts at ERP source localization. Initial successes in these efforts have begun to produce "movies" of brain activity that have millisecond temporal precision and millimeter spatial resolution, and demonstrate the complex dynamic interactions that take place among diverse brain areas in even the simplest conditions (such as observing a flashing light). The use of independent methods can also be important in providing convergent support for a particular finding or in validating a new method. For example, validation of initial β-adrenergic receptor type I (BARI) findings against PET was an important step in validating fMRI (and establishing confidence in

the results of each). Similarly, comparing findings of new methods such as optical imaging against fMRI or PET will be an important step in validating these new methods. Finally, the availability of diverse types of measurements, such as CBF, scalp electrical signals, eye movements, pupillometry, and GSR provide a rich set of constraints on the development of theories of integrated brain function. Ultimately, more comprehensive theories will have to be able to simultaneously account for changes in all of these variables. Although this sets a high benchmark for theory development, success should bring with it the rich rewards of a greater understanding of both normal brain function and the complexities of function associated with damage to any one component.

Neuroinformatics. As the use of neuroimaging techniques proliferates, both in basic and in clinical research, there is an increasing need to manage and make sense of the large amounts of data that are being generated. For example, a single fMRI scanning session can generate as much as 1 gigabyte of data, a typical study can involve as many as 20–30 subjects, and there are an estimated 1,500 new studies conducted per year. Thus, on the order of 30–50 terabytes of new fMRI data are generated each year. ERP recording generates equally large data sets. Unfortunately, most of the actual data generated never see the light of day, as findings are usually published in highly processed and summarized form (tables of brain areas activated, or two-dimensional figures). Electronic data sharing has become an important tool in most other scientific disciplines, especially for those that work with large and complex data sets, such as astrophysics, proteonomics, and, most recently, genomics. The benefits of such efforts are clear-cut: they can facilitate the comparison of findings across laboratories (to better assess the reliability of methods and reproducibility of results), encourage meta-analyses that explore phenomena not apparent in individual data sets, and provide investigators without access to neuroimaging facilities the opportunity to conduct research using existing data. All of these scenarios represent more efficient use of data that are often very expensive to collect. The public sharing of neuroimaging data faces unique technical and ethical challenges. However, the strong potential benefits have begun to attract increasing attention, and this is rapidly becoming a high priority for the field, with major efforts beginning to form. It is important that these efforts take into consideration both the technical and the ethical needs of clinical researchers if neuropsychiatric research is to participate in and benefit from such efforts. The heart of any data sharing effort is the definition of the information that will be stored and exchanged. Clinical research brings to the table a set of needs that overlap with, but go beyond, basic research. The data must contain additional descriptors (technically referred to as *meta-*

data) that define clinical evaluations, medication status, and other biological parameters that may not be of central relevance to basic research. The sharing of such clinical information on a subject-by-subject basis also significantly raises the stakes with regard to issues of confidentiality. All things considered, the clinical research community stands to benefit enormously from the sharing of neuroimaging data.

Summary

Over the past several decades, tremendous strides have been made in imaging the intact human brain, and the pace of these developments continues to accelerate. These methods promise to have a dramatic impact on psychiatry. Already they are providing a deeper understanding of the organization and function of the normal brain and of the relationship of brain disturbances to psychiatric disorders. Furthermore, an important new direction is the use of these methods in conjunction with modern genetic methods, with the goal of identifying *endophenotypes*—patterns of brain function that can be linked to a particular genotype—in an effort to further refine the understanding of the taxonomy and mechanisms associated with individual variability and psychiatric disorders.

Role of Ethnicity and Culture in Future Clinical Neuroscience Research

Ethnicity and culture represent important factors that should always be considered in clinical neuroscience research. As discussed above, a large body of recent literature now clearly indicates that ethnicity (population stratification) is crucial in the interpretation of most genetic studies. At the same time, it has long been known that factors associated with ethnicity and culture strongly influence individuals' vulnerability and resilience; determine their coping styles, cognitive response to stress, and the nature of social support; shape their psychopathology, their experiencing of distress, and their clustering of symptoms; and influence the course and outcome of psychiatric conditions. Any future research examining the relationship between genotypes and clinical (behavioral) phenotypes will thus need to carefully consider ethnic and cultural factors.

Although reports suggesting strong ethnic and cultural influences on endophenotypic manifestations of psychiatric conditions are not as robust as those related to genotype and clinical phenotype, there are theoretical reasons to believe that such associations also may be substantial. In addition to specific genetic characteristics, which may vary significantly across ethnicities (for example, the existence of *ALDH2*2* and *ADH2*2* alleles and

the sensitivity to alcohol), culture also significantly determine individuals' childhood experiences and influences their social and physical milieu, which interact with genetic factors to determine neurobiological activities. For example, significant ethnic differences have been reported in sleep electroencephalographic patterns (in both nondepressed volunteers and depressed patients), response to dexamethasone suppression test (DST), patterns of HPA axis activity, cardiovascular reactivity to stress, and a number of other proposed biological markers. Together, this literature indicates that ethnicity also is an important factor in research at the endophenotypic level. This may be especially true when such data are examined in conjunction with clinical and genetic characteristics.

In addition to methodological and practical reasons (for the control of potential confounds and for ensuring the applicability of findings across ethnic groups), the inclusion of ethnic and cultural factors in neuroscience research also may be important for theory building and hypothesis generation. Cross-ethnic and cross-cultural replication of findings strengthens the validity of results, whereas discrepancies may serve as the stimuli for searching for refined or alternative hypotheses that might lead to findings with greater generalizability and more universal applicability.

Concluding Comments: A Diagnostic System for the Future?

It is our goal to translate basic and clinical neuroscience research relating brain structure, brain function, and behavior into a classification of psychiatric disorders based on etiology and pathophysiology. It is possible, even likely, that such a classification will be radically different from the current DSM-IV approach. Prognostication is a risky business. However, we speculate that single genes will be discovered that map onto specific cognitive, emotional, and behavioral disturbances but will not correspond neatly to currently defined diagnostic entities. Rather, it will be discovered that specific combinations of genes will relate to constellations of abnormalities in many brain-based functions—including but not limited to the regulation of mood, anxiety, perception, learning, memory, aggression, eating, sleeping, and sexual function—that will coalesce to form disease states heretofore unrecognized. On the other hand, genes that confer resilience and protection will also be identified, and their interaction with disease-related genes will be clarified. The impact of environmental factors on gene expression and phenotype expression will be defined. The ability to discover intermediate phenotypes will be improved with advances in techniques such as neuroimaging. This will all lead to novel therapeutic targets of greater ef-

ficacy and specificity to disease states. Prediction of therapeutic response will be possible through genetic analysis and phenotype analysis. Disease prevention will become a realistic goal. Ethnicity and culture represent important factors that should be included in all of these research endeavors.

We conclude the chapter with a speculative outline for a possible future implementation of a multiaxial system that highlights how various facets of information about the patient, each conceptualized at a different level of abstraction, need to be recorded, synthesized, and integrated in order to fully understand and manage the patient clinically (Table 2–5). In this system, Axis I would be set aside for recording the patient's *genotype*, identifying symptom- or disease-related genes, resiliency genes, and genes related to therapeutic responses and side effects to specific psychotropic drugs. Axis II could be used for recording the patient's *neurobiological phenotype*, identifying intermediate phenotypes related to the patient's genotype and behavioral phenotype. The neurobiological phenotype may be discerned by neuroimaging, cognitive evaluation, and neurophysiological testing. The neurobiological phenotype could aid in selecting targeted pharmacotherapies and psychotherapies and monitoring the neurobiological response to treatment. Axis III would be the *behavioral phenotype*, which could detail the severity and frequency of specific cognitive, emotional, and behavioral disturbances. The behavioral phenotype would be related to genotype (Axis I), neurobiological phenotype (Axis II), and environmental modifiers or precipitants (Axis IV). Furthermore, the behavioral phenotype would also be related to specific medication approaches and psychotherapies (Axis V). Axis IV would be *environmental modifiers or precipitants* and would call for the recording of environmental factors that may alter the neurobiological and behavioral phenotypes. These effects would be evaluated in the context of the patient's genotype. Finally, Axis V would be devoted to *therapeutics.* This axis would examine the range of therapeutic options, both pharmacologic and psychotherapeutic, available to the patient based on the data revealed in Axes I through IV. It is possible that certain axis patterns will be logically grouped under broad disease states resembling those that are currently classified in DSM-IV. It is also probable that new broad disease entities will be discovered.

It is our hope and expectation that through advances in animal models, genetics, neuroimaging, and postmortem investigations psychiatry will ultimately have a diagnostic system based on etiology and pathophysiology. Such a system should result in reliable and valid diagnosis, more specific and effective treatments, and therapeutic strategies to delay and even prevent the development of psychiatric disorders.

TABLE 2–5. Outline for a possible future multiaxial system

Axis I: genotype
Identification of disease- /symptom-related genes
Identification of resiliency/protective genes
Identification of genes related to therapeutic responses to and side effects of specific psychotropic drugs
Axis II: neurobiological phenotype
Identification of intermediate phenotypes (neuroimaging, cognitive function, emotional regulation) related to genotype
Relates to targeted pharmacotherapy
Axis III: behavioral phenotype
Range and frequency of expressed behaviors associated with genotype, neurobiological phenotype, and environment
Relates to targeted therapies
Axis IV: environmental modifiers or precipitants
Environmental factors that alter the behavioral and neurobiological phenotype
Axis V: therapeutic targets and response

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