



Neural Sciences

▲ 1.1 Introduction and Considerations for a Brain-Based Diagnostic System in Psychiatry

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The human brain is responsible for our cognitive abilities, emotions, and behaviors—that is, everything we think, feel, and do. Although the early development and adult functioning of the brain are shaped by multiple factors (e.g., epigenetic, environmental, psychosocial experiences), the brain is still the final integrator of these influences. Despite the many advances in neural sciences over the past several decades, including the “decade of the brain” in the 1990s, and the wide acceptance of the brain as the biological substrate for normal and abnormal mental functions, there has not been a truly transformational advance in the treatment of mental disorders for more than half a century, specifically since the introductions of iproniazid, imipramine, lithium, chlorpromazine, and haloperidol in the 1950s. Although subsequent drugs such as serotonin-specific reuptake inhibitors and serotonin dopamine antagonists are safer, better tolerated drugs, the underlying molecular mechanisms for these drugs are derived from the original drugs from the 1950s.

The most obvious reason for the absence of more progress is the profound complexity of the human brain. A perhaps less obvious reason is the current practice of psychiatric diagnosis, which, for most clinicians, is based on syndrome-based classification systems, such as DSM-IV-TR and ICD-10, *which simply uses signs and symptoms to describe a diagnostic syndrome without any reference to its cause.* The purpose of this section is to introduce the following neural science sections describing various aspects of the human brain, and then to discuss how an evolution of thinking toward a brain-based or biologically based diagnostic system for mental illness might facilitate our efforts to advance brain research, *to develop better treatments, and to improve patient care.*

In other fields of medicine, diagnosis is based on physical signs and symptoms, a medical history, and laboratory and radiological tests of various types. In psychiatry, the diagnosis most commonly is based primarily on the clinician’s impression of the patient’s interpretation of his or her thoughts and feelings. The patient’s symptoms are then cross-referenced to a diagnostic or classification manual (e.g., DSM-IV-TR, ICD-10) containing hundreds of potential syndromes, and one or more diagnoses are applied to the particular patient. These standard classification systems represent significant improvements in reliability over previous diagnostic systems, but there is little reason

to believe that these diagnostic categories are valid, in the sense that they represent discrete, biologically distinct entities. Although a patient with no symptoms or complaints can be diagnosed as having diabetes, cancer, or hypertension on the bases of blood tests, x-rays, or vital signs, a patient with no symptoms cannot be diagnosed with schizophrenia, for example, because there are no currently recognized objective, independent assessments.

The current absence of such tests is not for lack of effort on the part of researchers. Many hypotheses that a specific biological variable may be associated with a particular diagnosis have been tested; however, these hypotheses all have been rejected because the biological variable failed to show sufficient selectivity (i.e., associated with the disease of interest, but not other diseases) or sensitivity (i.e., associated with affected patients, but not nonaffected individuals). A potential error in this approach is that if the diagnostic grouping (e.g., schizophrenia from DSM-IV-TR) comprises 10 or 20 different biologically based diseases, one would not expect any single diagnostic test to be specific or sensitive for the entire heterogeneous group of patients. An analogy to consider is the neurological condition of dementia, which, in contrast to schizophrenia, is widely accepted in clinical practice to represent a diverse group of biologically based disorders. To evaluate a patient with dementia, a clinician would order a wide range of laboratory and radiological tests in an attempt to find the specific etiology of the dementia, on which to base the treatment plan.

The goals of clinicians and researchers are to reduce human suffering through increasing our understanding of diseases, developing new treatments to prevent or cure diseases, and caring for patients in an optimal manner. If the brain is the organ of focus for mental illnesses, then it may be time to be more ambitious in building the classification of patients with mental illnesses directly from our understanding of biology, rather than only from the assessment of a patient’s symptoms. It is the authors’ hypothesis that the reification of DSM-IV-TR and other syndrome-based categories has convinced a many students, clinicians, researchers, payers, and government regulators that the “disorders” in DSM-IV-TR are, in fact, “diseases.” If we continue to try to advance the research and treatment of mental illnesses using a seriously flawed diagnostic system as an organizing principle, then there is a substantial risk that we will limit our progress to incremental improvements of current treatments that are focused on symptom reduction, rather than expanding our progress to include a more fundamental understanding of how discrete, biologically based dysfunctions of the brain result in specific, true brain diseases. *Such understanding of the brain and its pathophysiology could then allow us to attempt to develop treatments that were preventative or disease-modifying, rather than just symptomatic.*

THE HUMAN BRAIN

The following neural science sections each deal with a field of brain biology. Each of these fields could be relevant to the pathophysiologies

and treatments of mental illnesses. Although the complexity of the human brain is daunting compared with other organs of the body, progress can only be made if we approach this complexity consistently, methodically, and bravely.

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The neuronal and glial cells of the human brain are organized in a characteristic manner, which has been increasingly clarified through modern neuroanatomical techniques (see Section 1.2). Our knowledge of the development of the human brain (see Section 1.3) also has become more complete in the last decade. The human brain clearly evolved from the brain of lower animal species, allowing inferences to be made about the human brain from animal studies. Neurons communicate with one another through chemical and electrical neurotransmission. The major neurotransmitters are the monoamines (see Section 1.4), amino acids (see Section 1.5), and neuropeptides (see Section 1.6). Other chemical messenger molecules include neurotrophic factors (see Section 1.7) and an array of other molecules, such as nitric oxide (see Section 1.8). Electrical neurotransmission occurs through a wide range of ion channels (see Section 1.10). Chemical and electrical signals received by a neuron subsequently initiate various molecular pathways within neurons (see Section 1.9) that regulate the biology and function of individual neurons, including the expression of individual genes and the production of proteins (see Section 1.11).

In addition to the central nervous system (CNS), the human body contains two other systems that have complex, internal communicative networks: the endocrine system and the immune system. The recognition that these three systems communicate with each other has given birth to the fields of psychoneuroendocrinology (see Section 1.12) and psychoneuroimmunology (see Section 1.13). Another property shared by the CNS, endocrine system, and immune system is that they undergo regular changes with the passage of time (e.g., daily, monthly), which is the basis of the field of chronobiology (see Section 1.14).

PSYCHIATRY AND THE HUMAN BRAIN

In the first half of the 20th century, the advances in psychodynamic psychiatry, as well as in social and epidemiological psychiatry, led to a separation of psychiatric research from the study of the human brain. Since the 1950s, the appreciation of the effectiveness of medications to treat mental disorders and the mental effects of illicit drugs has reestablished a biological view of mental illness, which had already been seeded by the introduction of electroconvulsive therapy (ECT) and James Papez's description of the limbic circuit in the 1930s. This biological view has been reinforced further by the development of brain imaging techniques that have helped reveal how the brain performs in normal and abnormal conditions (see Sections 1.15–1.17). During this time, basic neural science research has made countless discoveries using experimental techniques to assess the development, structure, biology, and functioning of the CNS of humans and animals.

Psychopharmacology

The effectiveness of drugs in the treatment of mental illness has been a major feature of the last half century of psychiatric practice. The first five editions of this textbook divided the psychopharmacological treatments into four chapters on antipsychotic, antidepressant, antianxiety, and mood-stabilizing drugs. Starting with the sixth edition (1989), the psychopharmacological treatments were separated into approximately 30 different chapters that divided the drugs by molecular mechanism of action where possible. The rationale for this division was explained in the textbook as follows:

The prior division of psychiatric drugs into four classes] is less valid now than it was in the past for the following reasons: (1) Many drugs of one class are used to treat disorders previously assigned to another class. (2) Drugs from all four categories are used to treat disorders not previously treatable by drugs (for example, eating disorders, panic disorders, and impulse control disorders). (3) Such drugs as clonidine (Catapres), propranolol (Inderal), and verapamil (Isoptin) can effectively treat a variety of psychiatric disorders and do not fit easily into the aforementioned classification of drugs.

The basic recognition for this change was that the variety and application of the drug treatments no longer fit clearly into the division of disorders into psychosis, depression, anxiety, and mania. In other words, the clinical applications of biologically based treatments did not neatly align with our syndrome-based diagnostic system. An implication of this observation could be that drug response might be a better indicator of underlying biological brain dysfunction than any particular group of symptoms. For example, although DSM-IV-TR distinguishes major depressive disorder from generalized anxiety disorder, most clinicians are aware that these are often overlapping symptoms and conditions in clinical practice. Moreover, the same drugs are used to treat both conditions. Nevertheless, partly because of historical considerations regarding issues such as “neurotic” disorders and “dysthymic” conditions, our current diagnostic systems emphasize a distinction between these two conditions. If one hypothesized that these two conditions were, in fact, related, however, it is possible that research and clinical treatment could be advanced by expanding research designs to consider the combined population.

The animal models that are used to find new drug treatments may also have affected our ability to advance research and treatment. Many major classes of psychiatric drugs were discovered serendipitously. Specifically, the drugs were developed originally for nonpsychiatric indications, but observant clinicians and researchers noted that psychiatric symptoms improved in some patients, which led to focused study of these drugs in psychiatric patients. The availability of these effective drugs, including monoaminergic antidepressants and antipsychotics, led to the development of animal models that were able to detect the effects these drugs (e.g., tricyclic antidepressants increase the time mice spend trying to find a submerged platform in a “forced swim” test). These animal models were then used to screen new compounds in an attempt to find drugs that were active in the same animal models. The potential risk of this overall strategy is that these animal models are merely a method to detect a particular molecular mechanism of action (e.g., increasing serotonin concentrations), rather than a model for a true behavioral analog of a human mental illness (e.g., behavioral despair in a depressed patient).

Endophenotypes

A possible diagnosis-related parallel to how this textbook separated the four classes of psychotropic drugs into approximately 30 different categories would be to consider the topic of *endophenotypes* in psychiatric patients. An endophenotype is an internal phenotype, which is a set of objective characteristics of an individual that are not visible to the unaided eye. Because there are so many steps and variables separating a particular set of genes from the final functioning of a whole human brain, it may be more tractable to consider intermediate assessments such as endophenotypes. This hypothesis is based on the assumption that the number of genes that are involved in an endophenotype might be fewer than the number of genes involved in causing what we would conceptualize as a disease. The nature of an endophenotype is biologically defined on the basis of neuropsychological, cognitive, neurophysiological, neuroanatomical, biochemical, and brain imaging data. Such an endophenotype, for example,

might include specific cognitive impairments as just one of its objectively measured features. This endophenotype would not be limited to patients with a diagnosis of schizophrenia because it might also be found in some patients with depression or bipolar disorder.

Several groups have proposed specific endophenotypes for further study. Some of these researchers, however, have proposed endophenotypes as subtypes of an existing DSM-IV-TR diagnostic category, although this approach could limit the ability to detect the presence of a particular phenotype occurring in multiple DSM-IV-TR diagnostic categories. Other characteristics that are measures of the validity of a particular endophenotype include state-independence (i.e., associated with the underlying disease and not the specific stage of disease or treatment), heritability (i.e., associated with one or more specific genes), familial association (i.e., more prevalent in relatives of probands), cosegregation (i.e., associated with ill relatives of ill probands), and biological and clinical plausibility (i.e., makes logical sense in terms of known biological facts and clinical observations).

The potential role of an endophenotype can be further clarified by stating what it is not. An endophenotype is not a symptom, and it is not a diagnostic marker. A classification based on the presence or absence of one or more endophenotypes would be based on objective biological and neuropsychological measures with specific relationships to genes and brain function. Symptoms or impairment would not be required for the diagnosis of an endophenotype. A classification based on endophenotypes might also be a productive approach toward the development of more relevant animal models of mental illnesses, and thus the development of novel treatments.

PSYCHIATRY AND THE HUMAN GENOME

Perhaps 70% to 80% of the 25,000 human genes are expressed in the brain, and because most genes code for more than one protein, there may be 100,000 different proteins in the brain. As of 2008, perhaps 10,000 of these are known proteins with somewhat identified functions, and no more than 100 of these are the targets for existing psychotherapeutic drugs.

The study of families using population genetic methods over the past 50 years has consistently supported a genetic, heritable component to mental disorders (see Section 1.18). Using more recent techniques in molecular biology, specific chromosomal regions and genes have been associated with particular diagnoses (see Section 1.19). A potentially very powerful application of these techniques has been to study transgenic models of behavior in animals (see Section 1.20). These transgenic models can help us understand the effects of individual genes as well as discover completely novel molecular targets for drug development.

It may be a natural response to resist “simple” genetic explanations for human features that we emotionally value highly. Nonetheless, research on normal humans generally has found that approximately 40% to 70% of aspects of cognition, temperament, and personality are attributable to genetic factors. Because these are the very domains that are affected in mentally ill patients, it would not be surprising to discover a similar level of genetic impact on mental illness, especially if we were able to assess this impact at a more discrete level, such as with endophenotypes.

Individual Genes Have Modest Effects in the Development of Mental Disorders

Several types of data and observations suggest that any single gene is likely to have only a modest effect in the development of a mental disorder, and that when a mental disorder is present in an individual,

it represents the effects of multiple genes, speculatively on the order of five to ten genes. This hypothesis also is supported by our failure so far to find single genes with major effects in mental illnesses. Some researchers, however, still consider it a possibility that genes with major effects will be identified.

“Nature” and “Nurture” Interact Constantly within the CNS

In 1977, George Engel, at the University of Rochester, published a paper that articulated the biopsychosocial model of disease, which stressed an integrated approach to human behavior and disease. The biological system refers to the anatomical, structural, and molecular substrates of disease; the psychological system refers to the effects of psychodynamic factors; and the social system examines cultural, environmental, and familial influences. Engel postulated that each system affects and is affected by the others.

The observation that a significant percentage of identical twins are discordant for schizophrenia is one example of the type of data that support the understanding that there are many significant interactions between the genome and the environment (i.e., the biological basis of the biopsychosocial concept). Studies in animals have also demonstrated that many factors, including activity, stress, drug exposure, and environmental toxins, can regulate the expression of genes and the development and functioning of the brain.

Mental Disorders Reflect Abnormalities in Neuroanatomical Circuits and Synaptic Regulation

Although genes lead to the production of proteins, the actual functioning of the brain needs to be understood at the level of regulation of complex pathways of neurotransmission and intraneuronal signaling, and of networks of neurons within and between brain regions. In other words, the downstream effects of abnormal genes are modifications in discrete attributes such as axonal projections, synaptic integrity, and specific steps in intraneuronal molecular signaling.

Why Not a Genetic-Based Diagnostic System?

Some researchers have proposed moving psychiatry toward a completely genetic-based diagnostic system. This proposal, however, seems premature based on the complexity of the genetic factors presumably involved in psychiatric disorders, the absence of sufficient data to make these genetic connections currently, and the importance of epigenetic and environmental influences on the final behavioral outcomes resulting from an individual’s genetic information.

LESSONS FROM NEUROLOGY

Clinical and research neurologists seem to have been able to think more clearly than psychiatrists about their diseases of interest and their causes, perhaps because the symptoms are generally nonbehavioral. A previous example in this chapter was the approach to diagnosing and treating dementia, for which neurologists have biologically grounded differential diagnoses and treatment choices. This clarity of approach has helped lead to significant advances in neurology in the past two decades, for example, clarification of the amyloid precursor protein abnormalities in some patients with Alzheimer’s disease, the presence of trinucleotide repeat mutations in Huntington’s disease and spinocerebellar ataxia, and the appreciation of alpha-synucleinopathies, such as Parkinson’s disease and Lewy body dementia.

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The continued separation of psychiatry from neurology is, itself, a potential impediment to good patient care and research. Many neurological disorders have psychiatric symptoms (e.g., depression in patients following a stroke or with multiple sclerosis or Parkinson’s disease) (see Chapter 2), and several of the most severe psychiatric disorders have been associated with neurological symptoms (e.g., movement disorders in schizophrenia). This is not surprising given that the brain is the organ shared by psychiatric and neurological diseases, and the division between these two disease areas is arbitrary. For example, patients with Huntington’s disease are at much greater risk for a wide range of psychiatric symptoms and syndromes, and thus many different DSM-IV-TR diagnoses. Because we know that Huntington’s disease is an autosomal dominant genetic disorder, the observation that it can manifest with so many different DSM-IV-TR diagnoses does not speak to a very strong biological distinction among the existing DSM-IV-TR categories.

EXAMPLES OF COMPLEX HUMAN BEHAVIORS

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The goal to understand the human brain and its normal and abnormal functioning is truly one of the last frontiers for humans to explore. Trying to explain why a particular individual is the way he or she is, or what causes schizophrenia, for example, will remain too large a challenge for some decades. It is more approachable to consider more discrete aspects of human behavior. Three examples discussed in this section can be considered examples of particular complex feelings or sensations (pain in Section 1.21), behaviors (social interaction in Section 1.22), and thoughts (sense of self in Section 1.23). Examples of other complex behaviors that can be associated with mental illnesses are discussed elsewhere in this textbook, including appetite (see Section x.xx), substance abuse (see Section x.xx), and aggression (see Section x.xx).

DIAGNOSIS IN PSYCHIATRY

Mental illnesses are characterized by a wide range of abnormalities in emotions, cognition, and behaviors that interfere with normal development and function. The current way of classifying and diagnosing these illnesses is a syndromal classification system. DSM-IV-TR makes a point of naming the diagnoses “mental disorders,” rather than syndromes or diseases. The intent of the use of this term is to suggest that these diagnostic categories represent a level of biological distinction that is more robust than for a mere syndrome, although admitting that the available data do not support these categories as diseases.

DSM-IV-TR Diagnoses Are Biologically Heterogeneous

DSM-IV-TR diagnoses are based on the presence or absence of specific symptoms. It is known that many different biological causes can result in the same symptom. Therefore, any DSM-IV-TR syndrome is the potential summation of the many heterogeneous etiologies for each of its composite symptoms. It is not surprising that the range of treatment responses and clinical outcomes within each DSM-IV-TR category is so broad. It is also not surprising that attempts to find biological markers or treatments relevant to all patients with a particular diagnosis have been so difficult.

Functions of Diagnosis

Diagnosis serves many purposes; however, the most fundamental function is a predictive one that allows the physician to recommend a treatment that is more likely to be effective and to be able to pro-

vide the patient and family with some idea about the future course of the illness. If the understanding of a diagnostic condition is robust enough, it may even be possible for a physician to provide advice about the prevention of a disease. Diagnoses are used for many other purposes, some of which have the potential of distorting the fundamental clinical use of diagnosis. These include (1) guiding basic and clinical research; (2) aiding communication about groups of patients; (3) calculating disease burden and economic impact; (4) and helping to make decisions regarding such issues as access to benefits, reimbursement of providers, and forensic issues.

DSM-IV-TR and Other Syndromal Classifications

It is useful to understand a brief history of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) classification publications. DSM-I (1952) made a significant distinction between “organic” disorders and “reactive” disorders, which were defined as not being clearly organic, and thus hypothesized to be a reaction to environmental or psychosocial circumstances. DSM-II (1968) emphasized a distinction between the psychoses and neuroses as well as between endogenous and exogenous conditions, terms that had been introduced in the Research Diagnostic Criteria. DSM-III (1980) was a significant advance in developing more precise terminology and increasing the reliability of diagnoses across users. Some of the major tenets of DSM-III were reliable diagnostic criteria, syndromal diagnostic categories, a nonetiological approach, and a belief that the combined wisdom and knowledge of the consensus expert panel approach to develop the criteria was resulting in categories that had some biological validity. These assessments led to the naming of the categories as mental disorders, rather than just syndromes, even though they were not quite diseases. Nevertheless, DSM-III and subsequent DSM editions have been referred to as the “bible” of mental illnesses and are commonly used as the fundamental basis for teaching students about psychiatric illnesses. The DSM classifications also have been used by nonclinicians in the public sector and in governments as the only acceptable list and categorization of bona fide mental illnesses.

Numerous major characteristics of DSM-IV-TR merit mention to help understand the current status of diagnostic practice. DSM-IV-TR diagnoses are reliable, meaning that different clinicians in various settings can accurately understand the criteria and apply them to different patients. A reliable diagnostic system does not mean, however, that it is a valid system that defines biologically discrete entities. It is perhaps more accurate to consider DSM-IV-TR a system of nomenclature, rather than as a classification system, in the sense that classifying different animal species or plants represents true classification systems. Guided by the admirable motivation not to classify variations of normal behavior as abnormal, DSM-IV-TR specifically required the presence of clinically significant distress or disability to warrant a DSM-IV-TR diagnosis. This approach is inconsistent, however, with the rest of medicine in which it is possible, for example, to have a diagnosis of HIV or hypertension in the absence of impairment or distress. Another characteristic of DSM-IV-TR is that because symptoms are considered present or absent, each DSM-IV-TR diagnosis is also considered present or absent. The effect of this approach is that milder forms of each disorder are generally considered not to be diagnoses. Other crucial observations about DSM-IV-TR include unclear overlap of axes I and II diagnoses, confounding of symptoms and impairment, and weak association with course of illness and treatment response.

Categorical versus Spectrum Classification Systems

DSM-IV is considered a *categorical* classification system because each disorder is determined to be present or absent in an individual

patient. Categorical classification systems are characterized by their clear criteria for normal and abnormal, and the presence of patients with multiple diagnoses (i.e., comorbidity). In contrast to categorical classification systems, *spectrum* or *dimensional* classification systems accept that there is a range between normal and abnormal, and that patients with a particular diagnosis can vary in symptoms, severity, and impairment. Spectrum classification systems are characterized by having fewer diagnostic categories, reducing the number of comorbid diagnoses, and allowing for mild forms of disorders.

Many groups of researchers have suggested approaches to thinking about disease spectrums that include multiple DSM-IV-TR diagnoses. These include spectrums for schizophrenia (includes schizotypal personality disorder), depression (includes dysthymia, dependent personality disorder), bipolar disorder (includes cyclothymia, histrionic personality disorder), autism (includes pervasive developmental disorder, Asperger's syndrome), social anxiety (includes avoidant personality disorder, mutism), and obsessive-compulsive disorder (includes obsessive-compulsive personality disorder). Several studies in Europe using ICD-10 criteria have found that only about one quarter of the diagnostic categories were used for more than 1% of the patients, and the overwhelming majority of patients were diagnosed in one of a very few categories, including schizophrenia, alcohol or other substance abuse, personality disorders, stress-related disorders, bipolar disorder, depression, or mixed depression and anxiety.

CONSIDERATIONS FOR A BRAIN-BASED DIAGNOSTIC SYSTEM

Two major points are made in the previous discussion. First, understanding of the brain is now sufficient to make the conscious decision to build our assessment and treatment of mental illnesses on this knowledge. Second, our current syndromal, categorical system of classification could be a hindrance to the advancement of research and clinical practice.

Many specific suggestions for changes in the diagnostic system have been suggested in the literature. Some involve the inclusion of objective data (e.g., genetic, biological, physiological, neuropsychological) in diagnostic criteria, increased flexibility across current diagnostic categories (e.g., through the use of endophenotypes or spectrum classifications), and inclusion of other objective clinical information in diagnosis (e.g., family history, treatment response, clinical course information). One approach to capturing these types of diagnostic information would be through a multi-axial diagnostic system. However, the multi-axial system with DSM-IV-TR, as currently constructed, is not used often in either clinical or research settings. There would be risks associated with changing our diagnostic system, including potential disruption of current uses for diagnosis, treatment, and reimbursement; putting too much emphasis on biology and not enough on psychosocial considerations; and losing acceptance by individuals and organizations who had previously accepted the syndromal classifications as more or less fact.

It is not the role of textbooks to set policies or to write diagnostic manuals, but rather to share knowledge, generate ideas, and encourage innovation. The authors believe, however, that it is time to reap the insights of decades of neural science and clinical brain research and to build our classification of mental illnesses on fundamental principles of biology and medicine. *Regardless of official diagnostic systems, however, clinicians and researchers should fully understand the biological component of the biopsychosocial model, and not let research or patient care suffer because of a diagnostic system that is not founded on biological principles.*

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▲ 1.2 Functional Neuroanatomy

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The broad range of affective, cognitive, and behavioral characteristics of humans arises as a consequence of specific patterns of activation in networks of neurons that are distributed across the central nervous system (CNS). These patterns of activation are mediated by the connections among specific brain structures. Consequently, understanding the neurobiological bases for the disturbances in affective,