Deconstructing Psychiatric Disorders, Part 2

An Emerging, Neurobiologically Based Therapeutic Strategy for the Modern Psychopharmacologist

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Issue: *Psychiatric disorders comprise a collection of symptoms, each of which may have a unique neurobiological mechanism and be mediated by different neurocircuits that require an individualized psychopharmacologic treatment approach.*

Distinctions Without a Difference?

Psychiatry has long been preoccupied with distinguishing one psychiatric disorder from another. Lacking objective, biological measures, experts have clustered symptoms into syndromes and then constructed them into psychiatric disorders memorialized as numerous nosologic entities. Although many originally hoped that isolating specific syndromes in this way would assist in identifying their pathophysiology, the road from disease to gene and neurobiology in psychiatry has not been smooth.

In fact, it now appears that genes regulate brain circuits that control symptoms across many diagnostic entities (Table 1[1,2]), showing no genetic or neurobiological distinctions between disorders with the same symptoms.[1–3]

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Therapeutic Agents Burn Through Nosologic Firewalls

At the same time that psychiatric nosology has been preoccupied with diagnostic distinctions that are turning out to have no unique biological or genetic differences, psychopharmacology has been preoccupied with distinguishing one class of drugs from another, e.g., calling them antidepressants, anxiolytics, antipsychotics, mood stabilizers, and the like. The original notion of aligning drug classification with diagnostic syndromes seemed rational. What has transpired, however, is that psychopharmacologic treatments are now recognized to work in symptoms that cross many diagnostic entities, resulting in drugs classified for one disorder able to treat the same symptoms in another disorder.[4] Thus, an even more important paradigm shift is occurring in psychopharmacology. Agents treat the same symptom in different disorders and also treat many different symptoms in sometimes unrelated diagnostic conditions (Table 2).[5,6]

This surprisingly broad therapeutic utility of psychotropic drugs is burning through nosologic firewalls. Since the neurotransmitters that a specific drug modifies are active in several circuits mediating several different symptoms, a single drug acting on a given neurotransmitter can have simultaneous therapeutic actions in different circuits. A further elaboration of this model is that psychiatric disorders manifest themselves as a portfolio of symptoms, implying a portfolio of malfunctioning circuits. The neurotransmitters in these circuits are being clarified empirically as are the therapeutic actions of psychopharmacologic agents that can boost or block these neurotransmitters and thus expand their portfolio of therapeutic actions to symptom reduction in many disorders.

Nodes in the Nexus

Functional neuroimaging is beginning to map out the brain's reactions to emotions and cognitions in both health and disease.[1–3] Key to this concept is a nexus, or network of neurons involved in any given symptom generation, with key brain areas specializing in specific functions. The entire nexus can be associated with changes in neuronal firing patterns at various

Table 1.
Circuits Targeted by Abnormal Genes and the Disorders They Regulate

Gene Target	Circuit Activated	Disorders Regulated by Circuit
Amygdala	Fear	GAD, PTSD, social anxiety disorder, panic disorder
Dorsolateral PFC	Working memory	Schizophrenia, cognitive problems in depression, ADHD

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, GAD = generalized anxiety disorder, PFC = prefrontal cortex.

Take-Home Points

- Individual psychiatric symptoms may result from malfunctioning of unique neuronal circuits.
- On the one hand, to formulate a diagnosis of a psychiatric disorder, individual psychiatric symptoms must be constructed into syndromes.
- On the other hand, to formulate a treatment plan capable of providing maximum relief of symptoms, and thus the best outcomes, diagnoses may need to be deconstructed into the specific symptoms experienced by each patient so psychopharmacologic interventions can be chosen to target the malfunctioning neuronal circuits mediating each symptom.

Table 2.
Therapeutic Classes and Their Intended and Alternate, "Paradigm-Shift," Indications

Drug	Intended Indication	Alternate Indication
Antidepressants	Depression	Affective spectrum disorders, eg, anxiety, obsessive-compulsive disorder Functional somatic disorders, eg, bulimia, painful somatic states
Antipsychotics	Schizophrenia	Bipolar disorder, depression, cognitive disorders, relapse in schizophrenia and bipolar and other mood disorders
Anticonvulsants	Epilepsy	Mood disorders, chronic pain or anxiety, augmenting agent for schizophrenia

normalities at nodes in their nexus unless provoked by input from the environment, such as a fearful stimulus or a cognitive task, and a working hypothesis is that each symptom in each patient has a neurobiological basis which may arise from different circuits.

Psychopharmacologic agents hypothetically reduce symptoms by boosting or blocking neurotransmission within the abnormally functioning circuit. Direct action of therapeutic agents at the node of abnormal activity may not always be necessary because actions at other nodes within the same nexus may compensate for the abnormal activity elsewhere within the circuit mediating the symptom. The rich array of symptom relief that psychopharmacologic agents can generate by reducing many seemingly unrelated symptoms across separate diagnostic entities is explained, in part, by this compensation.

Targeting Symptoms in Circuits to Attain Remission

While neurobiologists are sorting out which circuits mediate which symptoms, their strategy can be empirically applied immediately by the neurobiologically informed psychopharmacologist. Thus, patients can have a symptom inventory taken at the time of evaluation. Treatments can be chosen to alleviate these symptoms from the known and best-characterized actions of drugs. However, at this point things get interesting, because in most cases, patients are not completely devoid of all symptoms after their initial treatment. The usual outcome is elimination of some symptoms, but often only partial relief of other symptoms, and no relief of still more symptoms.

A practical approach to treat these unresolved symptoms is to conceptualize which circuits might be mediating them, which neurotransmitters have been targeted by the current treatment, and which neurotransmitters must now be targeted to eliminate residual symptoms and attain complete remission. Thus, the common situation of antidepressants improving mood but not eliminating fatigue and somatic symptoms can lead to augmentation with a second agent targeted at fatigue in particular. Likewise, the situation of antipsychotics improving positive but not cognitive symptoms in schizophrenia can lead to long-term use of a monotherapy, in order to maximize the chances of the usually delayed procognitive actions of an atypical antipsychotic, rather than changing to another agent too early. The point is to have a proactive, neurobiologically based treatment strategy and to try and try again to target every symptom in every circuit by using rational drug selections and combinations from the therapeutic arsenal at hand. This approach could lead to better individualized treatment and patient outcomes. ◆

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