ing the ground- and excited-state predictions. The authors proved the existence of the $^4He_3$ Efimov state and confirmed its enormous size, largest of all known triatomic molecules. Not only do the experiments of Kunitski *et al.* give access to a new class of quantum halo systems, but also their method provides direct information on the structure of these peculiar objects. The predominant structure of the Efimov trimer turns out to be a triangle with a relatively small acute angle. Because of the universality of the Efimov phenomenon, other suitable systems of identical bosons probably should adopt similar structures.

The use of femtosecond laser pulses in the detection opens new perspectives in the field of Efimov physics. The electric fields in a femtosecond pulse can reach very high values of several volts per angstrom. In 1999, Nielsen *et al.* (*10*) proposed that such electric fields could be sufficient to modify interaction potentials of helium atoms and tune creation or destruction of Efimov states. With the advent of the experiment of Kunitski *et al.*, one can now imagine using a long-wavelength laser pulse to manipulate the interaction potentials between helium atoms, while the second pulse could induce the Coulomb explosion. Furthermore, the very short durations of the femtosecond pulses provide opportunities to study a new class of transient Efimov states with ultrashort lifetimes. Quantum halos involving electrons as one of the particles seem promising in this context (*4*).

Although the general treatment of three-body systems is still out of reach, the experimental technique of Kunitski *et al.* opens insights into new molecular systems exhibiting the Efimov effect. This approach not only provides information on their structure, but may in the future allow manipulation of the states and access to a completely new class of short-lived quantum halo systems. Prospective experimental achievements in the case of molecular Efimov states will be directly applicable to similar problems in other physical situations. ■

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MEDICINE

Brain disorders? Precisely

Precision medicine comes to psychiatry

By **Thomas R. Insel** *and* **Bruce N. Cuthbert**

Mental disorders represent a public health challenge of staggering proportions. In the most recent Global Burden of Disease study, mental and substance abuse disorders constitute the leading source of years lost to disability from all medical causes (*1*). The World Health Organization estimates over 800,000 suicides each year globally, nearly all of which are a consequence of a mental disorder (*2*). These high morbidity and mortality figures speak to the potential for overall health gains if mental disorders can be more effectively diagnosed and treated. Could a "precision medicine" approach find traction here?

Precision medicine—a more targeted approach to disease—is already becoming a reality in cancer, where molecular diagnosis is leading to better defined, individualized treatments with improved outcomes (*3*). Precision medicine is also the basis for planning large-cohort studies, using genomics and phenotyping (physiological and behavioral characteristics) to improve diagnostics and therapeutics across medicine. The idea is to integrate clinical data with other patient information to uncover disease subtypes and improve the accuracy with which patients are categorized and treated.

Diagnosis in psychiatry, in contrast to most of medicine, remains restricted to subjective symptoms and observable signs. Clinicians rightly pride themselves on their empathic listening and well-honed observational skills. But recently psychiatry has undergone a tectonic shift as the intellectual foundation of the discipline begins to incorporate the concepts of modern biology, especially contemporary cognitive, affective, and social neuroscience. As these rapidly evolving sciences yield new insights into the neural basis of normal and abnormal behavior, syndromes once considered exclusively as "mental" are being reconsidered as "brain" disorders—or, to be more precise, as syndromes of disrupted neural, cognitive, and behavioral systems.

But before research on the convergence of biology and behavior can deliver on the promise of precision medicine for mental disorders, the field must address the imprecise concepts that constrain both research and practice. Labels like "behavioral health disorders" or "mental disorders" or the awkwardly euphemistic "mental health conditions," when juxtaposed against brain science, invite continual recapitulation of the fruitless "mind-body" and "nature-nurture" debates that have impeded a deep understanding of psychopathology. The brain continually rewires itself and changes gene expression as a function of learning and life events. And the brain is organized around tightly regulated circuits that subserve perception, motivation, cognition, emotion, and social behavior. Thus, it is imperative to include measures of both brain and behavior to understand the various aspects of dysfunction associated with disorders. Shifting from the language of "mental disorders" to "brain disorders" or "neural circuit disorders" may seem premature, but recognizing the need to incorporate more than subjective reports or observable behavior in our diagnosis of these illnesses is long overdue.

> ***"...syndromes once considered exclusively as 'mental' are being reconsidered ... as syndromes of disrupted neural, cognitive, and behavioral systems."***

About 5 years ago, the U.S. National Institute of Mental Health launched a "precision medicine for psychiatry" project (*4*). This Research Domain Criteria (RDoC) initiative was seen by some as a radical attempt to immediately change the framework for how clinicians would diagnose and care for patients they were currently treating. But, the concept was actually to rethink research on psychopathology by building a framework beyond symptoms. Symptoms would be an important starting point, but the framework would include a focus on systems or dimensions that had both cognitive and biological validity. Genomic variants and brain circuit–level differences are evident in studies of people with psychopathology, but the findings cross current diagnostic boundaries rather than validating them (*5*, *6*). Similarly,

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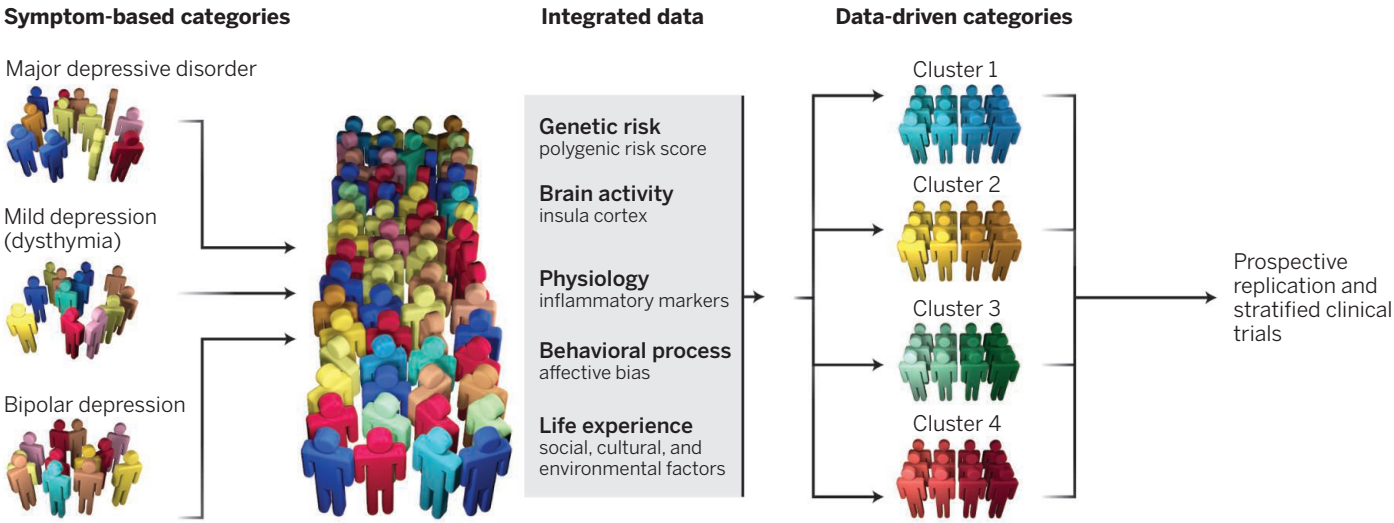
Deconstructed, parsed, and diagnosed.

A hypothetical example illustrates how precision medicine might deconstruct traditional symptom-based categories. Patients with a range of mood disorders are studied across several analytical platforms to parse current heterogeneous syndromes into homogeneous clusters.



constructs such as anhedonia (inability to experience pleasure) and executive function cut across many current diagnostic categories (*7*, *8*). RDoC asks researchers to shift from designing research projects narrowly built around current diagnostic categories to dimensions or systems, such as social processes or negative valence (responding to aversive objects or situations), which are supported by a deep cognitive and neural science and can be the basis for objective measures of psychopathology (see the figure).

An early promising result from this project has emerged from studies that deconstruct current diagnostic groups to identify subgroups that have biological validity, and predict treatment response. For instance, imaging and neurophysiology have demonstrated three subtypes of attention deficit hyperactivity disorder with quite different responses to stimulant medication (*9*). Preliminary reports from studies using cognitive testing, imaging, and/or genomic panels are finding biologically meaningful subgroups of psychotic or mood disorders (*10*, *11*). Notably, these biologically defined subgroups do not map neatly onto clusters of symptoms. Although these results will need replication and, most important, will need to be shown to be predictive of prognosis or treatment response, they illustrate the potential for empirically defined, convergent methods of stratifying patients. Indeed, results using information retrieval and natural language processing methods to extract RDoC dimensions from electronic health records suggest that RDoC domains, but not symptom-based diagnosis, predicted length of hospital stay or hospital readmission (*12*).

Already the scientific community has embraced the opportunity to think beyond current classifiers, with nearly 1000 papers addressing various aspects of RDoC over the past year. RDoC has also served as a catalyst for new efforts outside the United States to transform diagnosis, including the European Commission–funded Roadmap for Mental Health Research (*13*) and a new call from the European Union Innovative Medicines Initiative to link clinical neuropsychiatry and quantitative neurobiology. There is an emerging consensus that such new approaches are necessary to move the field forward, coupled with the realization that many challenges must be faced—such as the pressing need for new measurement instruments in the laboratory and the clinic, and for determining the degree of precision with which functions and neural systems must be assessed for optimal diagnosis and treatment.

As new diagnostics will likely be redefining "mental disorders" as "brain circuit disorders," new therapeutics will likely focus on tuning these circuits. What is the best way to tune a negative valence or social processing circuit? Medications might be useful, but recent attention has focused on devices that invasively (deep brain stimulation) or noninvasively (transcranial magnetic stimulation) alter brain circuit activity (*14*). Paradoxically, one of the most powerful and precise interventions to alter such activity may be targeted psychotherapy, such as cognitive behavioral therapy, which uses the brain's intrinsic plasticity to alter neural circuits and as a consequence, deleterious thoughts and behavior (*15*).

Just as the precision medicine approach for cancer can alter our approach to diagnosing mental disorders, psychiatry can leverage important therapeutic insights from cancer and other studies of chronic diseases. For complex, chronic disorders, from diabetes to hypertension, the search for a magic bullet is giving way to combinatorial or convergent solutions. Medications, devices, mobile health apps, social support, education, and team care are all part of the package needed for improving outcomes. Part of transforming treatments and improving outcomes for people with brain circuit disorders will include these kinds of packages built around patient choice, and individualized based on each person's needs and specific neural pathology. This will ultimately be the precision medicine that can bend the morbidity and mortality curves for people with disorders previously known as "mental disorders." ■

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