develop more targeted treatments for individuals classified according to current diagnostic systems. This will allow the research to remain relevant to the needs of clinicians and health care systems (which need stable diagnoses to function) and, thus, continue to receive the political support it needs to get sustained funding. Once this approach has generated evidence of its ability to improve treatments by identifying distinct subgroups within current diagnostic categories, NIMH will then be in a much better position to recommend changes in the diagnostic system focused on regrouping conditions that respond to (or can be prevented by) similar interventions.

A diagnostic system is first and foremost a *cultural* product, a community's attempt to create meaning, to categorize phenomena of interest in ways that facilitate predicting and, possibly, changing future outcomes. Many institutions within a community – ideological, cultural, social, economic, and scientific – participate in the process of classifying and managing health conditions considered departures from "normal". Scientific research is only one of many stakeholders in this process and it does not operate independently of the other stakeholders; both the outcomes of scientific research about health and the utilization of these outcomes are heavily influenced by the socioeconomic environment in which they arise and are used. The involvement of a wide range of stakeholders in the development of both DSM-5 and ICD-11 is a clear example of this process. In contrast, the RDoC initiative will attempt to develop a diagnostic system with as little input as possible from the non-neuroscientists: the not-so-implicit message is that economic realities, social factors and cultural preferences should wait until the neuroscientists have discovered the "truth" and then fall into line accordingly. This biological reductionist approach is naïve about the role of diagnostic systems in the real world. A diagnostic system must serve the ever-changing needs of *all* stakeholders. Moreover, these stakeholders need to be integral to the process of developing successive iterations of the diagnostic system, not bystanders.

Will major mental health funders in other countries follow NIMH down the RDoC road? In the past, the economic strength of America and its ability to attract leading specialists from around the world has allowed it to maintain intellectual leadership in many fields, including mental health. But as middle-income countries gradually increase their research funding for mental health and as other high-income countries increase their funding for multinational mental health projects, the proportional contribution of NIMH to global funding for mental health research will inevitably decrease. As this happens, it is likely that the intellectual leadership in global mental health will become increasingly multipolar. At present, it remains unclear how this gradual changing of the guard will affect priorities in global mental health research.

The siren call of biological fixes for biopsychosocial problems has dominated medical research for several decades, so mental health research priorities in other countries may follow the NIMH Pied Piper. But the new emphasis on the public health burden of mental disorders highlighted by the GBD findings and the urgency of the need to resolve these pressing problems highlighted by the WHO Mental Health Plan may induce some countries to disengage from NIMH at the RDoC juncture, and allocate increasing proportions of mental health research funding to the universal problems of expanding the range, quality and utilization of services. If that happens, the inevitable slow decline of American intellectual leadership in global mental health will accelerate.

References

1. Vos T, Flaxman AD, Naghavi M et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380: 2163-96.
2. Whiteford HA, Degenhardt L, Rehm J et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013;382:1575-86.
3. World Health Association. Mental Health Action Plan 2013–2020. Geneva: World Health Organization, 2013.
4. Insel TR. Transforming diagnosis. www.nimh.nih.gov.
5. Belluck P, Carey B. Psychiatry's guide is out of touch with science, experts say. New York Times, May 6, 2013.
6. Insel TR, Lieberman JA. DSM-5 and RDoC: shared interests. www.nimh.nih.gov.
7. World Health Association. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings. Geneva: World Health Organization, 2010.
8. Prince M, Patel V, Saxena S et al. No health without mental health. Lancet 2007;370: 859-77.

DOI 10.1002/wps.20098

Approaching human neuroscience for disease understanding

Carol A. Tamminga
Department of Psychiatry, University of Texas Southwestern Medical School, Dallas, TX, USA

In psychiatric research, neuroscience knowledge is growing at a record rate, in both the acquisition of facts and the development of mechanistic understanding, at the level of the molecule, the synapse, the cell and the neural system. Whereas, only 20 years ago, we talked about brain function in terms of a "black box", today we understand many dimensions of brain function mechanistically, especially where molecules and physiology support characteristic behaviors (1). It is not only within genetics and synaptic function where

knowledge is growing, but also in identifying postsynaptic signaling pathways, cognition mechanisms, epigenetic modifications and systems neuroscience, to name just a few areas.

Translational scientists are challenged to keep up with relevant new knowledge. Science administrators are thoughtful about motivating the field to use basic knowledge both for the purpose of understanding normal brain function and to identify disease-causing perturbations in disease. There never has been a better time for neuroscience growth or for developing biomarkers and molecular targets for brain diseases. The RDoC system challenges every brain scientist focusing on psychiatric diseases to synthesize and apply relevant brain facts to advantage mechanistic disease understanding (2).

There already exist methodologies to examine *in vivo* brain function in humans histologically, molecularly and phenotypically, enabling measurements of human brain-based behaviors (3). Cognition is a good example of this, since cognitive capacity can be assessed experimentally and is routinely used to make inferences about functioning of the brain itself. Other approaches, like human brain imaging and evoked potential analyses with electroencephalogram (EEG), all use measures of brain molecular, metabolic or electrical activity to represent neuronal activity regionally. Then, also, some experimental approaches use human postmortem brain tissue for histological or molecular analyses directly, albeit in non-living brain tissue. Regional gene expression, generating region- or cell-specific proteins, could be critical for capturing complex brain function and its regional dysfunction in disease. And animal models, if carefully verified, can contribute improved experimental models.

Then, how do perturbations of these normal human-based systems associate with mental symptoms? Again, here is where the RDoCs system comes in. What the RDoC framework contributes is a system for generating and categorizing brain facts as they relate to putative cross-cutting basic behavioral states or functions of brain, leaving to experimental observation the identification of those perturbed in brain pathology.

It would be incorrect to conceptualize RDoC as a diagnostic system. It is, rather, an approach for systematizing brain knowledge to make it pertinent to functional and dysfunctional systems in the brain as they relate to behavioral outcomes. Nor is RDoCs ready to transform psychiatric diagnosis for all of the practically purposes that ICD and DSM are used for. But, the RDoC system does call attention to the essential need in translational neuroscience to base diagnosis on disease understanding and to tether molecular target development to a detailed and demonstrated disease pathophysiology.

The emphasis in the Cuthbert paper on developing dimensional approaches within mental illness is represented within the domain of psychosis by the Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP) project. References to "psychoses" have been made in the literature for many years, creating an expectation for measurable overlap of biomarkers in brain diseases with prominent psychotic features. Recently, the BSNIP study, using dense biomarkers to characterize psychosis, including schizophrenia, schizoaffective disease and bipolar disorder with psychosis, was launched to explore the dimension of psychosis with modern biomarkers (4).

The study recruited individuals with psychosis and phenotyped them densely, using cognition testing, evoked potential evaluation, eye movement assessment, brain imaging and resting EEG assessment, in addition to a full clinical assessment. The resulting phenotypic characterization of the psychoses diagnoses has created a rich database which can be analyzed for the purpose of creating biological markers for diagnosis.

The BSNIP study showed how biomarkers clustered within and across current DSM diagnoses and, in general, across the psychosis dimension. The high variability and the broad overlap of the biomarkers across diagnoses suggest that our DSM diagnoses are biologically heterogeneous. The additional surprise in these data was the considerable overlap in clinical and diagnostic characteristics. The current BSNIP question is how to move from the present state of partial knowledge in clinical phenomenology and emerging neurobiology, to a state of biological understanding in our psychiatric conditions, a research agenda in the field.

The implication of the BSNIP outcomes and RDoC predictions is that, if we examine current diagnostic groups of psychosis using ideal neural biomarkers, we are still likely to be unsuccessful at defining pathophysiology, because of the gross heterogeneity of the identified groups (5). If we approach disease with a dimension, instead of a single diagnosis, we anticipate, in fact utilize, the marked heterogeneity of the group to recognize biologically similar clusters within the dimension and use the clustering of biomarkers to generate biologically-defined disease groups. The development of validating characteristics for the clusters is the research challenge, namely a common systems understanding or a unifying molecular pathology for these biomarker clusters. The BSNIP approach begins dimensionally, using dense biomarker characterization, to form biologically common clusters, potentially useful as disease identifiers with biological targets.

On the other hand, as Cuthbert suggests, we can also approach disease definitions biologically through identifying the genes, molecules, cells and circuits of normal behaviors, then see which normal functions could be altered when these systems are perverted. The framework of the RDoC system, as it is currently articulated, starts at a detailed level of knowledge of domains for normal behaviors (6). Several of these domains are already relatively well understood. Examples are the constructs of "declarative memory", "acute threat" and probably also "reward learning". These normal systems, if abnormally executed, could manifest themselves as "psychosis", "post-traumatic stress disorder" or "drug abuse", respectively, if the normal tract is perverted.

In our current state of knowledge which lacks even basic biological clues

about the nature of psychiatric illnesses, let alone biological targets, it is not an over-extension to say that we should involve both approaches in discovery and use overlap as concept demonstration.

References

1. Charney DS, Buxbaum J, Sklar P et al. Neurobiology of mental illness, 4th ed. New York: Oxford University Press, 2013.
2. Cuthbert BN. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry 2014;13:28-35.
3. Tamminga CA, Pearlson GD, Keshavan MS et al. Bipolar and Schizophrenia Network for Intermediate Phenotypes (B-SNIP): outcomes across the psychosis continuum. Schizophr Bull (in press).
4. Tamminga CA, Ivleva EI, Keshavan MS et al. Clinical phenotypes of psychosis in the Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Am J Psychiatry 2013;170:1263-74.
5. Hill SK, Reilly JL, Keefe RS et al. Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Study. Am J Psychiatry 2013;170:1275-84.
6. Keshavan MS, Clementz BA, Pearlson GD et al. Reimagining psychoses: an agnostic approach to diagnosis. Schizophr Res 2013;146:10-6.

DOI 10.1002/wps.20099

RDoC: a roadmap to pathogenesis?

Assen Jablensky, Flavie Waters
Centre for Clinical Research in Neuropsychiatry, School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, Australia

> "*It is now necessary to turn away from arranging illnesses in orderly, well defined groups and to set ourselves instead the undoubtedly higher and more satisfying goal of understanding their essential structure*" (1).

In the last few years we have witnessed unmistakeable signs of a sea change in psychiatric genetics and basic neuroscience. Genome-wide association studies, conducted by large international consortia and using data from more than 100,000 individuals, have, *inter alia*, identified common polymorphisms shared by seemingly unrelated disorders, including schizophrenia, bipolar disorder, autism, attention-deficit/hyperactivity disorder and possibly certain forms of intellectual disability and epilepsy (2). This provides a strong argument for pleiotropy as a rule, rather than as an exception in the genetic underpinnings of psychiatric disorders.

Next-generation sequencing of exomes and whole genomes of psychiatric patients, gathering speed owing to the increased affordability of advanced technologies, may eventually supply the final answer. The ENCODE project is providing novel information on the regulatory network of transcription factors, which is crucial for interpreting personal genome sequencing and understanding basic principles of human biology and disease (3). The recently launched Brain Activity Map Project (4) aims to achieve over the next 10 years a comprehensive mapping of the activity of single neurons and their connectivity by applying nanotechnologies and large-scale computation techniques.

Against this rapidly changing background, the clinical practice of psychiatry is hampered by a knowledge gap which obstructs the translation of such groundbreaking advances into "personalized" diagnostic formulations and targeted prevention or treatment. While part of the reason is the forbidding complexity of psychiatric disorders, another part is the "reification" of current diagnostic and classificatory schemes, whose basic postulate of discrete nosological categories remains essentially unchanged since the times of Kraepelin and Bleuler.

All of the above underpins the motivation and rationale of the National Institute of Mental Health initiative to propose and implement the Research Domain Criteria (RDoC) project as a strategic science alternative (or counterpart) to the DSM/ICD classification. Its "seven pillars" (5) include: primacy of translational research; integration of neuroscience and behavioral science; a quantitative dimensional approach to psychopathology; development of interviews and measurement scales allowing studies of the entire range of variation from normal to abnormal; sampling strategies unbiased by DSM/ICD diagnoses or any fixed definitions of disorders; and a selective approach to the independent variables which may be chosen among any one of the "units of analysis" or "constructs" of the conceptual model.

There are obvious and appealing strengths in the RDoC design. The study of fundamental processes that cut across the conventional diagnostic boundaries will reveal unexpected patterns of associations with symptoms, personality traits and behavior. The mapping of clinical phenomenology onto specific brain dysfunction will result in a "functional psychopathology" (6) that may add substantially to recasting the taxonomy of mental disorders. Thus, RDoC sets a common agenda and framework for psychiatric and neuroscience researchers that could unify and focus the efforts towards the ultimate goal of reconceptualizing our understanding of the "essential structure" of psychiatric disorders. If and when achieved, this would align psychiatry with other medical disciplines, such as cardiology and oncology, which are considered to be pioneers in translation research.

Yet there are uncertainties, challenges and caveats along the road of the RDoC project. First, the relationship between the RDoC philosophy and clinical reality is ambiguous. Patients