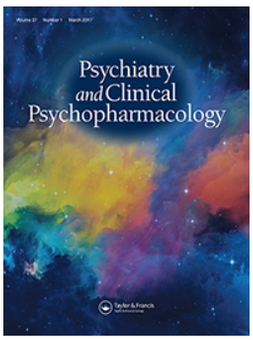

Psychiatry and Clinical Psychopharmacology

ISSN: 2475-0573 (Print) 2475-0581 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp21

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To cite this article: Samet Kose & Mesut Cetin (2017) The Research Domain Criteria framework: transitioning from dimensional systems to integrating neuroscience and psychopathology, Psychiatry and Clinical Psychopharmacology, 27:1, 1-5, DOI: 10.1080/24750573.2017.1293255

To link to this article: https://doi.org/10.1080/24750573.2017.1293255

Published online: 31 Mar 2017.

PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY, 2017
VOL. 27, NO. 1, 1–5
http://dx.doi.org/10.1080/24750573.2017.1293255

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EDITORIAL

The Research Domain Criteria framework: transitioning from dimensional systems to integrating neuroscience and psychopathology

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ABSTRACT

Although recent research in neuroscience and genetics is providing new insights into the etiology of psychiatric disorders, progress in treatment development has been hindered by reliance on diagnostic categories that are based primarily on presenting signs and symptoms. The NIMH Research Domain Criteria (RDoC) framework seeks to provide a neuroscience-based nosological background for future research on psychopathology, categorizing individuals for research purposes using a dimensional approach that benefit from significant progress in modern neuroscience. These scientific advances combined with new approaches to classification can inform the development of novel, circuit-based interventions and the personalization of treatments available. In this editorial, we describe the RDoC framework compared with Diagnostic and Statistical Manual/International Classification of Disease systems and highlight some of the emerging progress in RDoC-based research that is consistent with these developments.

ARTICLE HISTORY
Received 1 January 2017
Accepted 22 January 2017

KEYWORDS
RDoC; neuroscience; psychiatric diagnosis; psychiatric treatment

> Study me as much as you like, you will not know me, for I differ in a hundred ways from what you see me to be. Put yourself behind my eyes and see me as I see myself, for I have chosen to dwell in a place you cannot see. (Jalaluddin Rumi)

Despite significant progress has been made in the fields of neuroscience, genetics and biomarkers, and psychiatric disorders, a growing frustration still exists with the rate of translation of these efforts into an understanding of fundamental mechanisms underlying dysfunctions and corresponding psychiatric treatments. One important reason for this is the widespread reliance of categorical classification systems, based upon presenting signs and symptoms such as the International Classification of Diseases (ICD) [1] and the Diagnostic and Statistical Manual of Mental Disorders (DSM) [2]. Both systems have contributed greatly to the reliability of psychiatric diagnoses for both research and clinical purposes, and improved the communication between clinicians, researchers, mental health policy-makers, and patients. However, their categories and criteria were formulated long before modern advancements in neuroscience and the validity of the diagnoses is widely questionable. One consequence of this has been to slow down the development of new treatments targeted to underlying pathophysiological mechanisms in the human brain.

In lieu of this demand, in 2008 the National Institute of Mental Health (NIMH) has launched the Research Domain Criteria (RDoC) project to create a framework for research on pathophysiology, especially for genetics and neuroscience, which ultimately will apprise for future classification systems [3]. The RDoC project is intended to be the next step in a long journey, incorporating data on pathophysiology in ways that eventually will help identify new targets for treatment development, identify subgroups for treatment selection, and provide a better match between research findings and clinical decision-making.

RDoC classification is based on three essential assumptions. First, the RDoC framework conceptualizes psychiatric disorders as brain disorders with a primary focus on neural circuitry and network, in contrast to neurological disorders with identifiable structural lesions, and they can be viewed as disorders of brain circuitries (reward circuitry, fear/extinction circuitry, executive function, impulse control/ disinhibition, etc.). Secondly, RDoC classification assumes that the dysfunction in neural circuitries can be identified with the tools in clinical neuroscience, including electrophysiology (EEG), functional neuroimaging (fMRI, DTI, CBV mapping, etc.). Finally, the RDoC classification assumes that data from genetics and clinical neuroscience will ultimately yield bioprints which will improve patients' clinical signs and symptoms. The clinicians in future could supplement a clinical evaluation of what we now call a "personality disorder" with data from functional or structural imaging,

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genomic sequencing, and laboratory-based evaluations of corresponding brain circutries to determine prognosis and appropriate treatment, analogous to what is done routinely today in treatments of infectious diseases, endocrine disorders, and oncology/cancer patients.

How will RDoC alter clinical practice will largely depend on how well RDoC would perform for research. Following Robins and Guze's postulates for the Research Diagnostic Criteria [4], the critical test is how well the new molecular and neurobiological parameters predict prognosis or treatment response. While maintaining a clear focus on the full-blown psychopathology, researchers will be encouraged to elucidate the complete range of a given dimension to develop thresholds for different types of interventions and identify early opportunities for preventive treatments. If a serotonin polymorphism identifies patients with mood/anxiety disorders who do not respond to behavior therapy, if a copy number variant defines a form of mood disorders with high remission rates, if neuroimaging yields a subtype of psychotic disorder that consistently responds to a certain antipsychotics, the RDoC is capable of providing a rating system which will improve these outcomes.

The DSM-5 displayed almost no influence of the remarkable progress in new technologies and substantive knowledge in neuroscience and behavioral science since the DSM-IV release in 1994. Hence, Thomas Insel, the Director of NIMH, outlined the common consensus in the research community regarding the issues with the DSM system and declared that the NIMH would re-orient its research away from the DSM-5 towards the RDoC project, incorporating methods such as genetics, neuroimaging, and cognitive neuroscience into future diagnostic systems based upon behavioral dimensions and neural systems [5]. David Kupfer, the head of the DSM-5 task force, was confirming this by stating:

> The problem that we have had in dealing with the data that we have had over the five to ten years since we began the revision process of DSM-5 is a failure of our neuroscience and biology to give us the level of diagnostic criteria, a level of sensitivity and specificity that we would be able to introduce into the diagnostic manual. [6]

His comment raised the question how the field of mental health would go about changing directions to meet this demand. The DSM/ICD system has become the international *de facto* standard for submitting research grant applications to funding agencies, and review processes are typically quite unforgiving of any deviations from conventional systems. Furthermore, the system has served so well for clinical services, administrative, and legal purposes that any changes are now concerned about the ripple effects that even the smallest changes in categories or criteria can have upon eligibility for mental health services, insurance payments, trends in prevalence rates, health care costs, etc. Hence, the system's own structure has become one of the biggest obstacles to change. In order to attain groundbreaking nosological approaches in the future that are based upon neuroscience, an essential literature is required that can inform these innovations in classification and diagnostic systems. However, such a research literature cannot be created as long as studies are conducted solely within the limitations of ICD/DSM categories. Therefore, main goal of RDoC is to facilitate research to validate dimensions defined by neurobiology and behavioral measures that intersect current disorder categories, and that can inform future revisions of psychiatric diagnostic systems. In other words, RDoC is intended to support research toward a new classification system with an ultimate goal to build a research literature that reflects advances in genetics, neuroscience, and behavioral science to provide a foundation for precise diagnosis and treatment of psychiatric disorders.

Most psychiatric disorders are now viewed as neurodevelopmental disorders, and maturation of the neurons in the nervous system interacts with a wide variety of external influences beginning at conception. There has been considerable research on multiple risk factors such as prenatal infections and early childhood abuse/neglect and trauma. However, the current diagnostic systems do not necessarily promote integrative developmental models that may differentially lead to resilience or psychiatric disorders, nor a precise understanding of why a particular insult may lead to different disorders (for instance, that early life stress represents a risk for major depressive disorder, post-traumatic stress disorder, or borderline personality disorder). A major goal of RDoC is to focus research on relevant systems to document the unfolding of trajectories as they interact with various events, not only in childhood, but across the life span. Many paradigms have been developed that can provide measures both of behavioral performance and of related functional brain activity in different populations, providing some sense of the normal distribution of behavior; this capability, in turn, permits a quantitative specification of the extent to which various aspects of human functioning deviate from normality. Notably, these new developments are not confined only to laboratory tasks, but also to robust psychiatric scales and inventories that relate strongly to real-world functioning [7].

In terms of the RDoC system, several consequences arise from these developments. First, RDoC adopts a translational approach to disorders, construing pathology in terms of deviations in *fundamental functional systems*. RDoC marks a subtle but significant shift in direction for psychiatry. The standard approach to psychiatric illness has been to define a mental disorder on the basis of signs and symptoms and then seek a pathophysiology recounting to those symptoms. In contrast, RDoC asks the following questions: What is the normal

distribution for a certain trait or characteristic; what is the brain system that primarily implements this function; and, how can we understand, at various levels of mechanism [8], what accounts for the development of dysregulation or dysfunction in these systems alongside normal-to-abnormal dimensions? This strategy has obvious advantages in terms of applying basic research at all levels of analysis to clinical problems, as the translation is relatively straightforward. On the other hand, it may be more difficult for clinical researchers, since the symptoms that they are accustomed to study literally may not appear in the RDoC matrix. A further implication of the translational approach is that RDoC is agnostic to current disorder categories. There is no claim to understand or explain DSM/ICD disorders in terms of these functions; rather, the aim is more simply to seek an understanding of how these various systems may become dysregulated to various extents and to relate such dysregulation to relevant observed symptoms.

The RDoC approach argues that conceptualizations and scientific approaches to mental disorders should be similar to those used for other complex medical disorders in which there are degrees of illness and impairment that are distributed along a dimension. Most psychiatric research, on the other hand, uses the *infectious disease model* in which the presence or absence of disease sorts individuals into distinct groups. This between-groups approach ignores the substantial number of individuals whose number or severity of symptoms places them in-between diagnostic categories, or in a sub-clinical sphere that is often ignored by researchers. In fact, the RDoC framework intentionally omits any disease definitions, disorder thresholds, or cut-points for various levels of psychopathology. Because such boundaries can bias the way research is conducted, the aim is simply to gather data about the dimensions that will support future decisions in this regard, made on the basis of quantitative data rather than clinical consensus. Furthermore, the availability of reliable and valid quantitative measurements could permit adjustments over time consequent to epidemiological studies of risk and outcome, similar to what happened over the years in such areas as hypertension [9].

Some observers might argue that this translational emphasis oversimplifies the richness of psychopathology, or that complex psychiatric symptoms are not yet ready to be explained in such a direct translational manner. Sooner or later it will be essential to explain complex symptoms in terms of dysregulation in basic brain operations. For instance, hallucinations might be broached in part via a consideration of systems that represent the integration of perceptual information [10], while the networks that mediate functions involved with language, working memory, declarative memory, and learning would appear to be promising avenues for the study of delusions [11]. The growing realization that some degrees of psychotic phenomena are present in the normal population [12], and also in broad ranges of psychiatric outpatients [13], is consistent with a view of these symptoms as dimensionally arrayed in the population and not simply a manifestation of qualitatively distinct severe pathology. Therefore, an essential component of an experimental classification system involves challenging researchers to depart from traditional ways of thinking about disorders in order to seek promising new experimental ideas.

A critical aspect of the RDoC program is helping researchers make the transition, both conceptually and practically, from the ICD/DSM to a dimensional view. This has been a matter of ongoing concern for the NIMH workgroup, as the DSM/ICD system has been used for so long in research and clinical practice that some transition is needed to consider psychopathology from other perspectives. These issues would depend not only on becoming accustomed to the significance of new scale values (e.g. for anhedonia or working memory), but also on achieving a mental model for patients seen through the RDoC lens. The same psychopathology would be present, of course, but conceived and measured in different ways. The general approach to this transition would incorporate various combinations of RDoC constructs and DSM/ICD disorder categories in experiments. While these steps may be useful in transition, there are potential drawbacks as well. One problem is the temptation for the disorder categories to remain privileged with respect to the dimensions: researchers might continue to regard the diagnostic thresholds as demarcation points for *ill versus well*, and also continue viewing pathology through the DSM/ICD lens rather than neural systems-based functional constructs. There is also the obvious potential bias in sampling mostly patients who meet current diagnostic criteria, in treatment-seeking samples or with other recruiting strategies, thus short-circuiting dimensional examination. These transitional steps pose the risk that psychiatric researchers would continue to regard their patients, both clinically and in terms of research designs, in familiar DSM terms, failing to grow a sufficient appreciation of the *precision-medicine zeitgeist* that RDoC is intended to facilitate. For these reasons, transitional research designs are best regarded as temporary heuristics for a limited number of studies if the full potential of the RDoC framework is achievable.

While the above steps have been oriented towards psychopathology, relatively near-term possibilities for using RDoC concepts in treatment are present. The common element for any treatment trial in RDoC will require the development of a valid set of measures that can reliably distinguish a particular subtype, or critical location alongside a dimension, to predict successful treatment outcomes. For example, given the well-known heterogeneity of ICD/DSM categories,

establishing current disorder subtypes may enhance matching of patients to treatments. For instance, PTSD is often regarded as a prototypical "fear circuitry" disorder. However, many patients with PTSD show a blunted affective response to affective challenges [14], which may relate to multiple traumas and/or a chronic course [14]. Accordingly, classic exposure therapies for PTSD might be predicted to be effective only for highly fear-reactive patients (where the fear can be extinguished), while different therapies should be indicated for those with a blunted response pattern. Appropriate assessments for measuring the fear response in a reliable manner would permit a test of this hypothesis, similar to other anxiety disorders [15]. In the same way, development of new treatments can be facilitated by the identification of more homogeneous subgroups of patients. By increasing the mechanistic understanding of disease and matching the right treatments to the right patients, one can move from one-size-fits-all to targeted therapies and increase the benefit-risk ratio for patients [16]. In other words, new treatments that target a mechanism associated with one particular symptom may have a low probability of success in a trial for a DSM/ICD indication, because the particular symptom is not shared by all patients with the diagnosis. Instead, an exemplary research topic in RDoC might involve an enhanced understanding of how various aspects of reward-related systems relate to clinical anhedonia (a symptom of depression which itself may be a multifaceted clinical construct). If a new anhedonia treatment were developed that targets a novel mechanism based upon such research progresses, the prediction would be that the treatment has therapeutic effects only for those depressed patients with anhedonia, but should be efficacious for patients with other diagnoses who have measurable anhedonia. Measurable anhedonia is a key phrase that necessitates prior validation of widely accepted procedures for this kind of experimental evidence.

The RDoC framework is often misjudged as tilting at the windmills of DSM. During its early days, RDoC cannot be expected to compete with the massive research portfolio DSM has accumulated nor with the tremendous clinical experience that the DSM is heavily based. RDoC is not designed to replace DSM in the near future. Yancey et al. [17] built an exceptionally large database of self-report and biological measures that was carefully chosen to reflect clinically important RDoC constructs, pursued a promising validation strategy, and found moderate associations with more conventional symptom measures [17]. Their study exemplifies one intriguing means of pursuing the RDoC framework. In fact, psychophysiological measures, such as fMRI, Quantitative EEG, magnetoencephalogram, startle reflex, eye tracking, and diverse autonomic measures, are superbly positioned to serve goals of the RDoC.

One of the main criticisms of the RDOC framework is that RDoC embodies a reductionistic approach that focuses solely on genetics and biomarkers to the exclusion of social environmental influences [18]. In fact, this is not true. There is a strong emphasis on developing a more mechanistic understanding of how such factors as life events and the social environment interact with development to produce a range of outcomes observed. RDoC adopts very unique perspectives compared to traditional systems with respect to psychopathology. As some of the implications are nuanced and subtle, additional processing will be useful regarding how the RDoc would operate.

In conclusion, the main objective of the RDoC framework is to provide a launch pad for conceptual thinking and grant psychiatric researchers more freedom in their work, rather than binding it to an artificial framework of illness-based categories. The RDoC is no longer a new initiative and has entered the jargon of the scientific and regulatory agencies. NIMH has already funded more than couple of dozens of grants via RDoC-specific funding opportunities and over 10 times that number of researchers who incorporate RDoC principles into applications submitted under general funding announcements. Researchers are engaged in a challenging and exciting discussion about new approaches to psychiatric nosology, focusing on integrative methodologies, dimensional conceptualizations, and alternatives to heterogeneous diagnostic classifications. The RDoC framework encourages use of multiple measures of analyzes, from genetics and molecular, and from clinician assessment to self-report. When the RDoC project becomes successful, future versions of the DSM and ICD would be informed by the findings that emerge from RDoC-guided research. The process will not be easy or quick, but already the Institute has seen an accelerating number of RDoC-themed grant applications. Time will tell whether such interest is the precursor of a *paradigm shift* in how the researchers and clinicians conceptualize psychiatric disorders. The RDoC's integrative approach seems likely to generate new perspectives with respect to the of brain and behavior relationship in psychiatric disorders. While the immediate thrust of the RDoC project sets it apart from the established structures of the DSM and ICD, we maintain our hopes that the long-term aspirations for all three systems converge on reducing the burden of suffering for individuals with psychiatric disorders.

Disclosure statement

No potential conflict of interest was reported by the authors.

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