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RDoCs redux

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We are delighted to share in the debate about the RDoC program, as we feel some responsibility for its birth. Indeed, the notion articulated in RDoC to inform "future versions of psychiatric nosologies based upon neuroscience and behavioral science rather than descriptive phenomenology", by providing "a framework for conducting research in terms of fundamental circuit-based behavioral dimensions that cut across traditional diagnostic categories" (1), is a direct outgrowth of studies that began in the Clinical Brain Disorders Branch of the Intramural Research Program of the National Institute for Mental Health (NIMH) at St. Elizabeth's Hospital in the early 1980s.

This body of work led to the creation of the Genes, Cognition and Psychosis program, an interdisciplinary research program which in its title recognized that the biology of psychopathology was not linked to diagnostic nomenclature. The work of this program in identifying mechanisms in the brain by which risk factors influenced biological susceptibility was a foundation of the Strategic Plan launched by the NIMH in 2008 and in which the RDoC plan was proffered.

Given our experience with work that forms so much of the rationale for RDoC, we should be enthusiastic. So, why are we not?

Actually, the debate between "lumpers" and "splitters", whether in the realms of descriptive psychopathology or in brain imaging measurements or in genetics, has been going on literally for over a century in psychiatry. The RDoC project claims to be a new and enlightened way to split and then lump, because it argues that the neuroscience and genetics of psychiatric disorders open new arenas for such progress. This sounds really good, but to paraphrase a popular beer advertisement in the USA, does it taste great?

We see the main concerns about the RDoC mindset not with its conceptual foundations, but with its reliance on the presumed validity of the behavioral, neural functional and genetic dimensions it highlights as fundamental to a revision of psychiatric nomenclature. Ultimately, any revision of psychiatric diagnosis, which clearly is the RDoC goal, must be better than the existing system, better in the sense of what diagnosis is about. Diagnosis is primarily an instrument used by clinicians for two primary purposes: to predict the natural history of an illness and to predict the most appropriate treatment. This will be the standard also for RDoC, if its long-term goal of replacing existing diagnostic practices is to be realized.

Even clear and important dimensions of behavior and its reward-based underpinnings may have unexpected complexities when viewed through the RDoC lens. In an incisive and elegant study, Gold et al (2) demonstrated that negative symptoms in schizophrenia are associated with overestimating the cost (or effort) involved in attaining an outcome. One could easily view this as a metric or dimension, suggestive of "degrees" of negative symptoms. One can imagine elegant neuroimaging studies of effort estimation showing varying engagement of prefrontal, insular, and striatal function.

Cuthbert's suggestion that a good research study would be to explore such behavioral and neural system dimensions across current diagnostic groups and in subjects without psychiatric diagnoses presents a daunting conundrum. For example, "overestimating the cost (or effort) involved in attaining an outcome" also seems to be a suitable operational definition of laziness, as used by lay individuals. Thus, an important question is whether this or any of the RDoC dimensions have the same meaning when associated with schizophrenia qua schizophrenia, or if they are observed across other diagnoses and in a spectrum of otherwise normal, albeit, lazy individuals. Moreover, would the neural systems and genomics that are associated with this set of behaviors be the same in all cases? Several recent papers focus on this issue. They suggest, for example, that mechanisms for auditory hallucinations in otherwise healthy functioning individuals (so called "voice-hearers") may be different than the mechanisms associated with such symptoms in schizophrenia (3).

It has become increasingly popular to believe that similar patterns of brain activity in patients with psychiatric illness and in some non-psychiatric research samples underlie RDoC-type dimensions of psychopathology. These studies are based on specific protocols that elicit physiological responses critically dependent on the context. It is an old saying in the functional neuroimaging research lexicon that functional neuroimaging data reflect what the brain was doing during the imaging protocol, but the challenge for the investigator is to figure out what the brain was actually doing. The meaning of this saying is that patterns of engagement of brain functional systems during an imaging experiment do not necessarily reflect a specific or even definable brain state. A clear illustration of this is the current fascination with the so-called resting state functional magnetic resonance imaging (fMRI) experiment, where subjects, including diverse samples of psychiatric patients, are allowed

to lie in the confining and noisy environment of the MRI scanner for five to ten minutes doing nothing. This is said to be a resting or unstimulated state and the pattern of activity typically seen in normal subjects after they have acclimatized to the scanner environment is called the "default network". Part of the appeal of this paradigm is that it is easy to do and easy to find differences between patient and control samples.

Patients with a variety of psychiatric diagnoses have been observed to have deviations from the default pattern, and it is often stated that they show a deficiency or abnormality of the default network as if this is some sort of neural defect. Clearly, the relative engagement or lack thereof of the default network is a dimension putatively linked to a neural circuit. Do we imagine that patients currently diagnosed with schizophrenia, or children with autism, or patients with Alzheimer's disease, all of whom may show similar patterns of default network deviations, share pathology in this dimension? Sounds good, but does it taste great? In fact, it is highly implausible that patients with schizophrenia or with autism will experience the MRI environment analogously to a paid healthy volunteer and it is unlikely that they will each experience it the same, either. The different ways in which they are liable to think and feel about the noise and the confinement will interfere with the so-called default system, producing a potentially similar degree of abnormality on this dimension, but based on dissimilar reasons.

The current approach to caseness is rooted in many decades of clinical observation and detailed description of clinical course and natural history, and many academic debates about how best to represent clinical reality. This rich history has also witnessed many self-proclaimed enlightened movements to change the scheme. In the absence of pathognomonic findings, diagnosis is imprecise and multidimensional, as it is in other fields of medicine. The idea that RDoC is a blueprint for research to fill in this multidimensional landscape is appealing and attractive. But, as an approach to ultimately revise the concept of caseness, it has a much more difficult task.

One of the most important components of any diagnostic scheme that is conspicuously missing from the RDoC phenomenology matrix is the dimension of time. The DSM-5 regards time as an essential aspect of most diagnostic categories. In neurology, it is said that time is the best diagnostician. Good psychiatric clinicians know that cross-sectional phenomenology is problematic, and what looks like obsessive-compulsive disorder today, may turn out to be psychosis tomorrow. What looks like schizophrenia early on in the course of a patient's history turns out to be bipolar disorder down the road. Were these examples to have been treated based on the RDoC dimensions, the outcome might not be optimum, to say the least. Indeed, as much as there is overlap phenomenologically and perhaps genetically in what we call schizophrenia and what we call bipolar disorder, and patients across these categories will share many RDoC dimensions, it is indisputable that for some patients with the latter diagnosis, lithium is as miraculous as any treatment in psychiatry, yet it is entirely without antipsychotic effects in patients with the former diagnosis.

There is good evidence that diagnosis per se is a social construct and is dependent on where on a continuum some relatively arbitrary threshold a caseness call gets made (4). The DSM system has always recognized that having symptoms is not sufficient for a clinical diagnosis. There must also be disability. Illness and disability or functional compromise are inseparable concepts. Regardless of the in vogue phenomenology, illness begets disability. Even between mild cognitive impairment and Alzheimer's disease there is a grey area. An unbiased way at looking at symptoms, cognition, etc., involving threshold-free dimensions, has been thought to be a valid alternative. However, this fails to account for notable differences at the severe ends of the spectrum that may encompass multiple dimensions and the possibility that "disease" neurobiology can accelerate.

It's a no brainer that psychiatric diagnosis is imperfect, subjective and not based on pathophysiology or causation, and the field is eagerly anticipating a future where this would be different. Psychiatric practitioners are faced with real world patients with real world problems and their decisions are not readily informed by rarefied fMRI paradigms and weak genetic associations. They use diagnosis to help them organize the complex clinical landscape.

Most clinicians know that the diagnoses they apply are approximations, that they refer to syndromes not distinct disease entities, and that they do not express distinct boundaries. They understand that our diagnoses are constructs, and that patients do not *have* schizophrenia or bipolar disorder, per se; they are given these diagnoses. These realities seem to have surprised researchers, many of whom unfortunately know about psychiatric illnesses only from what they read in the literature or on their computer screens.

Our current approach to psychiatric diagnosis is the result of many decades of deep clinical experience and scholarly debate. As imperfect as it is, it is a practical and clinically useful tool that has helped transform psychiatry from subjective, impressionistic categorization of clinical syndromes to more objective, diagnostically reliable definitions. The field would be dramatically enhanced by a better system, as would many other fields of medicine. But, the adoption of an alternative phenomenology must be viewed with caution and it must result in something better than what we have. This means more clinically valuable to practitioners and to patients.

We suspect that RDoC will be liberating to some researchers, because they will be encouraged to move beyond current diagnosis in designing clinical research projects. Does this require a major NIMH initiative that co-opts the grant review process and has the unintended consequence of actually reducing creativity by its very mandate and also of potentially undermining clinical practice? One might hope that researchers and clinicians alike are continuing to think outside the box and are exploring

new ways of solving old problems without the NIMH telling them that they are not.

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Wittgenstein's nightmare: why the RDoC grid needs a conceptual dimension

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RDoC attempts to finesse an existential dilemma facing psychiatry: psychiatry is most persuasively a medical field if mental disorders are understood as brain disorders, but brain disorders seem to fall under neurology. The RDoC attempts to resolve this dilemma by distinguishing brain circuit malfunctions as the distinctive domain of psychiatry: "the RDoC framework conceptualizes mental illness as brain disorders; in contrast to neurological disorders with identifiable lesions, mental disorders can be addressed as disorders of brain circuits" (1). RDoC further locates brain circuit function within a grid of analytical and developmental levels and dimensions that together are supposed to replace DSM/ICD categories with more valid diagnoses.

Wittgenstein famously said: "In psychology there are experimental methods and *conceptual confusion*... The existence of the experimental method makes us think we have the means of solving the problems that trouble us; though problem and method pass one another by" (2). RDoC is a paradigmatic expression of Wittgenstein's concerns. It joins an ambitious empirical research program with a conceptual framework so weak that it is difficult to envision success. I consider below some of the RDoC's apparent conceptual challenges.

RDoC embraces brain-circuit construct validity without addressing conceptual validity, thus gets the relationship wrong between itself and the DSM/ICD. The RDoC sees the DSM/ICD's failures when it comes to construct validity (i.e., each diagnosis identifying one etiological category), but fails to appreciate DSM/ICD's essential role in psychiatric legitimacy. The DSM/ICD identifies conditions that, judging from surface symptoms, context, and background knowledge of normal human functioning, fall under the concept of disorder. Correctly distinguishing between disorder and normality is what I have labeled *conceptual validity*. Conceptual validity is independent of construct validity: a DSM/ICD disorder category can encompass ten different disorders and thus lack construct validity, but be conceptually valid if it encompasses only disorders, and it can be construct valid but identify a non-disorder and thus be conceptually invalid. Most criticisms of DSM-5 were accusations of conceptual invalidity, that criteria encompassed normal variations. Whatever its errors, DSM/ICD remains an attempt to delineate the domain of psychological conditions that fall under the concept of disorder. RDoC offers nothing to replace the DSM/ICD efforts to delineate the domain of disorders and provide a target at which construct validation can aim. DSM/ICD provides the only thoughtful guidance to what conditions the RDoC must explain in terms of malfunctioning circuits.

RDoC pays inadequate attention to context. RDoC's grid includes environmental influences, but by this RDoC means environmental risk factors like early traumas or disturbed attachment relations that influence the trajectory of disorder development. Nowhere in the RDoC grid is there adequate recognition that human psychological mechanisms are biologically designed to respond sensitively to the social and environmental context. No diagnostic scheme can be valid without building ample contextual references into diagnostic criteria, as does the DSM (3).

RDoC is confused about which of two meanings of "etiology" is pertinent to disorder diagnosis. Ultimately, etiology individuates disorders. This is why, when multiple etiologies are discovered in formerly unified diagnostic entities, they divide into several disorders, as in recent developments regarding breast cancer. But, what is an etiology? In the context of mental disorder, "etiology" is ambiguous, having a broader and narrower meaning (4). In the broad sense, "etiology" refers to the causal story by which a disorder comes about. Such causal histories can encompass anything that led to the disorder, including risk factors, environmental events, common genetic variations, and other factors that are not in themselves disordered but were part of the pathway that led to the disorder. As indicated in its grid, RDoC studies the entire developmental trajectory that leads to disorder, adopting what I call a "kitchen sink"