entering the psychiatrist's office present with their phenotype and not with their genotype or biosignature. It is unlikely that making diagnostic sense of their stories would ever evade the necessity of a first-line, sound phenomenological approach and assignment of a categorical, rule-based diagnosis to be followed by a referral for laboratory investigations and a treatment plan – both supported by the best available evidence. Thus, both categories and dimensions are likely to continue co-existing as two sides of the same coin, reminiscent of the “particle-wave” paradigm in physics. The utility of any future versions of DSM/ICD will therefore depend on the extent to which they deliver non-trivial information about prognosis, likely treatment outcomes and/or testable propositions about biological and social correlates (7,8).

Second, there is at present a huge explanatory gap in genetic research between findings of statistical associations of common genomic variants with particular disorders, symptoms or traits and the demonstration of causality. Considering that the vast majority of such associations have minuscule effect sizes, recent data suggest that many hundreds of genes make statistically significant but minor contributions to the estimation of disease risk. It remains uncertain if rare variants, such as copy number variations, “private” point mutations and genomic sequences, would provide in the individual case more than a probabilistic assessment of risk rather

than a deterministic aetiological *causa prima* of the disorder. In contrast, future refined neurophysiological measurements and neuroimaging are more likely to yield reliable endophenotypes and biomarkers, thus being of pragmatic utility in the evaluation of patterns of individual pathogenesis.

Lastly, the present five domains of the RDoC framework require conceptual enrichment in at least two of its components. The “self-representation areas” need further elaboration to include disorders of self-awareness which are at the core of psychotic disorders (schizophrenia, acute transient psychotic disorders), as well as of neurological disorders such as temporal lobe epilepsy with complex partial seizures: depersonalization and derealization experiences, identity confusion, thought interference, ambivalence and loss of the sense of agency (9). Furthermore, common symptoms, such as auditory hallucinations, are complex and heterogeneous and need to be decomposed into several phenomenological features, each mapping onto a range of cognitive and social processes (10).

In conclusion, notwithstanding such caveats, the RDoC will provide a “road-map” towards a better understanding of the pathophysiology and pathogenesis of mental illness by integrating knowledge across different fields of research and lead the way to improved diagnosis and treatment. Its focus should not only be on what neuroscience and genetics can offer, but even more on the interac-

tion between biological, psychological and social research.

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The journey from RDC/DSM diagnoses toward RDoC dimensions

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Successive revisions of the DSM and the ICD have served to improve reliabil-

ity of psychiatric diagnoses. In particular, the development of the Research Diagnostic Criteria (RDC, 1) led to the major revisions in DSM-III toward this goal. However, these classifications continue to suffer from heterogeneity within disorders, blurred boundaries between disorders, frequent use of “not-otherwise specified” (NOS) cate-

gories, and high levels of comorbidity. All these have served to limit clinical utility. Importantly, validity, the holy grail of psychiatric classification, remains elusive, and accounts for the lack of biomarkers for diagnosis in psychiatry (2).

Heterogeneity is not unique to psychiatry; many common medical disor-

ders are heterogeneous, with diverse risk factors and complex pathophysiology (e.g., hypertension, non-insulin dependent diabetes (NIDDM)). However, the latter group of disorders is not ensnared in debates such as those seen in psychiatry, because biological measures known to be relevant to the disorder are now available for clinicians. It is not surprising that some patients with NIDDM develop kidney failure while others go blind and still others have coronary artery disease or need a lower extremity amputation, as long as glucose, insulin, or hemoglobin A1C levels can be measured to show that these are diverse presentations of the same underlying metabolic abnormality. Psychiatric neuroscience research seeks exactly these kinds of measure to aid in psychiatric classification. While there is no dearth of biomarkers in psychiatry, they simply lack specificity, because symptomatic diagnoses, such as DSM and ICD categories, are inadequate as gold standards to validate such biomarkers (2).

To address this impasse, Cuthbert (3) offers a visionary outline of the steps needed for psychiatry to march ahead in the difficult road from symptom-based typology toward a neuroscience-informed nosology using the Research Domains Criteria (RDoC) framework. The key goal for the field is how to transition from the current DSM classification (DSM-5) toward a neuroscience-based dimensional approach (4). The impressive advances in knowledge of neurobiology and genetics of psychiatric disorders in recent years makes this goal timely and offer unprecedented opportunities. In our view, some key steps are critically needed for such efforts to bear fruit.

The first is incorporating RDoC measures in clinical practice. The DSM-5 has made a significant, yet modest effort toward a dimensional approach by including cross-cutting symptom measures (Section III). This allows assessment of a comprehensive set of psychopathological domains (similar to the review of systems in medicine) that may or may not fit neatly into the diagnoses suggested by the presenting complaints. For example, cognitive impairment, one

of DSM-5's proposed dimensions of psychosis severity, is rated on a 0-4 scale based on extent of deviation from age appropriate norms. To rate this, the clinician would have to carry out a cognitive battery of assessments that include key domains such as working memory, verbal memory, attention, etc., already well known to be widely prevalent, persistent, and predictive of outcome in schizophrenia (5). Cognitive measures such as working memory are RDoC domains, and their neurobiological and genetic correlates are being worked out rapidly (6). Thus, we might already be in a position to incorporate some of the specific RDoC domains into the clinician's practice. However, DSM-5 did not go far enough (4), and includes a global cognitive measure only in an optional section of the manual. Thankfully however, DSM is a "living document", and hopefully the DSM and RDoC measures will synergize in the near future. Once implemented in clinical practice and field trials, such measures can provide dimensional data that can then be examined in relation to pathophysiological and etiological measures, thereby moving toward a neuroscience based classification.

As stated earlier, lack of validity remains the major limitation in the ICD/DSM approach to classification. A key direction to address this in future research is proposed by Cuthbert, i.e. to examine RDoC-like relationships between behavioral and neurobiological domains within a given DSM disorder, within and between related groups of disorders in the DSM/ICD metastructure. Pathophysiological and etiological (genetic and environmental) correlates of symptom domains across RDoC units of analyses elucidated in this way are then expected to pave the way toward etiologically based classification of mental disorders (7). However, etiopathology is only one of the key external validators toward a clinically meaningful classification; the clinician needs to be able to diagnose disorders that are sufficiently demarcated from each other, to characterize pre-morbid antecedents and predict natural course and outcome as well as treatment

response (8). The RDoC dimensions will therefore have to be mapped on to etiological, as well as clinical, outcome and treatment response validators in future research. We here outline some potential directions.

RDoC dimensions can potentially inform disease-related variations between individuals that map on to pre-morbid developmental trajectories better than symptom-based categories. Thus, it may be worth asking whether neurocognitive RDoC domains may better track with premorbid cognitive and learning disorders, while aberrations in positive or negative valence might more likely be associated with temperamental difficulties that suggest impaired affect regulation.

A useful research design for outcome prediction, for example, would be to longitudinally characterize RDoC domains in first episode psychosis patients across the DSM/ICD spectrum (schizophrenia, schizoaffective and psychotic affective disorders) and examine the DSM, RDoC dimension and interaction effects on putative outcome/treatment response measures (e.g., cognitive decline, persistent negative symptoms, lithium response). A similar design could be used in young relatives at risk for major psychotic disorders to see whether one can predict emergent psychosis, affective episodes, or both during follow-up in the critical risk period of adolescence.

Another potential value of the RDoC approach may be to help treatment response prediction to identify subgroups of patients within the same disorder who may respond differentially to one treatment over another. Thus, an impairment in one RDoC domain in schizophrenia such as working memory might indicate treatment with one approach such as cognitive remediation, while another RDoC domain alteration such as heightened negative valence might indicate a different approach, such as cognitive bias training. Identifying neuroscience based predictors and markers of treatment response might therefore be valuable.

A longitudinal approach to investigating RDoC domains can also resolve

the oft-stated problem of diagnostic stability, i.e. clinical diagnoses being not always stable over time (9). Neuroscience inquiry can provide convergent evidence about whether this instability is due to the inadequacy of our diagnostic system to capture disease presentation over time, or whether there is genuine evolution of disease presentation. Why clinical presentations change in the same patient over time is one of the many unsolved questions in our field where the neuroscience-based approach can supplement the work that has been done to date.

The goals of clinical and neuroscience based approaches to classification of psychiatric disorders are convergent. As these silos get broken down, time becomes ripe for the two traditions to come together. The road from RDC (and DSM) toward RDoC may be long,

but will have promise for the practice of psychiatry.

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The RDoC program: psychiatry without psyche?

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Cuthbert's dense synopsis of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) proposal (1) raises a lot of questions. I will restrict myself to a few, quite general, theoretical and psychopathological issues.

The RDoC proposes to develop "psychiatric nosologies based upon neuroscience and behavioral science rather than descriptive phenomenology", i.e. "based on dimensions of observable behavior and neurobiological measures". The RDoC's theoretical underpinning appears to be a neurocentric "type-type" reductionism: specific chunks (types) of mental life (e.g. hallucination, anhedonia) are identical with, or nothing else than, certain specific chunks (types) of neural activity (say, a certain configuration of interactions between dysfunctional neural networks). It is hard to follow the logic of

Cuthbert's assertion that the RDoC is *non-reductionistic* when he repeatedly emphasizes a "mechanistic understanding" as the RDoC's ultimate goal. "Type-type" reductionism is, of course, a legitimate theoretical position, but one that is far from being universally shared and is perhaps even obsolete (2).

There is no concern in the RDoC that biological reductionism, so successful in somatic medicine, may be confronting in psychiatry the complications of what philosophers call the "explanatory gap" (3), "the hard problem of consciousness" (4) or the defiant distinctiveness of the ontology (nature of being) and epistemology of human consciousness (5). These issues cannot be adequately addressed by an outright denial of "human exceptionalism" because of the genetic continuity between fruit flies and humans. The RDoC is programmatically silent on the issues of consciousness and subjective experience. Although acknowledging, *in passing*, that "verbal report" is the patient's primary gesture in a clinical context, the RDoC does not offer any suggestion on

the nature of psychopathological enterprise that is needed to decode the pathologies of subjectivity expressed through such "verbal report".

Cuthbert claims that conventional clinical concepts (e.g., post-traumatic stress disorder) are not "cohesive psychological constructs", but he fails to specify what a "cohesive" psychological (or biological) construct might be.

The etiological project in psychiatry presupposes a serious study of the *explanandum* itself, i.e., consciousness and its pathologies, because "without some idea... of what the subjective character of experience is, we cannot know what is required of... (reductive) theory" (6). The object of psychiatry is the patient's altered experience, expression and existence, associated with suffering in self and/or others. A psychiatrist treats a *person* and not a brain circuit. We will therefore continue to need a classification anchored in phenomenology, and into which the brain enters in so far that the neural pathology is diagnostically or therapeutically *relevant* to this suffering and not because