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.

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RDoC: a roadmap to pathogenesis?

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> "*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

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 "roadmap" 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 interaction 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 reliability 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) categories, 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-