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Clashing Diagnostic Approaches: DSM-ICD Versus RDoC

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Abstract

Since at least the middle of the past century, one overarching model of psychiatric classification has reigned supreme, namely, that of the *Diagnostic and Statistical Manual of Mental Disorders* and the *International Statistical Classification of Diseases and Related Health Problems* (herein referred to as DSM-ICD). This DSM-ICD approach embraces an Aristotelian view of mental disorders as largely discrete entities that are characterized by distinctive signs, symptoms, and natural histories. Over the past several years, however, a competing vision, namely, the Research Domain Criteria (RDoC) initiative launched by the National Institute of Mental Health, has emerged in response to accumulating anomalies within the DSM-ICD system. In contrast to DSM-ICD, RDoC embraces a Galilean view of psychopathology as the product of dysfunctions in neural circuitry. RDoC appears to be a valuable endeavor that holds out the long-term promise of an alternative system of mental illness classification. We delineate three sets of pressing challenges—conceptual, methodological, and logistical/pragmatic—that must be addressed for RDoC to realize its scientific potential. We conclude with a call for further research, including investigation of a rapprochement between Aristotelian and Galilean approaches to psychiatric classification.

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INTRODUCTION

I can calculate the motion of heavenly bodies, but not the madness of people.

—Sir Isaac Newton

In a classic article, Lewin (1935) contrasted two approaches to apprehending the state of nature. The Aristotelian view conceptualizes different entities in the world as underpinned by qualitatively different essences. Rocks and feathers fall at different rates, Aristotle supposed, because they are composed of fundamentally different “stuff.” In contrast, the Galilean view regards diverse entities as underpinned by similar underlying causal forces. For Lewin, the slow but steady march of science has been characterized by a transition from Aristotelian to Galilean modes of thinking. As our knowledge of the world has grown, we have come to recognize that similar causal variables underpin the actions of seemingly disparate phenomena.

The approach enshrined in recent editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and the *International Statistical Classification of Diseases and Related Health Problems*

(ICD), which we heretofore dub the DSM-ICD model, adopts—at least implicitly—an Aristotelian model of categorization (Carson 1996). In this approach, which has been dominant in American psychiatry over at least the past half century, disorders are presumed to constitute largely discrete entities: They are commonly assumed to differ qualitatively from normality and from each other. For example, the influential framework for the validation of mental disorders advanced by Robins & Guze (1970) delineated five criteria for ascertaining whether a diagnostic entity is genuine. Among them was the “delimitation [of the disorder] from other disorders” (p. 108), the assumption being that a diagnosis that overlaps extensively with others is of doubtful validity.

DSM-ICD and Kraepelin: Hints of a Paradigm Shift

The reigning DSM-ICD approach is frequently referred to as neo-Kraepelinian (Blashfield 1984) in recognition of the contributions of the German systematist Emil Kraepelin, who initially believed that superficially similar mental disorders, such as dementia praecox (now termed schizophrenia) and manic depression (now termed bipolar disorder), could be differentiated by a detailed documentation of their (a) signs (observable manifestations), (b) symptoms (subjective reports), and (c) natural history (trajectory over time). Kraepelin, following in the footsteps of Linnean botanists (Compton & Guze 1995), regarded different mental disorders as akin to differing species or subspecies that could be distinguished largely by their topography.

A key assumption of the neo-Kraepelinian approach is that signs and symptoms are often sufficient to differentiate mental disorders. Nevertheless, the history of medicine reminds us that this assumption may be unwarranted. For example, in the early twentieth century, physicians diagnosed dozens of different fevers—ranging alphabetically from blackwater fever to yellow fever—and distinguished them on the basis of other co-occurring signs and symptoms (Kihlstrom 2002). Today, physicians recognize that fever is a nonspecific indicator of a plethora of pathologies rather than a disorder per se, and they attempt to identify the etiology of the fever prior to initiating treatment.

Despite the enormous impact of the DSM on everyday research and practice, there are growing indications that its hegemony may at last be beginning to wane. Over the past several years, rumblings of what some have described as a paradigm shift (Fu & Costafreda 2013) or reboot (Kendler 2014) in psychiatric classification have become increasingly audible. Ironically, many scholars appear to have neglected the fact that, late in his career, Kraepelin (1920) expressed doubts regarding his now familiar distinction between dementia praecox and manic depression on the grounds that the overlap between these two conditions was too substantial: “We cannot satisfactorily distinguish between these two diseases. *The suspicion remains that we are asking the wrong questions*” (p. 527, italics added; see also Greene 2007).

Among the first responders to the call to ask the right questions, or at least better ones, has been the National Institute of Mental Health (NIMH) and its Research Domain Criteria initiative (RDoC; Insel et al. 2010). Though more of a promissory note than a formalized system at present, RDoC aims to develop a system of psychiatric classification based not on signs, symptoms, and course, à la Kraepelin, but instead on markers of psychobiological systems linked to adaptive—and maladaptive—functioning.

DSM AND ICD: ORIGINS AND ASSUMPTIONS

The history of the DSM and its revisions has been recounted in numerous sources (e.g., Lieberman & Ogas 2015, Lilienfeld et al. 2014, Widiger & Clark 2000, Wilson 1993), so we reprise it only briefly here. In response to the perceived shortcomings of the first two DSMs, especially their

often vague diagnostic descriptions and the low, or at best modest, interrater reliabilities of their diagnostic categories, the American Psychiatric Association, with Robert Spitzer at the helm, released the third edition of DSM in 1980 (DSM-III; Am. Psychiatr. Assoc. 1980). DSM-III was influenced heavily by the seminal work of the psychiatric group at Washington University in St. Louis, which had introduced preliminary diagnostic criteria and algorithms (decision rules) for 14 major mental disorders in the early 1970s (Feighner et al. 1972). The more immediate precursor of DSM-III was the Research Diagnostic Criteria (RDC; Spitzer et al. 1978), which delineated criteria and algorithms for approximately 20 major diagnostic categories, along with subtypes within several of these categories.

Like the Feighner and RDC criteria, DSM-III was considerably more neo-Kraepelinian than its DSM predecessors (Compton & Guze 1995), as it emphasized the differentiation of conditions on the basis on their signs, symptoms, and natural history. In accord with its neo-Kraepelinian emphasis, DSM-III provided users with (*a*) standardized diagnostic criteria and (*b*) algorithms for each diagnosis. Rather than merely describing each diagnosis, as DSM-I (Am. Psychiatr. Assoc. 1952) and DSM-II (Am. Psychiatr. Assoc. 1968) had done, DSM-III delineated the specific signs and symptoms comprising each diagnosis and the method by which they needed to be combined to establish it. In this way, it almost certainly boosted the interrater reliability of most diagnostic categories, although some critics have maintained that these increases were modest at best (Kirk & Kutchins 1992). Although DSM-III-R (Am. Psychiatr. Assoc. 1987) and DSM-IV (Am. Psychiatr. Assoc. 1994) introduced changes to many diagnoses, they retained DSM-III's basic structure and format.

In an effort to accommodate novel evidence that had emerged in the wake of the second millennium, DSM-5 (Am. Psychiatr. Assoc. 2013), spearheaded by David Kupfer and Darrel Regier, was published in May of 2013 amid a host of searing criticisms, many of which centered on alterations to a number of diagnostic categories in the absence of adequate data (see Frances & Widiger 2012). Although the early phases of planning for DSM-5 were rife with speculations regarding drastic changes in its content and structure, such as a heightened focus on neuroscientific markers or the inclusion of a dimensional system for personality disorders (Skodol et al. 2011), DSM-5 by and large retained the principal format of DSM-IV as well as most of its major diagnoses. Although DSM-5 is the predominant system of psychiatric classification around the world, chapter V of the tenth revision of ICD (ICD-10) of the World Health Organization (1992) (which is similar to the DSM in most important respects) is a neo-Kraepelinian alternative to DSM-5 that has been adopted in numerous countries outside of the United States. ICD-11 is under construction as of this writing.

The hue and cry regarding the most controversial changes in DSM-5, such as the deletion of the bereavement criterion for major depressive disorder (MDD) or the jettisoning of hypochondriasis as a diagnosis (Frances 2013), may have obscured a deeper point. With the potential exception of (*a*) the inclusion of dimensional scales to capture the functioning and impairment associated with major mental disorders and (*b*) the inclusion of a hybrid prototype-dimensional model for personality disorders, both of which appeared in section III ("Emerging Measures and Models"), DSM-5 was every bit as neo-Kraepelinian as its predecessors.

DSM-ICD Successes

Extreme skeptics of the DSM-ICD system (e.g., Greenberg 2013) have at times argued that this approach has yielded categories with negligible validity. Similarly, in a widely publicized blog post announcing the shift of the NIMH toward RDoC, NIMH Director Thomas Insel (2013) wrote that the DSM's "major weakness is its lack of validity."

The assertion that DSM categories lack validity paints with too broad a brush. Many DSM categories, such as major depression, panic disorder, bipolar disorder, and schizophrenia, display at least some construct validity, as demonstrated by consistent relations with laboratory indicators, biological correlates, natural history, and family history. For example, although the DSM diagnosis of schizophrenia almost surely encompasses a heterogeneous mélange of overlapping conditions, this diagnosis is associated with certain external correlates, such as smooth pursuit eye movement dysfunction, ventricular enlargement, a chronic and frequently relapsing course, and a family history of schizophrenia among biological relatives (e.g., Tsuang et al. 2000).

Moreover, the development of lists of empirically supported therapies—psychological treatments that have been demonstrated to be efficacious for specific disorders (e.g., cognitive-behavioral therapy for major depression, panic control treatment for panic disorder; Chambless & Ollendick 2001)—is a testament to the treatment validity (Hayes et al. 1987) of at least some DSM-ICD categories. If the DSM and ICD were entirely devoid of validity, one could not identify psychological interventions that are differentially efficacious for different conditions (Garb et al. 2009; but see Inadequate Treatment Validity section). Moreover, by providing researchers and clinicians with a *lingua franca* for facilitating diagnostic communication, the DSM has accelerated scientific progress regarding the correlates, etiology, and treatment of mental disorders (see also Kendell 1975).

DSM-ICD Anomalies

At the same time, it has become evident that the DSM-ICD approach has been beset by a growing number of anomalies (Lilienfeld 2014b), many of which have not been adequately resolved across DSM editions. We touch on the most noteworthy anomalies here.

Scientifically arbitrary diagnostic cut-offs. The DSM is technically agnostic with regard to whether its conditions are categorical (taxonic) or dimensional in nature. Still, the DSM adopts a categorical approach as a working model for measurement purposes. This model is debatable for two major reasons. First, taxometric studies, which allow investigators to ascertain whether an observed distribution can be decomposed into two or more independent distributions (Meehl & Golden 1982), indicate that most DSM conditions, including the lion's share of mood, anxiety, eating, personality, and externalizing disorders, appear to be underpinned by one or more dimensions. The potential exceptions are schizophrenia spectrum disorders, autism spectrum disorders, and some substance use disorders (Haslam et al. 2012). The absence of a point of rarity (Sneath 1957) demarcating most DSM conditions from normality raises questions regarding the Aristotelian assumption of discrete conditions. Second, even if some DSM conditions are taxonic, this would not justify the imposition of a categorical measurement model. Such a model decreases reliability and validity relative to a dimensional model because it forfeits valuable psychometric information (Markon et al. 2011). Even for taxonic variables, dimensional measures almost always provide more sensitive indicators than do categorical measures, as they offer information regarding individuals' proximity to the natural cut point.

Heterogeneity. The polythetic model of DSM-III-R and later DSM editions, sometimes derided as the "Chinese menu" approach, provides criteria that are neither singly necessary nor jointly sufficient for a diagnosis. This model has generated marked phenotypic heterogeneity. As a particularly extreme example, in DSM-5 there are 636,120 ways to meet criteria for posttraumatic stress disorder (Galatzer-Levy & Bryant 2013). Although phenotypic heterogeneity does not necessarily imply etiological heterogeneity, it seems unlikely that two conditions that overlap minimally in

their expression would stem from similar, let alone identical, causal influences. In addition, such heterogeneity renders the search for etiological agents more challenging (for a discussion of this issue with respect to MDD, see Monroe & Anderson 2015).

Comorbidity. An ideal taxonomy yields categories that are largely mutually exclusive (Frances 1980). Yet across its multiple editions, the DSM has been bedeviled by the vexing problem of comorbidity, a term coined by Feinstein (1970) to denote the co-occurrence of two or more putatively distinct conditions. For example, in the Australian National Survey of Mental Health and Well-Being, 21% of participants with one DSM-IV disorder met criteria for three or more DSM-IV disorders (Andrews et al. 2002); comparable data derive from the United States National Comorbidity Study (Kessler et al. 1994). In one especially extreme case, a participant in a research study simultaneously met criteria for all 10 DSM-IV (and DSM-5) personality disorders (Lilienfeld et al. 2014)!

In the eyes of many authors, the presence of rampant comorbidity is a red flag that the DSM is not drawing the correct diagnostic borders. Other authors (e.g., Maj 2005) go further, suggesting that such comorbidity reflects the propensity of the DSM to attach different names to slightly different manifestations of a shared predisposition, an error known as the jangle fallacy (Block 1995). For example, most personality disorders appear to be complex constellations or configurations of normal-range personality dimensions (e.g., antagonism, low conscientiousness, introversion; Widiger & Trull 2007). Hence, it is hardly surprising that many of these conditions, such as narcissistic and borderline personality disorders, display substantial covariation.

Large number of intermediate cases. An optimal classification system also consists of categories that yield few intermediate cases (Frances 1980). Yet for most major classes of psychopathology, one of the most frequent diagnoses is NOS (not otherwise specified), meaning that most patients with mental disorders do not fit into any extant category (Stein et al. 2000, Westen 2012). Such patients must be diagnosed by means of a “wastebasket category” that encompasses individuals who are clearly disordered but whose signs and symptoms do not meet criteria for any extant diagnosis. For eating disorders, NOS has typically been the modal diagnosis in routine clinical settings (Fairburn & Bohn 2005); in unstructured interview studies of personality disorders, NOS is similarly the most frequent diagnosis (Verheul & Widiger 2004).

The high prevalence of NOS diagnoses probably derives from what Hyman (2010) termed the “problem of overspecification” (p. 166). For diagnoses, the DSM and ICD prescribe strict criteria and algorithms that almost certainly exclude many individuals who suffer from the same dysfunction as do most individuals within the category, but who fall barely short of the diagnostic threshold. For example, an individual in a study who met all criteria for DSM-5 MDD but whose episode lasted only 12 days (rather than the required two weeks) would be precluded from receiving a formal diagnosis of MDD. Nevertheless, it is unlikely that this person differs fundamentally from most people with MDD.

Inadequate treatment validity. As also noted previously, the presence of lists of empirically supported therapies suggests that at least some DSM categories possess treatment validity and clinical utility (Garb et al. 2009). Nevertheless, the linkage between diagnosis and treatment is not nearly as tight in psychiatry as in other domains of medicine. Increasing data suggest that although at least some treatment specificity exists (Lilienfeld 2014a), common factors—those that cut across most or all efficacious treatments—account for hefty chunks of variance in therapeutic outcomes (Laska et al. 2014). More broadly, the DSM era has not borne witness to large-scale reductions in the morbidity or mortality associated with major mental disorders, nor to decreases

in suicide rates. These sobering facts stand in stark contrast to sharp declines in the death rates associated with heart disease, stroke, cancer, and many other medical disorders (Insel 2009). It would be unfair to attribute all of the lack of progress in diminishing psychiatric morbidity and mortality to our contemporary system of classification. Nevertheless, this state of affairs raises the distinct possibility that fresh approaches to classification will be needed to achieve intervention breakthroughs.

Genetic and environmental nonspecificity. If DSM-ICD conditions were largely distinct, as would be expected from a neo-Kraepelinian framework, one might anticipate that their genetic and environmental architecture would similarly be largely distinct. Yet the more we learn about most DSM conditions, the more apparent it becomes that many of the influences impinging on them are nonspecific. For example, one recent genome-wide association study revealed that many single nucleotide polymorphisms (SNPs) of small effect contribute to risk for five mental disorders traditionally deemed to be etiologically disparate, namely schizophrenia, bipolar disorder, MDD, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder. For instance, the genetic correlation of SNPs in schizophrenia and bipolar disorder was 0.68 (Cross-Disord. Group Psychiatr. Genom. Consort. 2013). The genetic overlap in this study is especially striking given that several of these disorders (e.g., ADHD and schizophrenia) display little overt phenotypic resemblance.

Similarly, there is compelling evidence for substantial environmental nonspecificity in the etiology of mental disorders. For example, even after controlling statistically for childhood adversity, childhood sexual abuse has emerged as a modest nonspecific antecedent, and perhaps a causal risk factor, for a host of different mental disorders, including multiple mood, anxiety, and substance use disorders (Molnar et al. 2001). Although not undermining the possibility of some disorder specificity, these findings pose a challenge to the assumption that DSM-ICD conditions are associated with distinct specific etiologies (for a discussion of specific etiology, see Meehl 1977).

DSM-ICD Anomalies: Taking Stock

The anomalies we have reviewed reveal that all is not well with the scientific health of the DSM. With each new DSM edition, concerted efforts have been directed to attempting to salvage the essence of the neo-Kraepelinian framework by invoking a variety of ad hoc maneuvers, such as removing, adding, or revising diagnostic criteria; changing thresholds or age of onsets for diagnoses; adding new diagnoses or removing others; adding new disorder subtypes; and adding or removing hierarchical exclusion rules (which prohibit certain conditions from being diagnosed if they appear to be attributable to another condition). Yet repeated attempts to nibble around the edges of the DSM anomalies across editions of the manual have met with at best limited success. In the words of Kendler (2014), the DSM may have found itself in a box canyon: a deep gorge from which it cannot extricate itself. If so, small-scale revisions to the DSM-ICD, or, in the lingo of Lakatos (1978), modifications to the auxiliary hypotheses of the DSM-ICD research program, are unlikely to remedy its core shortcomings. In reacting to the lack of substantial scientific progress in the DSM-ICD research program, a growing chorus of critics has argued that this approach has failed to carve nature at its joints, to borrow Plato's hallowed phrase (see Gangestad & Snyder 1985).

The view that the DSM-ICD model is defective beyond repair is by no means new. In 1989, British psychiatrist R.E. Kendell (see also Widiger & Trull 2007) wrote:

Ninety years have now elapsed since Kraepelin first provided the framework of a plausible classification of mental disorders. Why then, with so many potential validators available, have we made so

little progress since that time? . . . One important possibility is that the discrete clusters of psychiatric symptoms we are trying to delineate do not actually exist. (Kendell 1989, p. 313)

Ironically, a similar alarm call was sounded 13 years later by the two principal architects of DSM-5: “Research exclusively focused on refining DSM-defined syndromes may never be successful in uncovering their underlying etiologies. For that to happen, an as yet unknown paradigm shift may need to occur” (Kupfer et al. 2002, p. xix). RDoC may be heralding the leading edge of this very paradigm shift.

RDOC: INTELLECTUAL ANTECEDENTS

Many of the intellectual precursors of RDoC can be traced to early successes in the biomedical sciences, which unearthed the etiology of what we now recognize as physical disorders masquerading as mental disorders (Schildkrout 2014). At the same time, many of the enduring failures of this approach to traditional mental disorders, such as schizophrenia, imparted valuable sobering lessons that were to inform RDoC.

Laboratory Methods in Medicine

It is easy to forget that by the middle or even the end of nineteenth century, medical diagnosis, much like modern-day psychiatric diagnosis, was based almost exclusively on a combination of careful history taking from patients and a physical examination, an approach known as bedside medicine (Ackerknecht 1967). Medical tests began to be introduced in the eighteenth and nineteenth centuries, with use of the stethoscope, ophthalmoscope, and laryngoscope becoming routine in medical examinations by the 1850s (Kihlstrom 2002). Nevertheless, it was not until the twentieth century that laboratory tests became de rigueur for diagnosing many medical conditions (Burke 2000). The examination of cerebrospinal fluid to detect meningitis emerged around the turn of the twentieth century, and the Wassermann test for the detection of syphilis was developed in 1906 (Berger 1999). Today, over 3,000 standardized laboratory tests are used in standard medical practice (Kapur et al. 2012).

Early Triumphs in Psychopathology Research

The laboratory revolution in medicine led to two sensational triumphs in the psychopathology domain. Specifically, medical science demonstrated that two conditions long presumed to be largely or entirely psychogenic, namely general paresis and pellagra, were of purely organic etiology. General paresis, also called general paralysis of the insane, accounted for 5% to 10% of hospital admissions around the turn of the century (Tsay 2013). Its primary psychological features included delusions, grandiosity, euphoria, concentration difficulties, and poor impulse control. In 1913, Hideyo Noguchi and J.W. Moore isolated the syphilis spirochete (*Treponema pallidum*) in the brains of patients with general paresis, demonstrating that the condition was an outcome of tertiary syphilis, in which the bacterium had invaded the central nervous system. Individuals suffering from pellagra, whose symptoms included irritability, depression, insomnia, paranoia, confusion, and memory problems, were also common fixtures in inpatient psychiatric hospitals around the turn of the twentieth century. Research later showed this condition to be a consequence of niacin deficiency (Sartorius 1993).

The discovery of the medical causes of general paresis and pellagra were justifiably hailed as triumphs of biomedicine, especially because they promptly led to effective treatments (penicillin

and niacin, respectively). Coming as they did against the backdrop of the discovery of Mendelian genetics and the germ theory of disease, they encouraged several generations of psychopathology researchers to believe that other major mental disorders, such as schizophrenia, bipolar disorder, and obsessive-compulsive disorder, would similarly be traceable to a single etiological agent (Kendler & Schaffner 2011). In many respects, however, these successes were misleading. In the case of schizophrenia, dozens if not hundreds of candidates for the “schizochete” (Neimark 2009)—a presumably unique biological cause of the disorder, such as dopamine hyperactivity, a dominant gene, or hypofrontality—were proposed over the years. Yet this “single bullet” approach ultimately failed, almost surely because the causes of these disorders are exceedingly multifactorial (Kendler 2005). This approach also foundered because these causes are not unique to schizophrenia but rather are shared across numerous DSM-ICD disorders. This belated realization was almost certainly one of many catalysts for the transdiagnostic approach embraced by RDoC.

Biological Markers

The appreciation of multifactorial causality notwithstanding, the 1970s and 1980s saw keen interest in the identification of biological markers for psychopathology (Iacono 1985). Sophisticated thinkers viewed these markers not as akin to the spirochete that causes general paresis but rather as fallible but nonetheless useful indicators that could assist in etiological and perhaps diagnostic efforts. For example, the early 1980s bore witness to the development of the dexamethasone suppression test (DST), an indicator of cortisol reactivity, to assist in the diagnosis of endogenous depression (Carroll 1982); the discovery of reduced rapid eye movement latency as an indicator of major depression (Kupfer et al. 1978); and the development of measures of smooth pursuit eye movement dysfunction (Iacono et al. 1981) as an indicator of schizophrenia.

Nevertheless, the much-vaunted search for biological markers, which continues apace today, has met with, at best, qualified success. Although some of these putative markers offered fruitful leads to etiology, no marker displayed sufficiently high levels of both sensitivity and specificity (as well as positive and negative predictive power) to qualify as proxies for research diagnoses, let alone as screening or laboratory tests for routine clinical use (Insel 2014, Kapur et al. 2012). For example, although the DST displayed reasonably high sensitivity for endogenous depression, its specificity was often poor, reflecting high levels of false positive identifications among patients with schizophrenia, alcoholism, anxiety disorders, and dementia (Coppen et al. 1983). As a consequence, a state of disenchantment regarding the DST and other biological markers gradually set in. As of today, the lone laboratory-based biological tests in the DSM are for a subset of sleep disorders, such as assay-based measures of hypocretin levels for narcolepsy (Am. Psychiatr. Assoc. 2013), and even these tests are hardly infallible.

Nevertheless, it has long been unclear whether the failure to detect highly sensitive and specific markers of mental disorders reflected on the failure of the biological strategy per se rather than on the gross imprecision of diagnostic phenotypes themselves. As the twentieth century drew to a close, researchers were increasingly placing their bets on the latter.

The Slow Progress of Psychopharmacology

Another impetus for RDoC has been the lack of progress in the psychopharmacology industry over the past few decades. The 1950s, which were marked by the explosive growth of psychopharmacology, witnessed the discovery of the first tricyclic antidepressant, imipramine (Tofranil), the first monoamine oxidase inhibitor, iproniazid (Marsilid), the first benzodiazepine, chlordiazepoxide (Librium), and the first antipsychotic medication, chlorpromazine (Thorazine; see Lopez-Munoz

& Alamo 2009). The next two to three decades were awash in the development of scores of variants (knockoffs) of these medications.

Yet for reasons that are still poorly understood, progress in psychopharmacology began to slow to a crawl. Although the advent of selective serotonin reuptake inhibitors in the 1980s and atypical antipsychotic medications in the 1990s substantially ameliorated the problematic side effect profiles of major classes of psychiatric drugs, little evidence indicates that these new classes of medications contributed to marked enhancements in therapeutic efficacy (Anderson 2000, Chakos et al. 2014). As another example, recent enthusiasm concerning the potential of glutamate antagonists for schizophrenia gave way to disillusionment in the wake of several failed clinical trials (Zink & Correll 2015). In 2011, two premier drug companies, AstraZeneca and GlaxoSmithKline, announced that they were terminating their search for new psychiatric medications in light of the bleak outlook for major discoveries (Cowen 2011), and other firms may soon be following suit. Although some of the lack of progress may stem from failures of innovation and risk taking in the psychopharmacology industry, much of it may also derive from the fact that the disorder phenotypes afforded by DSM-ICD are too crude and heterogeneous to afford effective medication targets.

Precision Medicine

A final intellectual crosscurrent that informed RDoC was the emergence of precision medicine, sometimes also called personalized medicine, a new branch of medicine that strives to harness the power of clinical-pathological laboratory measures, such as genetic tests, to tailor treatments to individuals (Mirnezami et al. 2012). For example, researchers have developed a targeted drug treatment for a small subset (4%) of patients with cystic fibrosis who possess a specific mutation (Insel 2014). Similarly, the treatment of breast cancer has been revolutionized by the development of onco-type testing, permitting physicians to move from a one-size-fits-all intervention approach to treatment geared to specific genetic profiles (Aftimos et al. 2014). The coming era of precision medicine has stirred hopes for a similar revolution in psychiatry and clinical psychology.

THE BIRTH OF RDOC: FUNDAMENTAL PRESUPPOSITIONS AND STRUCTURE

In many ways, RDoC has DSM to thank for its birth. During his tenure as NIMH director, Steven Hyman expressed his concern at seeing preclinical researchers striving to develop animal models that mimicked DSM-based diagnostic criteria. As Hyman put it, “The DSM system . . . created an unintended epistemic prison that was palpably impeding scientific progress. . . . Even animal studies that purported to develop disease models . . . were often judged by how closely they approximated DSM disorders” (Hyman 2010, p. 157). Under Hyman’s successor, Thomas Insel, the NIMH sought to develop a new framework for organizing research that could liberate clinical and translational researchers from the epistemic prison of DSM criteria. The primary concern was not that the DSM criteria lacked validity or utility for clinical practice; rather, the issue centered on whether the de facto wholesale appropriation of DSM criteria by the research community was impairing the elucidation of pathophysiology. In this sense, the birth of the RDoC initiative can be seen as inextricably linked to the NIMH’s growing emphasis on translational neuroscience to guide research priorities.

So-named as an homage to the RDC, the RDoC was formally launched in 2009 as a bold initiative to transform the current framework of psychiatric classification into an explicitly biological system (Cuthbert 2014a,b; Insel et al. 2010; Sanislow et al. 2010). RDoC’s aim is ambitious: to inaugurate nothing short of a paradigm shift in descriptive psychiatry. Rather than base psychiatric

diagnosis on presenting signs and symptoms, as do DSM and ICD, RDoC strives to anchor psychiatric classification and diagnosis in a scientifically supported model of neural circuitry. RDoC conceptualizes mental disorders as dysfunctions in brain systems that bear important adaptive implications, such as systems linked to reward responsiveness and threat sensitivity (see also Harkness et al. 2014).

An RDoC Primer

In a widely discussed and controversial blog posting issued several weeks prior to the release of DSM-5, then-NIMH Director Thomas Insel (2013) staked out a bold claim for RDoC: “NIMH will be reorienting its research away from DSM categories. Going forward, we will be supporting research projects that look across current categories—or subdivide current categories—to begin to develop a better system.” Nevertheless, in subsequent communications, Insel made clear that NIMH would continue to fund grants that included data on DSM categories, but that it would prioritize those that emphasized transdiagnostic etiological processes.

At least for the foreseeable future, RDoC is not envisioned as a system of psychiatric classification in its own right. Instead, in the near term, RDoC and DSM-ICD are expected to coexist. Nevertheless, RDoC is intended to provide scaffolding for a large-scale research program that will ultimately yield an alternative to DSM-ICD (MacDonald & Krueger 2013).

RDoC adopts no a priori stance on what form a new model of classification will eventually take (Insel 2014). In the words of a recent NIMH director and his colleagues, RDoC is “a vision for the future” (Insel et al. 2010, p. 749) rather than a fleshed-out proposal. As of this writing, RDoC is largely fluid in its mission. Such flexibility is probably justifiable in the early phases of scientific investigation, in which hypothesis generation (the context of discovery) should often take precedence over hypothesis testing (the context of justification; Kell & Oliver 2004).

Still, the RDoC research program is not entirely open-ended. RDoC provides researchers with an explicit rubric for guiding investigations. As can be seen in **Figure 1**, RDoC proposes that research efforts be conducted within a two-dimensional matrix (Morris & Cuthbert 2012, Weinberger & Goldberg 2014). This matrix took shape following a series of workshops held over an 18-month period that involved panels of experts in different domains of neural circuitry. On the horizontal axis are seven units of analysis organized roughly from more to less “basic”: genes, molecules, cells, circuits, physiology, behavior, and self-reports (the matrix also includes a column for paradigms, allowing investigators to indicate which tasks are useful for the research question at hand). On the vertical axis are five broad domains/constructs that correspond to brain-based circuits deemed relevant to psychopathology: negative valence systems (e.g., threat, loss), positive valence systems (e.g., approach motivation, responsiveness to reward), cognitive systems (e.g., attention, working memory), systems for social processes (e.g., theory of mind, dominance), and arousal/regulatory systems.

RDoC rests on several assumptions, four of which are especially crucial (Cuthbert & Insel 2013). First, RDoC is explicitly transdiagnostic in seeking markers of dysfunctional psychobiological circuitry that transcend multiple traditional disorder categories; in this respect, it is Galilean in its presuppositions. Second, RDoC is translational in emphasis, encouraging researchers to apply the basic science of brain systems and behavior to an understanding of mental disorders. Third, RDoC adopts a dimensional framework in light of evidence that the activity of most brain circuits, such as reward and threat systems, is continuously distributed, with few or no clear-cut boundaries demarcating normality from abnormality. Fourth, RDoC strives to accord roughly equal weight to different levels of analysis, including the biological and behavioral (Cuthbert & Insel 2013).

Domains/constructs	UNITS OF ANALYSIS							Paradigms
	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-reports	
Negative valence systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive valence systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for social processes								
Imitation; theory of mind								
Social dominance								
Facial expression identification								
Attachment/separation fear								
Self-representation areas								
Arousal/regulatory systems								
Arousal and regulation (multiple)								
Resting state activity								

Figure 1

The provisional matrix for the Research Domain Criteria (RDoC).

Consistent with the view of science as a self-correcting enterprise, RDoC is conceptualized as provisional and open to revision in light of new scientific data. As a consequence, novel brain-based constructs may be added to the matrix with the emergence of new neuroscience evidence.

The Scientific Promise of RDoC

As of this writing, there is justifiable excitement in many quarters regarding RDoC's scientific potential. RDoC has already begun to loosen the longstanding grip of the DSM-ICD system over research and grant funding. This hegemony has stifled investigators' capacity to explore scientifically promising alternatives to the status quo model of psychiatric classification (see also Berenbaum 2013, Harkness & Lilienfeld 2013, Markon 2013). Moreover, RDoC's adoption of a dimensional approach to psychopathology as a starting assumption accords with the bulk of the evidence derived from taxometric studies, which suggests that most conditions are underpinned by dimensions rather than by taxa, that is, natural categories (Haslam et al. 2012). In this respect, RDoC is more consistent with data on the latent structure of mental disorders than is the DSM. At the same time, RDoC allows for the possibility of threshold effects (tipping points) or other categorical effects (Cuthbert & Insel 2013), whereby certain psychopathological phenomena differ qualitatively rather than quantitatively from normality.

Furthermore, RDoC promises to capitalize on the burgeoning corpus of knowledge concerning affective and cognitive neuroscience by applying it to the classification of mental disorders. In this respect, it may ultimately allow for closer linkages between assessment and diagnosis, on the one hand, and treatment and prevention, on the other. More ambitiously, RDoC may eventually shift psychiatry and clinical psychology closer to the goal of precision medicine (Insel 2014), or at least the more modest goal of stratified medicine, in which interventions are tailored to individuals within well-defined subgroups demarcated by laboratory-based profiles (Kapur et al. 2012). With the enormous recent influx of research attention and grant funding to RDoC, there is renewed hope of uncovering laboratory-based assays with high levels of sensitivity and specificity for the proximal pathological processes that contribute to psychopathological signs and symptoms.

In all of these respects, RDoC appears to be a valuable alternative to the current approach to classification, especially given that the DSM-ICD's scientific yield, which has been substantial despite its noteworthy defects (Regier et al. 2009), appears to be reaching an asymptote. We regard RDoC as holding out the promise of generating a competing, and ideally more valid, system of classification relative to that of DSM-ICD. At the same time, RDoC confronts a number of challenges, many of which have received short shrift in ongoing discussions (but see Berenbaum 2013, Lilienfeld 2014b, Shankman & Gorka 2015).

In the following section, we examine three overarching sets of challenges to RDoC: (*a*) conceptual, (*b*) methodological, and (*c*) practical/logistical (see also Lilienfeld 2014b). Although there is overlap among these three sets of challenges, we differentiate them for expository purposes. Given that we intend to be constructive, we devote considerably more space to RDoC's potential weaknesses than to its potential strengths. Nevertheless, this differential space allotment should not be construed as implying that we view RDoC's weaknesses as outweighing its strengths. To the contrary, we focus on these weaknesses in the hope that researchers and theorists, including RDoC's architects, will pay them greater heed and thereby increase the likelihood that RDoC will bear scientific fruit. Because we do not perceive any of these challenges as insurmountable, we hope that our delineation of them plays a role in shaping the future direction of RDoC.

RDOC: CONCEPTUAL CHALLENGES

Falsifiability

Popper (1959) famously argued that for a theoretical model to be scientific, it must be capable in principle of being proven wrong. Although few contemporary philosophers of science accept Popper's premise that falsifiability is the lone demarcation criterion separating science from non-science (Pigliucci & Boudry 2013), many concur that this feature is one key indicator of a model's scientific status. Moreover, Popper maintained that science ideally progresses by means of "severe" or "risky" tests (see also Meehl 1978), those that place theories at grave risk of falsification.

In the case of RDoC, it is not evident what findings would suggest that it is not mapping well onto the state of nature, or at least falling considerably short of its avowed goals. Nor is it entirely clear what would constitute "negative" findings—results that would indicate that RDoC is a flawed endeavor that is not leading to a feasible alternative model of classification. In our view, it is incumbent on RDoC's developers to lay out a set of provisional but explicit benchmarks by which its progress, or lack of progress, can be gauged.

In a related vein, it will be critical to address the question of whether RDoC, especially once it is better developed, is superior to the DSM-ICD model in predicting theoretically and pragmatically relevant external criteria, such as natural history and treatment response. Based on our conversations with current and would-be RDoC grantees, it is our impression that researchers submitting

proposals within the RDoC framework are being discouraged from pitting RDoC-relevant markers against DSM diagnoses in their capacity to predict such criteria. Such advice would be ill conceived, as it could hamper long-term efforts to ascertain whether RDoC is performing as well as, or ideally better than, the extant system.

A further issue that bears on the falsifiability of RDoC is the distinction between convergent and discriminant validity (Campbell & Fiske 1959, Cole 1987). The lion's share of RDoC research focuses on convergent validity, such as demonstrating that presumed markers are predictive of their hypothesized RDoC domains (Shankman & Gorka 2015). For example, it is useful to demonstrate that fear-potentiated startle is related to intrusive memories, and fear-related memories are associated with a traumatic event (Norrholm et al. 2014). This finding suggests that fear-potentiated startle is a valid indicator of the RDoC negative valence domain, especially its acute threat (fear) subconstruct. Nevertheless, it will be at least equally crucial to demonstrate that putative markers are not associated with, or at least are less associated with, nonhypothesized RDoC domains. For example, it will be important to show that fear-potentiated startle is largely unassociated with markers of the RDoC arousal/modulatory domain, which should theoretically be largely independent of fear, although it may be predictive of levels of baseline startle.

Potential Overemphasis on Biological Dysfunction at the Level of an Individual

RDoC posits that mental disorders are “disorders of brain circuits” (Insel et al. 2010, p. 749). As a corollary, RDoC presumes that “The tools of clinical neuroscience . . . can be used to identify dysfunction in neural circuits” (Morris & Cuthbert 2012, p. 33). At some level, this assumption is merely a truism given that all psychological disorders, and all psychological phenomena for that matter, must be mediated by the brain and the remainder of the central nervous system (Kendler 2005). Still, researchers who adopt the RDoC framework must be careful not to confuse biological mediation with biological etiology.

In the phraseology of Graham (2013), all mental disorders are *in* the brain, but are not necessarily *of* the brain. That is, at least some conditions regarded as mental disorders may stem from neural systems reacting more or less normally to harsh or extreme environmental input. Such reactions may be acute, such as rapid, overgeneralized fear responses to trauma, or gradual, such as the slow accumulation of glucocorticoid resistance and chronic inflammation following prolonged periods of life stress that may result in structural changes to key brain regions involved in the regulation of mood (Treadway et al. 2015). Similar phenomena are observed in other areas of medicine: Hypothermia reflects the activity of the body reacting normally to extreme environmental input, and some forms of cardiovascular disease may be mediated in part by normal biological responses to a chronically unhealthy lifestyle. In other cases, biological mediation may be more akin to a lesion, in which there is a genuine loss of function due to an environmental insult or a genetic predisposition, or their interaction. Many clinical neuroscience studies neglect to specify these different classes of hypothesized mechanisms clearly, sufficing to label observed differences between patient and healthy groups simply as deficits, dysfunctions, or alterations. A limitation of the RDoC project as currently implemented is that it makes few demands for better delineation of mechanisms at this level.

Although RDoC does not conflate biological mediation with etiology, it may inadvertently foster this error by placing considerably less emphasis on psychosocial than on biological variables (Hershenberg & Goldfried 2015, Lilienfeld 2014b). The RDoC matrix focuses almost exclusively on intraindividual variables, with little or no explicit coverage of extraindividual variables, such as the social, developmental, or cultural context (Berenbaum 2013, Shankman & Gorka 2015, Whooley & Horwitz 2013). This omission is significant given that the phenotypic expression of

biological vulnerabilities may often be constrained by sociocultural factors. For example, religious beliefs, as well as regional differences in the pricing and availability of alcohol, are associated with—and probably causally linked to—risk for alcohol use disorder (Kendler 2012). Hence, even individuals with a potent genetic propensity toward alcohol use disorder may display low rates of this condition if raised in a socially traditional environment.

Furthermore, five of the seven RDoC units of analysis focus explicitly on biological indicators, raising concerns that biological levels of analysis may receive undue attention by investigators (Berenbaum 2013). Although several RDoC publications (e.g., Morris & Cuthbert 2012) have acknowledged the importance of psychosocial variables and developmental considerations in the RDoC program, these processes are not explicitly represented in the matrix, an omission that RDoC may wish to remedy.

Fueling this concern is the fact that some researchers appear to have assumed erroneously that indicators drawn from one level of analysis (e.g., physiological, behavioral) are necessarily best suited for detecting abnormalities at that level. For example, in response to Berenbaum's (2013) concern that RDoC underemphasizes the role of beliefs, emotions, and other potential emergent phenomena that are not reducible strictly to neural events (O'Connor, 1994), Cuthbert & Kozak (2013) wrote that "Berenbaum is right in supposing that research that relies exclusively on self-report data would fall outside of the RDoC approach" (p. 933). The reasons for this a priori exclusion are unclear. Such decisions should be adjudicated by data, not by fiat. There is no inherent reason why self-report measures, which can readily capitalize on aggregation across indicators of behavior, cognition, and emotion across diverse situations, cannot provide equally—or more—construct-valid measures of biological systems relative to biological markers of these systems.

Biological Predispositions Versus Their Behavioral Manifestations

A key distinction that has received little attention in the RDoC literature is that between biological predispositions to psychopathology and their behavioral manifestations (Lilienfeld 2014b). In this respect, the distinction between basic tendencies and characteristic adaptations in the personality literature provides a useful organizing framework (Harkness & Lilienfeld 1997, McCrae & Costa 1995; for a discussion of the concept of multifinality in developmental psychopathology, see Franklin et al. 2014). Basic tendencies are personality traits, such as negative emotionality, whereas characteristic adaptations are the behavioral expressions of these traits, such as an anxiety disorder. Wakefield's (1992) influential harmful dysfunction framework is broadly consistent with this distinction; this model posits that the definition of mental disorder is a conjunction of (a) a failure in, or breakdown of, a naturally selected psychological system (dysfunction) and (b) impairment (harm) (but see Lilienfeld & Marino 1998 for a critique of aspects of Wakefield's framework). This model proposes that the presence of biological dysfunction alone is not sufficient for psychopathology; this dysfunction must also be manifested in social harm.

The distinction between basic tendencies and characteristic adaptations underscores the point that certain adaptations to personality traits may be largely unhealthy, whereas others may be largely healthy. For instance, an individual with high levels of negative emotionality may manifest this predisposition in an anxiety disorder; alternatively, the individual may manifest it in artistic productivity, which is associated with high levels of negative emotionality. As another example, the mean sensation-seeking scores of prisoners are essentially indistinguishable from those of firefighters (Zuckerman 1994), suggesting that sensation seeking can be manifested in either socially and personally destructive outlets (e.g., crime, substance abuse) or socially and personally constructive outlets (e.g., firefighting, law enforcement).

The distinction between basic tendencies and characteristic adaptations highlights the point that individuals with similar biological predispositions toward psychopathology can manifest these predispositions in different ways, in part as a consequence of developmental and psychosocial factors. If so, RDoC may be insufficient as a model for mental disorder, as it may often be unable to distinguish physiological risk factors for psychopathology from psychopathology per se (see also Wakefield 2014). If so, RDoC, at least in its present form, may be better suited as a model of predispositions toward mental illness than of mental illness itself.

Challenges Posed by Network Models of Psychopathology

A growing body of research on network models of psychopathology raises the possibility that commonly observed covariance patterns among disorder features may be due to causal relations among signs and symptoms themselves (Borsboom & Cramer 2013). Such relations can complicate RDoC's emphasis on dimensionality, as they suggest that multiple patients may arrive at the same score on an RDoC construct for different reasons. For one patient, a tendency to ruminate may lead to difficulty sleeping, producing fatigue, which then leads to less energy for social activities, and ultimately to social isolation and a depressed state. For this patient, symptoms related to fatigue and depression lie causally downstream of rumination, representing a normal biologic response to an extreme (internal) environment that is probably mediated by altered default network function (Pizzagalli 2011). A similar end state may be attained through different pathways: A second patient may suffer from chronic inflammation, which induces hypodopaminergia and symptoms of anhedonia and fatigue (Felger & Miller 2014, Miller et al. 2009). RDoC does not explicitly address this type of heterogeneity underlying common symptom severity.

RDOC: METHODOLOGICAL CHALLENGES

Neglect of Measurement Error

Consistent with the RDoC's mission, several authors have argued that psychiatric diagnosis should transition to a laboratory-based approach (Kihlstrom 2002; for a review, see Widiger & Clark 2000) and thereby bring psychiatry in line with the rest of medicine (Nemeroff et al. 1999). Nevertheless, this ambitious vision, echoed by RDoC, may be considerably more challenging to achieve than is commonly appreciated.

Laboratory measures are typically associated with largely unappreciated psychometric weaknesses. As Epstein (1980) noted, psychologists have long granted such measures an undeserved scientific cachet, often giving them a pass with respect to psychometric requirements (see also Tryon 1973). Laboratory measures of psychological constructs frequently display low levels of temporal and cross-situational consistency, largely because they contain substantial elements of situational uniqueness. Performance on such measures can be affected by a plethora of contextual and situational factors, including the mood and alertness of the participant, time of day, experimental instructions, nature of the laboratory setting, perceived attitude of the experimenter, demand characteristics, and idiosyncrasies of the laboratory paradigm itself (Kendler & Neale 2010). These concerns apply not merely to standard laboratory indices but also to neuropsychological measures. For example, although many authors treat neuropsychological measures of prefrontal functioning (e.g., Wisconsin Card Sorting Test, Stroop color-naming task, Tower of Hanoi) as largely interchangeable, the correlations among these measures are modest (typically below $r = 0.25$; Miyake et al. 2000). These relatively low associations stem in part from the task impurity problem (Miyake & Friedman 2012; see also Abramovitch & Schweiger 2015), the tendency of many neuropsychological measures to detect deficits stemming from multiple psychobiological processes.

In his classic book *Personality and Assessment*, Mischel (1968) observed that even seemingly trivial changes in experimental paradigms can lead to dramatic changes in a measure's inter-correlations and correlations with other measures. Ironically, Kidd et al. (2013) demonstrated this point using the very paradigm that Mischel (1974) made famous: the marshmallow test of delay of gratification in children. They showed that a seemingly trivial alteration in the experimental set-up—namely, whether an adult who had promised to bring a set of attractive art supplies to the child immediately prior to the task actually did so—resulted in massive changes in outcomes. Specifically, children exposed to the “reliable” adult waited an average of 12 minutes, whereas children exposed to the “unreliable” adult waited an average of only 2 minutes. Kidd and colleagues interpreted this result as suggesting that children who encounter unpredictable environments are less likely than other children to delay gratification, as they have ample reason to doubt whether expected rewards will materialize.

Block (1977; see also Tellegen 1991) similarly noted that T data (test data), that is, data derived from isolated laboratory indicators, are more unreliable and erratic in their relations with (a) each other and (b) other measures compared with S data (self-report data) and R data (rating data). Although S and R data possess their own psychometric limitations, these data are typically aggregated across multiple diverse situations. Such aggregation is often accomplished by summing items within scales, or in more sophisticated analyses, by creating latent variables using such techniques as structural equation modeling, which minimizes situational error and yields more reliable and construct-valid composites of behavior across situations (Epstein 1980, Rushton et al. 1983). In contrast, T data are rarely aggregated across situations, at best being combined only across multiple trials of the same measure.

These problems may be especially acute in the domain of neuroimaging. Few investigators have examined the test-retest reliability of measures of functional magnetic resonance imaging (fMRI; Bennett & Miller 2010), even though this form of reliability is a basic expectation of measures in other psychological domains. In an analysis of 63 studies, Bennett & Miller (2010) found that the test-retest reliability of fMRI measures was typically modest, with intraclass correlations (ICCs) averaging 0.50 (see also Vul et al. 2009). Furthermore, only 29% of activated voxels that were statistically significant in one study were significant in a second study. Although test-retest reliabilities for fMRI data were higher with briefer intervals, even back-to-back scans (taken within one hour) exhibited an average cluster overlap of only 33%.

At the same time, because some of the neural processes examined in these studies may have been influenced substantially by state variables, these modest test-retest values may reflect inherent short-term fluctuations in the neural processes themselves rather than measurement error. Scanning can be an unfamiliar experience for many participants, and initial anxiety or discomfort in the scanner may change over repeated exposures. Moreover, repeated exposures to cognitive tests will invariably lead to learning, even if only at the level of greater familiarity and fluency. It would be surprising if these changes were not reflected in differences in neural responses. One recent study used a relatively large sample to examine how activity in the ventral striatum (VS) during the feedback phase of a rewarded instrumental conditioning task changed over time as compared with activity during the anticipation phase (Chase et al. 2015). As would be predicted by temporal-discounting models of reinforcement learning (Schultz et al. 1997), VS responses to better-than-expected outcomes during the first scanning session were robust but were nearly absent during the second session. Conversely, VS responses to anticipation were absent during the first session but significant during the second. Moreover, the magnitude of feedback-related VS activity at session 1 predicted the magnitude of anticipatory VS activity at session 2. This outcome-to-cue transfer in VS activity patterns suggests a change due to learning, but it also contributes to low interclass correlations when simply comparing the same condition across testing sessions.

These effects may also vary across different types of tasks and conditions. For example, Sauder et al. (2013) reported that the reliability of fMRI measures of amygdala activation was adequate in response to fearful faces (ICCs ranged from 0.32 to 0.43) but inadequate in response to angry faces (ICCs ranged from -0.24 to 0.11). In contrast, structural MRI measures appear to have considerably higher test-retest reliability (Kendler & Neale 2010). For example, the stability of measures of cortical thickness as assessed by structural MRI is on the order of $r = 0.95$ (Wonderlick et al. 2009).

Even the fMRI research center at which the study is conducted accounts for approximately 8% of the variance in fMRI blood oxygen-level dependent (BOLD) signal results, suggesting that the laboratory itself is a potential source of error in analyses (Costafreda et al. 2007). Another investigation revealed that the median ICC of fMRI findings across different imaging centers that contained identical hardware set-ups was only 0.22 (Friedman et al. 2008).

All of these psychometric limitations may impede the replicability of functional imaging findings unless addressed analytically. Adding to these concerns are findings that the average statistical power of functional brain imaging studies is only about 0.20, which is considerably lower than in most domains of psychological and psychiatric research (Button et al. 2013). Low power not only increases the chances of type II errors (false negative results), but also boosts the likelihood of overestimating the effect sizes of statistically significant findings, a phenomenon known as the winner's curse (Button & Munafò 2016). Replicability concerns are not limited to functional brain imaging studies. Using a fresh sample of college students as participants, Boekel and colleagues (2015) attempted to replicate 17 published studies on the relation between structural brain imaging findings and psychological findings derived from self-reported data and other measures (e.g., a previously reported positive correlation between amygdala gray matter and number of Facebook friends). Using Bayesian methods, they found minimal support for any of the findings from the previous 17 studies.

The Limitations of Endophenotypes

Endophenotypes (phenotypes located “beneath the skin”) are a core intellectual progenitor for RDoC's conceptualization of brain circuit dysfunction, and many RDoC studies have borrowed heavily from endophenotype designs. Because they are presumed to be more proximal to genes than are exophenotypes, endophenotypes should ideally provide purer and more construct-valid indicators of genetically influenced psychobiological systems (Gottesman & Gould 2003). Moreover, because many endophenotypes cut across traditional disorder categories, endophenotypes accord with RDoC's transdiagnostic approach to etiology (Miller & Rockstroh 2013). Nevertheless, RDoC is broader than the endophenotype approach, as it does not mandate that candidate biological markers be heritable.

Despite high initial expectations and provisional successes for certain conditions, such as schizophrenia (Cannon & Keller 2006, Miller & Rockstroh 2013), the endophenotypes identified to date have not necessarily proven to be more genetically informative than traditional exophenotypes, such as DSM criteria. Flint & Munafò (2007) examined this issue in meta-analyses of studies of catechol-O-methyltransferase (COMT), an enzyme that metabolizes dopamine (among other neurotransmitters), and schizophrenia, a disorder associated with dopamine overactivity in mesolimbic regions. They tested whether the COMT genotype displayed higher effect sizes with candidate neuropsychological and psychophysiological endophenotypes of schizophrenia, such as performance on the Wisconsin Card Sorting Test, the N-Back Task, and P300 amplitude and latency, than with DSM schizophrenia itself. Flint & Munafò (2007) found no evidence that the ostensible endophenotypes were more highly related to the COMT genotype than

was schizophrenia. Their findings suggest that investigators should not assume that candidate endophenotypes will necessarily yield higher effect sizes than do exophenotypes in genetic studies (for a more sanguine view of the status of endophenotypes for schizophrenia, see Tan et al. 2008).

In contrast, Jonas & Markon (2014) reported more encouraging results. They examined the relation between (*a*) three polymorphisms in the dopamine and serotonin systems that are potentially relevant to impulsivity and (*b*) diagnostic (e.g., measures of ADHD), trait (e.g., self-report measures of impulsivity), neuropsychological (e.g., continuous performance tasks), and neurobiological (e.g., functional imaging indices of right inferior prefrontal activity) phenotypes relevant to impulsivity. Neurobiological measures were the most highly associated with the genetic markers, with trait and neuropsychological measures roughly tied for a distant second, and diagnostic measures last. These analyses suggest that neurobiological measures, such as functional brain imaging indices, may be promising endophenotypes of impulsivity. Still, as the authors observed, neurobiological studies were characterized by considerably lower statistical power than studies from other domains, raising the possibility that the effect sizes of the former studies were inflated.

One prominent model of endophenotypes conceptualizes them as intermediate phenotypes, operating as mediators between genes and exophenotypes. Nevertheless, the evidence that candidate endophenotypes mediate the relation between genes and behavioral phenotypes is slim. In a twin sample, Kendler et al. (1993) found that although neuroticism was associated with elevated rates of major depression, it did not mediate the association between genetic risk and major depression. Waldman (2005) reported inconsistent findings concerning whether scores on the Trail Making Test mediate relations between dopamine genes and ADHD, with partial mediation for Trails A but no significant mediation for Trails B.

Such mediation should not be presumed, as certain putative endophenotypes may lie causally downstream of the exophenotypes with which they are associated (Kendler & Neale 2010). For example, P300 amplitude appears to be a valid endophenotype for a broad predisposition toward externalizing behavior and disinhibition (Patrick et al. 2006). Nevertheless, P300 amplitude is exquisitely sensitive to attention (Polich 2012). Hence, this marker may be a consequence, not an antecedent, of the attentional and motivational deficits associated with externalizing disorders, such as antisocial personality and substance use disorders, which covary extensively with ADHD (Lilienfeld & Waldman 1990, Torgersen et al. 2006).

One crucial assumption guiding the search for endophenotypes is that the biological indicators in question are trait rather than state markers, as a measure of a biological vulnerability would be expected to be stable over time. Again, the trait status of such markers must be demonstrated empirically rather than assumed (Stoyanov & Kandilarova 2014). For example, motion discrimination appears to be impaired in both patients with schizophrenia and in their nonaffected relatives, suggesting that it is a useful trait marker of the disorder. In contrast, motion integration appears to be impaired in patients with schizophrenia but not in their nonaffected relatives, suggesting that it is influenced by state variables (Chen et al. 2006). One major challenge for researchers will be to demonstrate that endophenotypes, as well as other ostensible vulnerability markers of RDoC domains, are present even between disorder episodes or exacerbations.

RDOC: LOGISTICAL/PRAGMATIC CHALLENGES

The Dangers of Premature Reification of the RDoC Matrix

As noted previously, the RDoC matrix is intended to be provisional. It comprises cells directing investigators to well-supported neural circuits linked to psychopathology while leaving open the possibility of modifying extant cells or adding new ones on the basis of new evidence (Cuthbert

& Insel 2013). In this regard, this matrix appears to represent a reasonable compromise between excessive open-endedness and excessive prescriptiveness.

At the same time, there is a danger of premature reification of the matrix and of the RDoC endeavor more broadly; it would indeed be unfortunate if the march to freedom from the DSM's "epistemic prison" (Hyman 2010, p. 157) led merely to a padded cell in the matrix penitentiary. A number of scholars have cautioned against such reification in the frequent (mis)interpretation of DSM categories as settled truths (Kendler 2014), and RDoC must be careful to avoid the same error. In fairness, the RDoC framers have repeatedly described their intentions for the matrix to be a working document. Good intentions, however, may afford inadequate protection against ossification, which can easily insinuate itself through the mundane, bureaucratic activities required by any large-scale administrative effort. For instance, several recent requests for applications (RFAs) from NIMH have noted that "Applications must focus on at least one of the constructs that have been defined in these RDoC workshops" (NIH RFA-MH-14-050; see Shankman & Gorka 2015). Such wording appears to vitiate RDoC's avowed goal of being self-correcting, as it will be difficult or impossible to ascertain whether to add novel cells to the matrix unless these cells are explicitly investigated. Social cognition research suggests that once mental categories are set in place, they can quickly become implacable (McCrae & Bodenhausen 2000). To avoid the error of reification, RDoC should encourage researchers to examine psychobiological constructs that have the potential to bridge, transcend, or challenge current matrix boundaries, as well as articulate an explicit process of matrix evaluation and revision. Additionally, RFAs should offer as much consideration to proposals that seek to explicitly challenge matrix boundaries as they do to proposals that operate within them.

Although the RDoC matrix was constructed to be broad and flexible, a number of fruitful hypotheses exist that may be challenging to capture within its framework. For example, some studies suggest that emotional numbing and alexithymia may be core facets of reduced approach-related behaviors, but only in the context of response to a traumatic experience, as in posttraumatic stress disorder (Kashdan et al. 2006). It is not clear, however, how this type of etiology-by-symptom interaction would be examined within the RDoC framework.

Implications for Grant Funding in Non-RDoC Domains

The RDoC initiative developed from an explicit desire to support translational neuroscience in mental health research. It is therefore perhaps unsurprising that the RDoC has hastened the already significant shift in NIMH extramural funding priorities away from psychosocial research, including research on psychotherapy (Goldfried 2015). Although we welcome the emphasis on translational neuroscience, there is a legitimate concern that this approach may burn the candle too far at both ends. On the one hand, as a consequence of RDoC, basic neuroscience efforts to understand circuit function more generally may be at risk for being underfunded, raising the concern of insufficient knowledge available for translation. On the other hand, the promise of neuroscience-guided treatment and diagnosis appears to be on the distant horizon (Frances & Widiger 2012, Paulus 2015), whereas research devoted to improvements to empirically supported treatments for psychopathology could alleviate the suffering of thousands in the near term. It would therefore be beneficial for RDoC to coexist with research programs focused on (*a*) developing basic science knowledge without necessarily requiring immediate demonstration of clear translatability and (*b*) clinical outcome and process research that can yield important short-term treatment breakthroughs.

Translating RDoC Findings into a Feasible Classification System

One crucial challenge for RDoC will be to delineate how the large and diverse corpus of findings emanating from its investigations will be meaningfully synthesized into the rudiments of an alternative model of classification. The RDoC matrix is a heuristic blueprint to guide research, but it is not a classification system in and of itself, nor is it intended to be. A key unanswered question, then, is how RDoC findings will be translated into a usable system that can ultimately guide clinical practice. Although it may be too early to address this question, it will be incumbent on RDoC architects to sketch out an overarching plan for how RDoC research will be used to inform classification and diagnosis. In the absence of such a rubric, it may be difficult to convert the enormous wealth of data yielded by RDoC investigations into a concrete model that can supplement, or perhaps eventually substitute for, the DSM-ICD model.

THE DSM-ICD AND RDOC: QUO VADIS?

The DSMs, especially DSM-III and its progeny, were noteworthy achievements in psychiatric classification, and they brought considerable order and diagnostic reliability to previously disorganized territory. In certain respects, the DSM-ICD model has served us well (cf. Greenberg 2013), as it has facilitated epidemiological and etiological research and contributed to the development of efficacious interventions that have alleviated the suffering of countless individuals. Moreover, by mapping onto signs and symptoms, the DSM does a serviceable and face-valid job of capturing the essence of individuals' distress and impairment. It is difficult to imagine a comprehensive system of psychiatric classification bereft of any reference to the subjective and behavioral manifestations of people's psychological suffering.

At the same time, it has become evident that many central features of the DSM-ICD model do not map adequately onto the state of nature (Sanislow et al. 2010). The high levels of covariation among putatively distinct categories, the large number of intermediate cases, and the substantial phenotypic and etiological heterogeneity of numerous diagnostic categories, among other vexing anomalies, suggest that something is deeply awry with at least some core presuppositions underpinning the neo-Kraepelinian model of psychiatric classification. Moreover, these problems have proven stubbornly resistant to repeated efforts at amelioration across multiple DSM and ICD revisions. The shortcomings of the DSM-ICD edifice therefore appear to reflect an inherent deficiency in its architectural floor plan that cannot be fixed merely by adjusting some of its walls.

The RDoC initiative emerged in the new millennium to address these mounting anomalies (Insel 2014), and it appears to be a valuable effort to ground psychopathology in well-supported biological systems that carry important implications for adaptation and maladaptation (Lilienfeld 2014b). In this respect, RDoC has the potential to map more closely than the DSM-ICD onto psychobiological reality. Moreover, even its critics acknowledge that RDoC has already exerted one important salutary effect: loosening the stranglehold of the DSM over research and grant funding. Such hegemony has impeded the investigation of fruitful alternatives to classification and etiology, and we experience few qualms in bidding it a greatly belated adieu.

In this respect, RDoC must heed some of the lessons of the past. One historical feature shared by DSM-ICD and RDoC is that neither was intended to become a fixed system in terms of guiding research priorities. Yet, the DSM system eventually acquired such sovereignty over research that it became difficult for investigators to examine clinical problems that fell outside of traditional disorder boundaries (Hyman 2010). RDoC must make concerted efforts to avoid the same reification error.

Table 1 A baker's dozen recommendations for RDoC

1. Lay out explicit benchmarks for ascertaining what findings, or patterns of findings, could falsify the RDoC research framework or at least suggest that it is not making adequate scientific progress
2. Examine how RDoC is performing relative to the DSM-ICD approach for statistically predicting important external criteria, such as response to treatment and natural history
3. Explicate alternative models for dysfunction in psychobiological systems (e.g., lesion, hyperactivity, or hypoactivity in the functioning of these systems; a network model in which there are bidirectional causal relations among diagnostic signs and symptoms)
4. Accord adequate attention to environmental (e.g., social and cultural context) and developmental influences, and incorporate such influences explicitly into the RDoC matrix to encourage their investigation
5. Adopt no a priori assumptions regarding what measures will be optimal for detecting individual differences in neural circuitry relevant to psychopathology, and be guided exclusively by data in this regard
6. Accord adequate attention to the role of measurement error inherent to laboratory measures (T data), and capitalize on the power of statistical aggregation across indices
7. When conducting research on endophenotypes, test statistical models of pleiotropy and mediation, and do not presume that such phenotypes are necessarily more heritable or straightforward in their genetic architecture compared with exophenotypes
8. Do not assume that endophenotypes or other candidate biomarkers are more traitlike than statelike; the assertion that such indicators are stable over time must be demonstrated empirically
9. Remain cognizant of the possibility that psychobiological predispositions can be expressed in a host of diverse behavioral manifestations
10. Avoid premature reification of the RDoC matrix, and remain open to research that examines cells not explicitly represented in the current matrix
11. Develop broad guidelines for beginning to translate the growing body of RDoC findings into a usable system of psychiatric classification
12. Seek ways in which RDoC can coexist with both (a) basic research on neural circuitry and (b) applied research on empirically supported treatments tied to DSM categories
13. Explore the possibility of a combined system that incorporates both diagnostic signs/symptoms and psychobiological predispositions

Abbreviations: DSM, *Diagnostic and Statistical Manual of Mental Disorders*; ICD, *International Statistical Classification of Diseases and Related Health Problems*; RDoC, Research Domain Criteria.

As we have noted, RDoC confronts a number of conceptual, methodological, and logistical/pragmatic challenges, none of which appears to be insuperable (Lilienfeld 2014b). Many of these challenges have received insufficient discussion in RDoC documents and will require careful consideration for RDoC to realize its considerable scientific potential. In **Table 1**, we offer a baker's dozen of recommendations for addressing these challenges in the coming years of RDoC research.

One of the foremost challenges to RDoC's effort to offer a viable alternative to DSM-ICD is the fact that psychobiological predispositions can be expressed in a host of diverse behavioral patterns, some of them largely healthy and others largely unhealthy (Harkness & Lilienfeld 1997). In this regard, it may be unrealistic to expect RDoC to fully supplant a classification system, such as the DSM, that provides a remarkably rich compilation of the variegated ways in which human behavior, both subjective and observable, can break down. Signs and symptoms, their inevitable shortcomings notwithstanding, will always be necessary for a complete characterization of mental disorder. Indeed, we suspect that the most informative and construct-valid system of classification will ultimately necessitate some form of rapprochement between the Aristotelian and Galilean perspectives afforded by the DSM-ICD and RDoC approaches, respectively. Although we have

heretofore portrayed these two models in bold relief as competing, we are inclined to regard them as complementary in certain key respects. Each approach is necessary; neither is sufficient.

In our view, the DSM-ICD will never provide a sufficient foundation for a comprehensive classification system, because psychiatric signs and symptoms, like fever, are inevitably nonspecific indicators of a host of psychobiological dysfunctions. Conversely, RDoC will never be sufficient for a comprehensive classification system, because psychobiological dysfunctions can be manifested in a host of markedly diverse signs and symptoms as a function of innumerable moderating variables. As a consequence, a full characterization of psychopathology will require the DSM-ICD's remarkably astute descriptive observations, informed by the best available research on neural circuitry relevant to psychopathology. If it attends carefully to the constructive challenges posed here, RDoC and the fruits of its labor hold the potential to complete the story that Emil Kraepelin, the Washington University group, and Robert Spitzer started.

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