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EDITORIAL

Dimensional thinking in psychiatry in the era of the Research Domain Criteria (RDoC)

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The biological mechanisms underlying psychiatric diagnoses are not well defined. Clinical diagnosis based on categorical systems exhibit high levels of heterogeneity and co-morbidity. The Research Domain Criteria (RDoC) attempts to reconceptualize psychiatric disorders into transdiagnostic functional dimensional constructs based on neurobiological measures and observable behaviour. By understanding the underlying neurobiology and pathophysiology of the relevant processes, the RDoC aims to advance biomarker development for disease prediction and treatment response. This important evolving dimensional framework must also consider environmental factors. Emerging evidence suggests that gut microbes (microbiome) play a physiological role in brain diseases by modulating neuroimmune, neuroendocrine and neural signalling pathways between the gut and the brain. The integration of the gut microbiome signature as an additional dimensional component of the RDoC may enhance precision psychiatry.

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Categorical psychiatric diagnostic systems, based on clusters of symptoms and signs have allowed the determination and comparison of the frequency and impact of mental disorders across countries, can facilitate communication between professionals, and can assist treatment plan formulation. However, given the complexity of the brain, categorical diagnoses also render high levels of heterogeneity in terms of symptom profile, causality, psychopathology and treatment response (Trivedi *et al*. 2006; Baca-Garcia *et al*. 2007; Goldberg, 2011). Indeed, many phenomena vary continuously within and between psychiatric patients and in the population at large and become pathological only at the extremes of an otherwise normal distribution (Adam, 2013; Bebbington *et al*. 2013). The overlap of presumed distinct psychiatric diagnoses have been demonstrated at the genetic (Craddock & Owen, 2010; Smoller *et al*. 2013), molecular (Krishnan & Nestler, 2010), cellular (Swardfager *et al*. 2016), brain circuit (Hulshoff Pol *et al*. 2012; Drysdale *et al*. 2017), pathophysiology (Garn *et al*. 2016) and psychological levels (Catalan *et al*. 2016).

In 2008, the United States National Institute of Mental Health (NIMH) strategic plan called for the development 'for research purposes, new ways of classifying mental disorders based on dimensions of observable behaviour and neurobiological measures' (http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml). This exciting advance in the conceptualization of psychiatric disorders emerged as the Research Domain Criteria (RDoC) (Insel *et al*. 2010). In contrast to the categorical diagnostic approach, the RDoC matrix attempts to reconceptualize psychiatric disorders into transdiagnostic functional dimensional constructs grouped into domains such as negative valance, positive valence, cognitive, social processing and arousal/regulatory systems (Table 1), examined across units of analysis from genes, molecules, cells, circuits, physiology, behaviour and self-report. Thus, the RDoC aims to extend diagnostic systems based on symptoms, to elucidate the biological mechanisms underlying psychiatric disorders, an approach that aligns well with the endophenotype concept (Miller & Rockstroh, 2013), with a view to develop biomarkers for disease prediction and treatment response (Gururajan *et al*. 2016). A similar venture – the 'Roadmap for Mental Health Research' has been launched in Europe (Schumann *et al*. 2014).

In the same year the NIMH launched the strategic plan, that gave rise to RDoC, the National Institutes of Health launched a 'roadmap effort to use genomic technologies to explore the role of microbes in human health and disease' – the Human Microbiome Project (http://hmpdacc.org/), an ambition which was also matched in Europe and other jurisdictions (e.g. MetaHIT, www.metahit.eu). Since then, a growing

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Table 1. *Units of Analysis and functional domains of the Research Domain Criteria*

NIMH Research Domain Criteria							
Units of analysis							
Genes	Molecules	Cells	Circuits	Physiology	Behaviour	Self-reports	Paradigms
Functional domains							
Negative valence systems		Positive valence systems		Cognitive systems	Social processing systems		Arousal and regulatory systems
Acute threat (fear)		Approach motivation		Attention	Affiliation and attachment		Arousal
Potential threat (anxiety)		Initial responsiveness to reward attainment		Perception	Social communication		Circadian rhythms
Sustained threat		Sustained/longer-term Responsiveness to reward attainment		Declarative memory	Perception and understanding of self/others		Sleep-wakefulness
Loss		Reward learning		Language			
Frustrative non-reward				Cognitive control			
		Habit		Working memory			

NIMH, United States National Institute of Mental Health.

body of pre-clinical evidence has shown that the gut microbiome can impact brain development, function and behaviour by modulating neuroimmune, neuroendocrine and neural signalling pathways between the gut and the brain (Cryan & Dinan, 2012). This fusion of microbiology and brain research has been postulated as a paradigm shift in neuroscience (Mayer *et al*. 2014). Moreover, recent translational studies indicate that the gut microbiome plays a role in the pathophysiology of stress-related psychiatric disorders (Kelly *et al*. 2016*a*). The incorporation of the gut microbiome signature, as an additional dimensional component of analysis, may provide further ways of stratifying patients and may lead to novel treatment strategies to enhance precision medicine in psychiatry, though is not without significant challenges (Kelly *et al*. 2016*b*).

A dimensional system encourages collaboration between all disciplines. As pointed out by Yee *et al*. (2015), it should be noted that five of the seven units of analysis in the RDoC matrix can be characterized as biological (e.g. genes, physiology), while virtually all of the rows are psychological constructs, articulating the interplay between biological and psychological mechanisms. The RDoC matrix could thus consolidate multiple disciplines, by removing the constraints of classical psychiatric disease diagnosis. It also has the potential to better align pre-clinical and clinical studies to build a common framework of comparable neurobiological abnormalities, for example, to help stratify subgroups of patients on the basis of similar pathophysiology, rather than diagnostic categories based on phenomenology (Kapur *et al*. 2012).

It is worth re-iterating that the majority of pharmacological advances in psychiatry have been spurred on by useful serendipity, but in the last 40 years and the current interest in ketamine (as a fast acting antidepressant) notwithstanding (Naughton *et al*. 2014), very few therapeutics with novel mechanisms of action have progressed to phase III clinical trials or regulatory approval (Umbricht *et al*. 2014). Major pharmaceutical companies have shifted drug discovery efforts away from psychiatric towards non-psychiatric disorders with identified biological targets (Miller, 2010). The overall probability of success of bringing any new drug, through pre-clinical stages and clinical trial stages I through III to market is ~8% (Dimasi *et al*. 2003). Given this stasis in psychiatric drug development, innovative solutions to novel drug development based on the capacity of the RDoC framework to uncover biological mechanisms and improve stratification of mental disorders is one potential way to address some of these issues (Insel, 2012; Insel & Cuthbert, 2015). The RDoC framework could allow researchers to study basic mechanisms as they cut across traditional diagnostic categories with the hope of increasing personalized precision medicine. By increasing the possibility of successful translation of research into practise and the development of novel therapeutics, not just pharmacological, the RDoC offers new hope of tangible benefits for psychiatric patients (Insel *et al*. 2013).

The first exploratory steps have been taken. 'Engage' is a streamlined psychotherapy that uses

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neurobiological constructs to target the behavioural expression of the positive valence system in late life depression by using reward exposure (activation and retraining of positive valence system) coupled with strategies to mitigate negative valence (negativity bias), arousal (apathy) and cognitive control (Alexopoulos & Arean, 2014). The Training for Awareness, Resilience, and Action treatment programme for adolescents proposes subtypes of adolescent depression driven by limbic hyperactivation related to sustained threat (anxious arousal, increased conflict detection, attentional bias to threat, helplessness behaviour, punishment sensitivity and avoidance) with clinical features such as emotional hyper-reactivity, agitation and dysphoric mood (Henje Blom *et al*. 2014). Interestingly, existing trial data, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (Joyce *et al*. 2017) and the Sequenced Treatment Alternatives to Relieve Depression (Chekroud *et al*. 2016; Chekroud *et al*. 2017) have now been re-analysed using a dimensional approach, in an effort to improve tools necessary to implement stratification.

The RDoC is not without critics and the incorporation of categorical and dimensional systems is a major challenge within a field with many divisions (Carpenter, 2013). Significant neuroscientific advances have frequently been lost in translation and not had appreciable benefits for psychiatric patients as yet. But the premise of RDoC is that clinical research should be built on the best available genetic, neuroscientific and psychological science concepts to bridge the gap between bench and psychiatric bedside. Indeed, the RDoC and categorical systems should be viewed as complementary, not antagonistic (Kraemer, 2015). In the future, with further understanding of the underlying neurobiology and pathophysiology of the relevant processes in animals and humans, the RDoC approach may well yield therapeutic advances. A discernible endeavour along the lines of the RDoC, is the European College of Neuropsychopharmacology neuroscience-based nomenclature project (http://nbnomenclature.org/). This project has reclassified psychopharmacology according to mechanisms of action rather than by diagnoses and is a step towards a more biological-based approach that also reflects the clinical application of these drugs across diagnostic boundaries. Although, the challenge to fuse clinical psychiatry and neuroscience is significant, some argue the process is overdue (Ross *et al*. 2015*b*).

There are many hurdles to overcome. Enhanced communication and collaboration between neuroscientists and clinicians will be required to facilitate integration of neuroscience into the clinical domain. This will require culture change and a modified approach to training (Lehner & Insel, 2010). Indeed, it will be critical to have skilled educators to translate neuroscience findings to the psychiatry clinic. In the United States, the incorporation of neuroscience into the psychiatry curriculum has been increasing over recent years (Roffman *et al*. 2006). More recently, the progressive National Neuroscience Curriculum Initiative (http://www.nncionline.org/), which aims to integrate neuroscience into psychiatry training and education has been launched (Ross *et al*. 2015*a*). It remains to be seen how this ambitious neuroscience training endeavour will influence clinical work, but it is noteworthy that the recruitment and retention problems in psychiatry in the United Kingdom and Ireland (Mukherjee *et al*. 2013) are not reflected in the United States, where recruitment has increased over the last 4 years.

Cleary it is vital for clinicians to be fully knowledgeable about categorical systems and aware of updated versions, such as the DSM-5 (Murphy & Hallahan, 2016). But the development of the concept of the dimensional approach as a framework to progress psychiatry from the current stalemate is essential. The RDoC may not be the final paradigm for psychiatry, rather it is an important dimensional beginning and an evolving process. Investigators are encouraged to refine and expand the matrix and hybrid constructs will evolve as other variables are added. An evolving RDoC that encompasses dimensions at every level, from genetic, molecular, physiological, imaging, psychological and environmental has the potential to advance our understanding of the brain and its many disorders.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval for publication of this editorial was not required by their local Ethics Committee.

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