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Precision psychiatry and Research Domain Criteria: Implications for clinical trials and future practice

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Abstract

Psychiatric disorders are associated with significant social and economic burdens, many of which are related to issues with current diagnosis and treatments. The coronavirus (COVID-19) pandemic is estimated to have increased the prevalence and burden of major depressive and anxiety disorders, indicating an urgent need to strengthen mental health systems globally. To date, current approaches adopted in drug discovery and development for psychiatric disorders have been relatively unsuccessful. Precision psychiatry aims to tailor healthcare more closely to the needs of individual patients and, when informed by neuroscience, can offer the opportunity to improve the accuracy of disease classification, treatment decisions, and prevention efforts. In this review, we highlight the growing global interest in precision psychiatry and the potential for the National Institute of Health-devised Research Domain Criteria (RDoC) to facilitate the implementation of transdiagnostic and improved treatment approaches. The need for current psychiatric nosology to evolve with recent scientific advancements and increase awareness in emerging investigators/clinicians of the value of this approach is essential. Finally, we examine current challenges and future opportunities of adopting the RDoC-associated translational and transdiagnostic approaches in clinical studies, acknowledging that the strength of RDoC is that they form a dynamic framework of guiding principles that is intended to evolve continuously with scientific developments into the future. A collaborative approach that recruits expertise from multiple disciplines, while also considering the patient perspective, is needed to pave the way for precision psychiatry that can improve the prognosis and quality of life of psychiatric patients.

Introduction

Psychiatric disorders not only represent a major burden on the personal health of individual patients, but they also impact on care partners, healthcare practitioners, and the socioeconomic status of countries. The World Health Organization (WHO) estimates that psychiatric disorders account for approximately 13% of the global disease burden, and by 2030 the associated annual global costs are estimated to be US$6 trillion.[1,2] The coronavirus (COVID-19) pandemic is also reported to have escalated the prevalence of psychiatric disorders, with an estimated additional 76.2 million cases of anxiety disorders and 53.2 million cases of major depressive disorder (MDD) in 2020.[3,4]

Despite evidence-based interventions the global burden of psychiatric disorders has not reduced since 1990, highlighting the need for new approaches to prevention and intervention.[4] The effect of available evidence-based treatments is limited due to patient heterogeneity, delays in accessing treatment, low adherence rates, and frequent adverse events.[5-11] Many patients need to try multiple treatments and treatment combinations, to seek relief of symptoms, and a substantial number of patients become treatment-resistant during this process.[12] In the National Institute of Mental Health (NIMH)-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, for example, it was found that only one-third of individuals receiving treatment for clinical depression achieve symptom remission within the first 2 treatments administered.[13] Patients who experience an inadequate response to medications (IRM) generally suffer from longer episodes of the illness and have an increased all-cause mortality compared with other patients with depression, leading to protracted suffering for patients and an increased burden on care partners.[12,14] Increased healthcare and unemployment-related costs

are also associated with IRM.[12,15] Depression is purported to be the single largest contributor to lost productivity globally, arguably due to untreated or inadequately treated conditions.[16] In patients who adhere to their treatment regimen, IRM impacts as many as 20–60% of patients, resulting in increased healthcare burden and incurring approximately 10-fold higher costs relative to patients in general.[17] In schizophrenia, nonadherence to medication is associated with additional burdens of disease and is linked with suicidal behavior, increased hospitalizations, and all-cause mortality,[7] and as such represents a critical contributor to poor clinical outcomes.[6,18] Adverse events to current treatments can also often contribute to loss of quality of life, daily functioning, and impede positive clinical outcomes.[10,19] Particularly in patients with schizophrenia, mortality due to adverse effects of medication is high, leading to thousands of deaths and serious injuries each year.[6,12,20-22]

The process used to select currently prescribed medications is often inadequate. For example, although there are several effective treatment options for clinical depression, there is no clear understanding of exactly which mechanisms these treatments modify, and thus it is difficult to determine which patients may benefit.[23] As such, there is a clear need for better diagnostic and therapeutic approaches that take into account patient heterogeneity. Efforts to discover and develop novel efficacious medications that might revolutionize disease treatment in psychiatry have been relatively unsuccessful.[24,25] However, in recent years there have been major advances in our understanding of the brain-behavior correlates of these disorders, spurred on by the emergence of new technologies and techniques that have progressed our understanding of pathophysiological mechanisms. Neuroimaging techniques and innovative technologies that provide comprehensive profiles of brain circuit function and genetic variation in disease states, both within patient subgroups and in individuals, make it possible to map alterations in these neural circuits and neurobiology with clinical features in disorders of the central nervous system.[5,26,27] These developments have led to a growing interest in precision psychiatry,[5,26] which takes into account these individual biological and clinical factors.

By integrating emerging pathobiological and biomarker data from neuroscience research, precision psychiatry has the potential to improve the accuracy of disease diagnosis, treatment decisions, and prevention efforts.[26] The primary aim of precision medicine is to tailor healthcare more closely to the needs of individual patients, which requires improvements not only in the ability to identify groups of patients clinically for whom existing treatments are likely to be the most effective, but also in the development of more precise treatments and, ultimately, preventions.[28] This approach can contribute to reducing stigma, which can also be a major barrier to accessing care for mental disorders.[29]

Despite advancements in the knowledge base of the neurobiological correlates of clinical features, translation to the clinic has been slow.[30] This is due mainly to the widespread reliance of preclinical and clinical research initiatives on categorical, symptom-based diagnostic nosology such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD). This current nosology has its foundations in epidemiology-derived concepts and self-report symptom assessments and was constructed and revised at a time when the technological capability and expertise to screen for, validate, and fully understand the biological correlates of psychiatric disorders were not established fully. One of the current challenges presented by the DSM/ICD classification systems is that recent biological evidence, which continues to evolve at a growing pace with the wider application of innovative techniques in neuroscience to clinical studies, cannot be easily incorporated into clinical or research settings. The DSM and ICD psychiatric classifications, established by professional bodies like the American Psychiatric Association (APA) and the WHO, currently lack etiological and biomarker correlates.[31] These current systems, by nature of the broad symptom-focused classification constructs, create patient cohorts that are too heterogeneous to further categorize based on candidate biological markers for the purpose of targeted diagnosis and treatment.[8] Thus, despite the accumulating knowledge within various areas of neuroscience, emerging neurobiological correlates of psychiatric phenotypes are still viewed by most clinicians as being of value in research contexts only, as opposed to in clinical practice. Although DSM/ICD nosology continues to represent the gold standard and dominate procedures for diagnosis, treatment, and clinical research,[32] there are growing efforts pushing for change in the field. For example, a recent Act to improve mental healthcare for veterans by implementing precision medicine was passed by the US Congress in 2020.[33] This Precision Medicine for Veterans Initiative aims to identify and validate brain and mental health biomarkers among veterans using a range of brain imaging, genetic and other biomarker analysis methods, with specific consideration for depression, anxiety, post-traumatic stress disorder (PTSD), bipolar disorder, and traumatic brain injury,[33] demonstrating a progressive shift in clinical strategies in mental health.

Similarly, the Research Domain Criteria (RDoC) are a research framework initiative developed by the US NIMH in 2010 that focuses on psychopathology as defined by both observable behavior and neurobiological measures.[32,34,35] RDoC represent a departure from traditional diagnostic approaches, where *a priori* disease definitions are based mainly on sets of presenting symptoms, and instead focus on fundamental biobehavioral features that are common to multiple heterogeneous disorders, or alternatively allow for a more homogeneous characterization of clinical features.[36] Given their origins as a research framework rather than one intended for clinical use, RDoC outline 7 distinct pillars that describe fundamental conceptual and practical differences from current psychiatric nosology and reflect NIMH's growing emphasis on translational neuroscience to guide research priorities.[36] The 7 pillars include incorporating: (a) a strong translational research approach; (b) a dimensional approach to psychopathology that ranges from healthy to disease states; (c) quantifiable measures of psychopathology; (d) a study sample and design that answers the specific research question; (e) an integrative model that considers both behavior and neurocircuitry; (f) a focus on constructs that have a solid base in scientific evidence; and (g) a flexible definition of disorders.[36] As such, RDoC represent a dynamic framework of flexible guidelines as opposed to a rigid set of domains, which should evolve and develop with the growing knowledge base in neuroscience.[35] The intention is that these guidelines can be applied in various ways, with the primary goal of facilitating the translation of research from basic studies in animal models or humans, to achieve a broader systems-based understanding of neuropathology and drug development.[36] With this approach, brain-behavior relationships common to a range of heterogeneous conditions or connoting subtypes of mechanisms within conditions can be addressed in research initiatives, rather than focusing on existing heterogeneous syndromes or disorders that are likely to consist of individuals with very different pathophysiological signatures.[36] As the main aim of precision psychiatry is to personalize treatments for patients with psychiatric disorders,

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the identification and measurement of common psychopathological mechanisms leading to diagnoses that have a greater emphasis on mechanisms of action is essential. Rather than focus diagnoses on syndromes not specific to diseases, precision psychiatry examines the independent components of each patient.[26] Biotypes are biologically defined subtypes of disease.[37] Their identification through precision psychiatry or RDoC approaches may, in some cases, align with the rich symptom classifications currently defined within the 5th revision of DSM (DSM-5),[38] in some may cut across diagnostic classifications, and in others may reflect unforeseen, novel subtypes within existing diagnoses.

In this review we aim to: (a) discuss the need for classification systems such as the DSM and ICD to evolve with scientific advancements and increase awareness in emerging investigators and clinicians of the value of this approach; (b) highlight the potential for RDoC to pave the way for transdiagnostic and improved treatment approaches and the growing interest in precision psychiatry globally; and finally, (c) examine current challenges and potential future directions and opportunities, acknowledging that RDoC's strength is that they provide a set of guiding principles that should continue to adapt with scientific developments into the future.

Limitations of current disease classification systems

The DSM-5 and the WHO's 11th revision of the ICD (ICD-11) currently represent the predominant systems of psychiatric classification around the world.[36,38-41] They rely heavily on the characterization of mental disorders by distinct symptoms, rather than incorporating other classes of measurements such as biological mechanisms. This is a reflection not only of the high degree of complexity of psychiatric disorders, but also of the lack of effective and noninvasive methods available to examine the complex biology of the nervous system in clinical settings, and the lack of knowledge of neuropathology at the time DSM-5 was developed. Psychiatric disorders such as MDD and schizophrenia are more heterogeneous than most disorders[42,43] and the considerable variability that exists in the course of the illness, treatment responses, and etiology has complicated the search for biomarkers.[42] A steady transition from viewing disorders such as schizophrenia as a disease entity, to understanding the syndrome status with several aspects of psychopathology and variation between individuals with the same diagnosis has been evident in recent years.[28-30] Many of the psychopathological markers identified are not unique to schizophrenia, supporting the emerging conceptualizations of psychiatric disorders as varying transdiagnostic collections of pathobiological features.[44] Similarly, the DSM-5 diagnostic criteria for MDD are highly diverse and span a broad range of symptoms; consequently, this clinical population is highly heterogeneous.[9] The diverse symptoms associated with MDD can impact differently on clinical factors such as daily functioning, responses to stressors, neurobiological and genetic correlates, associated risk factors, and even responsiveness to antidepressant treatment.[9] The impact of symptoms can often be masked by treatment-related side effects that resemble the very symptoms used to measure depression (eg, fatigue, insomnia or hypersomnia, weight and appetite changes, and sexual dysfunction).[9,45] Therefore, accurately identifying subtypes with homogeneous forms of this disorder is a crucial initial step to establishing more successful treatment strategies for MDD.

Despite this progress, it is only very recently that the promise provided by transdiagnostic approaches has been fully appreciated and applied in clinical trial design. It is possible that regulatory bodies such as the US Food and Drug Administration (FDA) may soon assess drugs based on their efficacy to address specific aspects of a syndrome, rather than on a syndrome heading such as schizophrenia. In DSM-5, subtypes of schizophrenia have been removed to encourage utilization of the dimensional assessments that are consistent with the heterogeneity that exists within this disorder.[46]

The expectation is that similar adaptations will be applied to the classification of other heterogeneous disorders in the future, with a gradual transition from the concept of a single major disease class to one where syndromes and dimensions of symptoms are considered. Establishing biomarkers of pathology in diagnosed patients that differ consistently from those of healthy controls is difficult when symptoms overlap across diagnoses and phenotypes are often shared. However, older DSM/ICD classification systems, which did not have the essential science to transform diagnostic approaches, are now framed such that new research approaches to the pathobiology of psychiatric disorders cannot be adequately accommodated. Although DSM/ICD classifications provide categorical diagnoses for psychosis, newer initiatives like the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP), which aims to characterize the intermediate phenotypes of psychosis, do not fit within this framework.[47-49] This has led to a growing number of anomalies in the diagnosis and treatment of psychiatric disorders. For example, the assessment of treatment efficacy within cohorts of patients diagnosed according to DSM disorder classifications is not particularly precise and tends to affect broad classes of symptoms. Whereas antidepressants, such as selective serotonin reuptake inhibitors, are mainstay treatments for depression; they are also routinely prescribed for general and specific anxiety disorders, PTSD, obsessive-compulsive disorder, and other disorders.[50] Similarly, antipsychotic drugs are prescribed in the treatment of bipolar disorder, borderline personality, and other severe disorders as well as schizophrenia and psychotic disorders.[51] These deficiencies in the framework of current nosology, combined with the lack of progress in the psychopharmacology industry over the past few decades, have led the research community to question the scientific status of DSM/ICD in recent years.[52] This resulted in the conceptualization of the RDoC, which aims to promote opportunities for discovery in aspects of psychopathology and drug discovery and has already made significant progress in transforming research approaches in psychiatry.

Conceptualizing RDoC

The RDoC are organized into 6 superordinate domains of functioning: negative valence, positive valence, cognition, social processes, arousal/regulatory systems, and sensorimotor systems (see Figure 1).[32] Each domain contains multiple constructs that are defined jointly by data from behavior or function, neural circuitry implicated in that function, and relevance to psychopathology.[32,34] Such domains and constructs are also intended to be exemplars of the kinds of mechanisms that trials can focus on. Instead of focusing on discrete disorders defined by DSM/ICD-based classifications, the RDoC capture mechanisms and features of brain-behavior inherent to normal-range functioning, and then determine how disruptions to these features correspond to psychopathology.[32,34,53] For the successful application of RDoC to generate personalized treatment, clinical study design should

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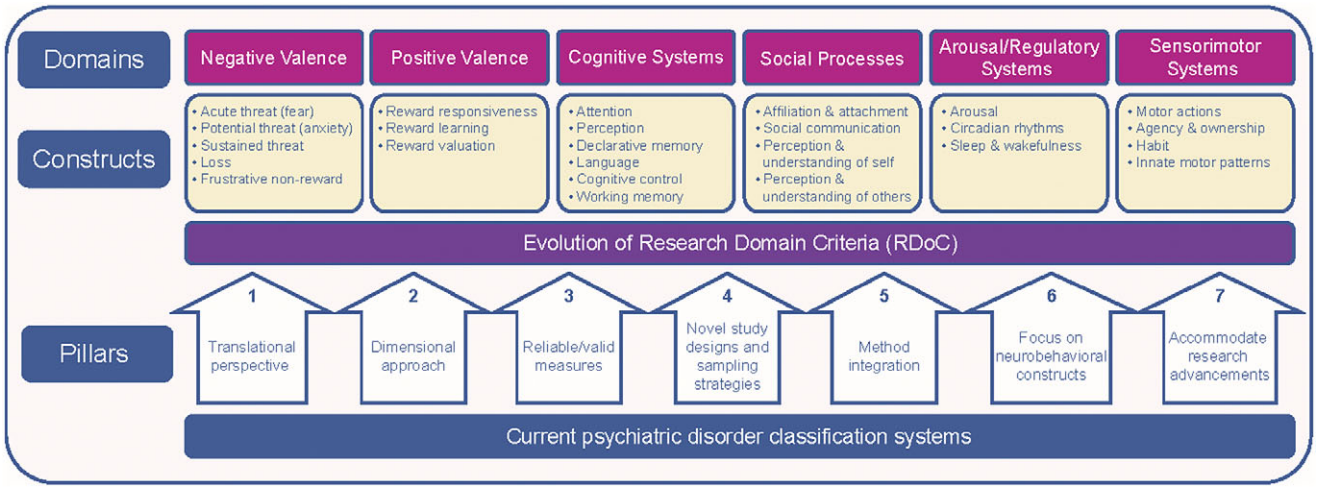

Figure 1. The Research Domain Criteria (RDoC) framework provides an organizational structure for research that evolved from 7 pillars exemplifying RDoC principles and considers mental health and psychopathology in the context of 6 major functional domains and associated constructs of basic human neurobehavioral functioning.

include biological analyses alongside reports of the patient's own subjective experiences of their illness when considering diagnosis and treatment options and generate clinical data where biology, behavior, and functioning are integrated.[26,52] The evaluation of symptoms through self-report is important in psychiatric disorders and often neglected in clinical judgments.[54,55] Further to the characterization of the neurobiology of clinical phenotypes, there is also a need to identify associations between specific treatment outcomes and neurobiological changes in psychiatric patients. Clinical studies that utilize consistent methods to examine brain-behavior changes across multiple treatment groups (as opposed to single treatment studies), would facilitate the identification of beneficial medications to specific patient subgroups. Identifying the biological correlates of successful treatment at an individual level would provide significant contributions to the knowledge base of specific treatment/symptom relationships and progress the implementation of personalized treatments in the clinic.

Application of RDoC in transdiagnostic research studies

Recent studies that have adopted the RDoC approach have explored how specific dimensional factors, relating to differences in neural, biological, and psychophysiological systems, demonstrate commonalities across patients in different DSM diagnostic categories, or equally have shed light on more homogeneous groups within existing diagnoses.[44,56-58] In the RDoC Anxiety and Depression (RAD) project that focused transdiagnostically on the spectrum of depression and anxiety psychopathology, associations between brain circuits, symptoms, behavior, and daily function were established in a manner that aligns tightly with units of measurement defined by RDoC.[59] The project developed and tested a system for quantifying neural circuits at an individual patient level.[59] Using these metrics, specific types of circuit dysfunction were mapped onto symptom-behavior profiles that were unrelated to diagnostic categories.[59] Circuit types also predicted response to different treatments, both pharmacotherapy and behavioral therapy.[59] The findings offer one approach to quantifying multiple units of data in a clinically applicable manner. In a complementary investigation across patients with anxiety and mood disorders, functional brain activity in the amygdala-ventral visual cortex circuit was disrupted during emotional processing.[60] This covaried transdiagnostically with trauma severity, PTSD symptoms, and functional impairment, where patients showing the lowest functional brain activity during emotional activation of the amygdala and ventral visual cortex reported the highest trauma scores, and those with the largest amygdala reactivity reported the lowest trauma scores, regardless of DSM diagnosis.[60] Similarly, the Human Connectome Project for Disordered Emotional States[61] provides another example of the growing trend in clinical research to establish definitive biological mechanisms that account for changes in RDoC domains (eg, negative valence, positive valence, cognitive systems) across psychiatric disorders as opposed to discrete DSM diagnoses.[61]

How RDoC can improve trial design and treatment outcomes

The recruitment of the RDoC framework in recent clinical studies has also transformed clinical trial design and the quality of trial outcomes.[62,63] In the past, regulatory bodies and funding agencies were bound by DSM criteria as the primary benchmark for clinical outcomes in clinical trial design. The RDoC now facilitate the targeting of transdiagnostic constructs across disease classifications in clinical research, including anhedonia, anxiety, cognitive functions, and suicidal behaviors.[62-65] For example, by using multiple levels of analysis, including brain imaging, behavioral performance, and clinical measures in a large sample of youths with anxiety, unique associations between anxiety severity, brain-behavioral measures of cognitive control, and responses to cognitive behavioral therapy (CBT) have been identified.[63] This knowledge provides essential guidance in relation to the treatment of clinically anxious individuals by distinguishing between subgroups for whom CBT would work and those for whom it would not.[63] Similarly, suicidal tendencies in adolescents with bipolar disorder were associated with reduced functional connectivity between the amygdala and left prefrontal cortex while viewing emotional stimuli, highlighting how the application of the RDoC framework in clinical studies can help identify biomarkers of psychopathology and targets for treatment.[65] The use of validated biomarkers of psychopathology to identify relevant patient groups and assess central engagement of new therapies represents a key opportunity in mental healthcare.[62,66] For example, the benefits of incorporating biomarker-based proof-of-mechanism assessments have been demonstrated in a study that examined brain activity using functional magnetic resonance imaging (fMRI) to confirm target

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engagement by a therapeutic agent for anhedonia in a mixed patient group of depressive and anxiety disorders.[62,67] Using fMRI as a biomarker in pharmacological trials for schizophrenia also offers important advantages and clinical benefits, including that it represents a relatively cheap and safe method to investigate alterations in regional brain activation and brain network connectivity during challenges with cognitive and behavioral tasks.[68] Adopting these approaches may accelerate the discovery of effective treatments for cognitive impairments associated with schizophrenia.[68] Other ongoing research initiatives aimed at identifying biomarkers of efficacious treatments across psychiatric disorders include the NIMH-funded multisite clinical trial Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC),[69] the Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT) study,[70] the Fast-Fail Trial in Mood and Anxiety Spectrum Disorders (FAST-MAS),[67] and the International Study to Predict Optimized Treatment in Depression (iSPOT-D).[58] These "fast-fail" approaches may improve misleading early phase drug development methods and promote the development of efficacious treatments.[23,62,66]

Precision psychiatry and why the incorporation of biological features is essential

Diagnosis based on self-reported symptoms alone, without an understanding of the biological complexities of an individual, may obscure the potential heterogeneity of biological factors underlying these symptoms that could contribute to differences in treatment responses in patients with similar diagnoses.[71] Personalized medicine that provides a detailed account and analysis of clinical symptoms through psychobiological assessment at an individual level, can be personalized, but not always precise. This view emphasizes that precision is reliant on measurement not only of biological parameters but also of symptoms and other psychosocial factors that contribute to the heterogeneity in the manifestation of psychiatric disorders across individuals. Identifying subgroups of patients who can be matched to their most effective treatments is the first step toward a fully personalized approach that tailors treatments to individuals. In psychiatry, the high degree of complexity involved in measuring brain function, coupled with the clinical diversity of psychiatric disorders and the need to incorporate measurement into systems supporting psychiatric practice, has meant that progress in the transition to precision medicine in psychiatry has been slower than in other specialties. However, a number of factors have made precision psychiatry a much more attainable goal in recent years: firstly, outcomes of consortium trials demonstrating that common biotypes and reproducible biomarkers for treatment prediction and response can be identified across multiple diagnostic classifications; secondly, the convergence and advancement of different fields, including neuroimaging, neuropsychology, and computational neuroscience; and thirdly, comprehensive datasets provided by multi-omics methods have made a clearer connection between genotype and phenotype. Indeed, genotype–phenotype relationships and how they impact on the clustering of clinical features, or biotypes, is evident within and across discrete diagnostic disease categories.

The identification of biotypes across psychiatric disorders

It has been demonstrated that common clinical features can also be associated with treatment response. For example, data emerging from the iSPOT-D initiative identifies pretreatment measures that predict or moderate MDD treatment response or remission to antidepressants in 1008 patients with a DSM-IV diagnosis.[10] Mapping the progression of side effects throughout the treatment course, and their association with treatment outcomes, can inform the development of predictive models to identify patient groups that may benefit from closer monitoring and revised treatment plans.

Across the spectrum of symptoms that are characterized in patients with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder, similar underlying patterns of neuropathology and common endophenotypes have been identified, despite different clinical diagnoses.[72,73] The B-SNIP consortium was established to investigate the broad array of intermediate phenotypes across psychotic disorders.[47] Significant overlap was reported in the clinical manifestation of symptoms, psychosocial functioning, and familial lineage across the 3 DSM-IV psychosis diagnoses used in B-SNIP, where patients with schizophrenia presented with more symptoms and lower psychosocial functioning relative to those with a psychotic bipolar disorder diagnosis.[47] Specifically, biotypes of psychosis associated with schizophrenia and schizoaffective disorder presented with the lowest scores on the Birchwood Social scale (worst psychosocial functioning) relative to those with psychosis from bipolar probands.[47] Although a difference in depressive symptoms was established across the 3 psychosis biotypes, a substantial overlap in the distribution of the affect characteristics was observed. Overall, data from the B-SNIP study suggest there is little evidence in support of distinct phenotypic clustering around traditional phenomenological diagnoses.[47]

In the same vein, the Tulsa-1000 study was initiated with the aim of using the RDoC framework to establish a robust and reliable set of variables to quantify positive and negative valence, cognition, and arousal domains in 1000 participants with mood, anxiety, substance use, or eating disorders.[74,75] Using a variety of measures including self-report, behavior (positive/negative valence, arousal, cognition), physiology (inflammatory and microbiome biomarkers), neural circuitry (neuroimaging and electroencephalography), cell, molecule, and gene units of analysis, these investigations plan to create a comprehensive clinical profile that transcends these diagnostic categories. The overarching goal is to establish an optimal set of assessments that could be used as a clinical tool to predict outcomes in these patients. Equipped with this information, computational models could be used by clinicians to match specific biotypes across these disorders with personalized, biologically based medical interventions. While the primary goal of the RDoC is to deepen the understanding of neurobiological correlates of psychiatric disorders, ultimately this understanding will inform and transform therapeutic developments and identify opportunities for prevention in psychiatric disorders.

The impact of the convergence of neuroscience and clinical fields

A deeper understanding of connectivity in the brain would undoubtedly strengthen our ability to precisely identify dysfunction at the individual patient level. Advancements in neuroimaging techniques such as fMRI that provide key information relating to neural circuit recruitment during behavioral tasks can significantly enhance our understanding of brain-behavior relationships in healthy and pathological states and offer more precise ways to classify psychiatric disorders and guide treatment choices.[26,76-78] In line with the RDoC approach, these brain imaging studies reveal a continuum of deficits in anxiety, depression, and psychosis.[60,78] In anxiety and depression, the precise pathophysiological

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mechanisms and neural circuits involved in symptoms of negative affect and cognition remain unclear.[79] To address this gap in knowledge, the mapping of large-scale neural circuits from functional imaging of the human brain to functions of self-reflection, emotion processing, and cognitive control in patients with depression and anxiety is under way at the Centre for Precision Mental Health and Wellness at Stanford University.[26] This program aims to bridge the knowledge gap between brain sciences and mental health to increase the accuracy and success of patient diagnosis and treatments.[26] To date, utilizing knowledge of the neural circuit disruptions generated from this research program has produced a rapidly increasing set of evidence that has helped guide clinicians in alternative treatment choices, leading to improved outcomes with pharmacotherapy and transcranial magnetic stimulation interventions.[26] Connecting neural circuit data from advanced imaging techniques with other common psychiatric assessments offers the potential for diagnostic subtyping and personalized tailoring of interventions in psychiatric disorders. Feedback from both clinicians and patients receiving neuroscience-related information indicated that having knowledge of neuroscience measures in advance of the first clinical appointment with the patient was useful for the implementation of clinical decision-making. From the patient perspective, receiving neuroscience-related information about their illness provided them with greater insight into their symptoms, how their brain functioned, and encouraged greater commitment to treatment.[26] Adopting a similar approach in a clinical study of mood and anxiety disorders, it has been proposed that the examination of brain circuit dysfunction associated with sleep impairment can effectively identify mechanistically coherent subtypes that may offer more promising targets for intervention.[80] Similarly, in patients with schizophrenia, where sleep disturbances are common, therapies that improve sleep may be of benefit.[81] Precision sleep technologies and physiological sensors offer a means to digitally phenotype variables such as sleep in real-time, providing unique opportunities to explore the biological correlates of sleep and identify links with depression/anxiety and schizophrenia symptoms and neural circuit abnormalities.[80,81] The FAST-MAS trial provides another example of a transdiagnostic study that demonstrated correlations between ventral striatal brain activity, improved measures of anhedonia, and a κ-opioid receptor antagonist in a diverse group of psychiatric patients. Other recent trials that have focused on uncovering the neurobiological basis of treatment outcomes in psychiatric disorders include the EMBARC research program. This study aimed to systematically identify and explore disease biotypes and potential biomarkers of antidepressant treatment outcome that could inform treatment management of depressive disorders and thus pave the way for personalized treatments.[68,72] Using diverse measures of reward processing from fMRI, clinical assessments, and demographics, changes in the prefrontal cortex and cerebellum were predictive of treatment outcomes for sertraline, and activity in brain regions such as the cingulate cortex, caudate, and orbitofrontal cortex predicted treatment outcomes with bupropion.[82] Similarly, the PReDICT study examined biological factors predictive of treatment outcomes that included functional connectivity, brain imaging, and pharmacokinetic analyses including effects on serotonin and norepinephrine transporter inhibition and hypothalamic–pituitary–adrenal axis sensitivity.[70,83,84] This study compared patient preference for CBT with antidepressants (escitalopram and duloxetine) on symptom severity and remission rates; although the moderating effect of patients' treatment preferences on outcomes did not impact on the remission rates, those that were matched with their preferred treatment were more likely to complete treatment.[70]

A lack of standardized common methodologies adopted across multimodal studies can make the integration and interpretation of findings relating to brain-behavior associations particularly difficult across individual studies.[80] To facilitate the clinical implementation of innovative digital tools, the continued use of hybrid models of neuropsychological evaluations has been proposed. These include technology-based assessments, integration of data science, and engaging with innovators in other fields to ensure continued optimization.[85] With this aim, recent NIMH initiatives such as the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) project and the Armamentarium for Precision Brain Cell Access project have been established to facilitate the incorporation of innovative neurotechnologies that will allow more dynamic spatial and temporal visualization of complex neural circuits and the targeting of specific cell types.[86,87] Within this framework, the BRAIN Initiative Connectivity across Scales (BRAIN CONNECTS) Network seeks to map the diverse techniques now available for brain imaging and align these with suitable research questions.[88] Similarly, the BRAIN Initiative Cell Atlas Network (BICAN) established in 2022 aims to generate a comprehensive atlas of cell types in the human brain, which would vastly increase our understanding of the complexity of the human brain in healthy and disease states.[86,89] It is expected that these advances will facilitate the implementation of precision psychiatry approaches and ultimately lead to novel methods for the treatment and prevention of brain disorders.

How omics analyses can progress precision psychiatry

Recent years have seen extensive advances in psychiatric metabolomic, genomic, and epigenomic techniques in disorders such as schizophrenia, bipolar disorder, MDD, autism spectrum disorder, attention-deficit hyperactivity disorder, intellectual disability, and anorexia nervosa.[30,90,91] The complex genetic architecture and gene–environment interplay that contribute to the etiology of many psychiatric disorders has posed challenges for attempts to translate genomic and epigenomic findings into mechanistic insights. In a systematic approach, the Trans-Omics for Precision Medicine program was established to investigate the genetic and biological correlates of heart, lung, blood, and sleep disorders, with the principal objective of improving clinical approaches to diagnosis, treatment, and prevention.[92] In psychiatry, the comparison of data from Genome-Wide Association Studies (GWAS) across disorders has provided increasing support for systematically related transdiagnostic mechanisms. Recent studies have demonstrated the considerable overlap in risk gene involvement and neuropathology between schizophrenia and early onset neurodevelopmental disorders such as autism spectrum disorders, intellectual disability, and attention-deficit hyperactive disorder.[93] Symptoms of these disorders also vary in severity, falling anywhere along a broad spectrum and thus, differ quantitatively as well as qualitatively. Similarly, results of a GWAS of mood instability as a trait in a large population cohort (UK Biobank) reported 46 unique loci associated with mood instability that may be relevant for the identification of novel transdiagnostic drug targets.[94] Although GWAS provide genetic targets that could potentially inform future drug development initiatives in mental health, their value in precision medicine at an individual level is limited.

Metabolomics is defined as a large-scale analysis of metabolic profiles in both healthy and diseased state systems. These techniques

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provide a comprehensive characterization of metabolic phenotypes at an individual level, which can then facilitate precision medicine at several further levels, including the discovery of pathological biomarkers and new therapeutic targets. Studies examining metabolomic changes across multiple psychiatric disorders, including schizophrenia, bipolar disorder, and MDD, suggest these analyses hold promise in identifying metabolic pathways linked to pathophysiology and treatment response, as well as its potential in biomarker identification.[91] In light of accumulating evidence supporting a role for environmental factors in the etiology of psychiatric disorders, particularly neurodevelopmental, the field of epigenetics has uncovered increasing evidence of genomic instability during brain development that may represent novel targets for diagnosis and treatment.[95,96] Epigenetic dysregulation is associated with neuropsychiatric diseases such as MDD, autism spectrum disorders, Fragile X, Rett syndrome, and schizophrenia, and as such, also represents a promising source of biomarkers of neuropathology that can aid in the parsing of distinct biotypes across psychiatric disorders.[90]

Other biological analyses such as oculomics, which measures nonophthalmological anatomical and physiological biomarkers in the eye, have also shown promise as biomarkers of brain health.[97] In schizophrenia, shrinkage of the retinal neural layers occurs in parallel with illness progression, brain volume loss, and cognitive impairment, and represents a means of assessing pathophysiology and treatment efficacy in patients.[98]

The integration of large-scale analysis of datasets from high-throughput sequencing and genotyping technologies, broad-spectrum omics studies in combination with the wealth of data from neuroimaging, consortia, repositories, and smartphone apps, can be achieved using artificial intelligence (AI) and machine-learning technologies (eg, support vector machines, modern neural-network algorithms, cross-validation procedures), thus affording new insights into complex patterns in brain, behavior, and genes.[99] These multifaceted initiatives could advance our understanding of disease pathology and accelerate the transition from current DSM classifications to a biological-based redefinition of major psychiatric disorders.[100,101]

Precision psychiatry and optimization using digital technologies

The COVID-19 pandemic has fast-tracked the implementation of digital technologies and telemedicine into everyday clinical practice and also into clinical trial design.[85,102,103] Technologies including smartphone apps for continuous behavioral monitoring, virtual reality assessment paradigms, and the capacity to integrate and analyze multiple heterogeneous variables using machine learning algorithms to develop clinical outcome prediction models, provide promising vectors for improving mental healthcare (Figure 2).[85,104-107] Considering that these technologies have already become embedded in everyday practice for many patients, facilitating patient–clinician communication that lies at the heart of diagnosis and treatment in psychiatry,[102] alongside the growing prevalence of mental health issues globally,[1] it is highly likely that telepsychiatry will continue to be utilized into the future.[108] Telepsychiatry, described as psychiatric consultations in either real-time or with a delay (synchronous vs. asynchronous) using a variety of media, has been shown to be effective in extending clinician–

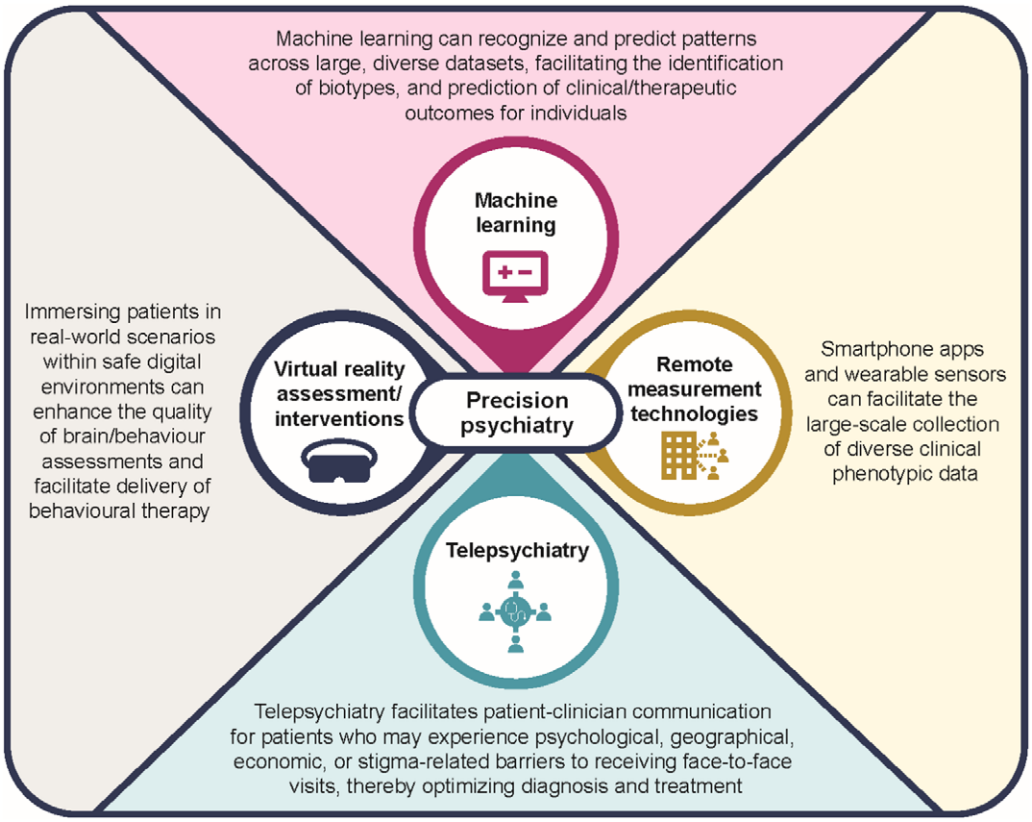

Figure 2. Summary of how AI and digital technologies can facilitate the implementation of precision psychiatry.

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patient access, maintaining high levels of patient satisfaction, diagnostic reliability, and positive clinical outcomes for patients.[108]

In addition to remote delivery of consultations and therapies, remote measurement technologies allow for more precise and objective clinical measures of function to be collected and analyzed. With worldwide ownership of smartphones already at 5.3 billion in 2018,[109] there is a unique opportunity to utilize these devices to screen, assess, monitor, and even intervene in psychiatric conditions. As well as being accessible to patients, smartphones have a host of embedded sensors (eg, light sensors, global positioning systems, cameras, and microphones) and capacity for software installation that can be leveraged to collect continuous real-time, clinically relevant behavioral information (eg, physical activity, social interactions, medication adherence, symptom self-reports) with the consent of their owners. In one study, smartphone-assisted remote data collection in patients with psychosis and individuals who are otherwise considered healthy revealed real-time/place phenomenological, affective, and behavioral differences between clinical and nonclinical samples of people who experience auditory verbal hallucinations.[107] By adopting this multimodal, smartphone data collection system, it was demonstrated that hallucinations present across a range of health states.[107] The clinical group reported more frequent and powerful experiences when compared with nonclinical individuals,[107] which has not been demonstrated by laboratory-based measures,[110] thus supporting the RDoC framework's dimensional approach to psychopathology.[107] Continuous and objective monitoring of clinical features by remote digital tools have also been beneficial in targeting impaired functional domains in patients with Alzheimer's disease,[111] even predicting depressive symptom severity in a healthy population.

In parallel with the growth of data collection technologies (eg, mobile health apps, digital phenotyping) that is increasing the variety of clinical parameters that can be measured, large volumes of data are also accumulating in clinical neuroscience, requiring the need for intelligent algorithms to generate meaningful analyses from these large and diverse clinical datasets. Over the decade, dramatic technological developments in AI, which encompasses disciplines such as machine learning and deep learning, have resulted in the progressive exploration of ways in which AI can be used to recognize and predict patterns across large and diverse clinical datasets in fields such as oncology and gastroenterology.[112,113] More recently, there has been a remarkable increase in the application of digital and AI technologies in clinical neuroscience research.[114,115] Support for the use of computational methods and machine learning algorithms alongside individual behavioral measures is provided by the NIMH Individually Measured Phenotypes to Advance Computational Translation in Mental Health (IMPACT-MH) initiative established in 2023, which aims to identify and characterize novel clinical signatures that can be used for personalized prediction and clinical decision making in psychiatric disorders.[116]

Despite the obvious benefits of adopting digital technologies and a transdiagnostic multimodal approach within the RDoC framework in clinical studies, these analyses can often be expensive to implement in a consistent manner. The cost-effectiveness of pharmacogenomics and big data analyses is still not well established and may restrict their use in clinical practice, especially in low-income countries.[117,118] However, new long-term development strategies for global genomic medicine that recognize the individual country's pressing public health priorities and disease burdens have been established to address geographical health disparities for precision medicine.[119]

RDoC in clinical practice: challenges and opportunities

Current challenges

The RDoC framework will need to confront a number of conceptual, methodological, logistical, and ethical challenges in order to facilitate its implementation in clinical settings.[52] These include the complicated and entrenched nature of psychiatric diagnoses, the complexity, and costs associated with the collection and analysis of multiomics data, the need for specialized training in precision health for healthcare staff, as well as the ethical challenges discussed below.[52]

Ethical challenges that warrant further consideration before this approach can be implemented include protecting the privacy and security of patients' data and addressing concerns about responsibility when collecting and analyzing comprehensive biological datasets, health risks associated with a lack of access to precision medicine, and maintaining health equity on a global level.[120-122] Ethics review committees face immense challenges when assessing risks and benefits in the absence of comprehensive regulatory policies and clear guidelines on appropriate data safeguards to address public concerns, such as the protection of individually identifiable information.[122] To address these issues, the recruitment of trained personnel on ethical review committees with expertise in data science, bioinformatics, and cybersecurity methods, alongside the development of clearer guidelines on the assessment of risk–benefit scenarios of big data research in psychiatry, is essential.[122] The National Institutes of Health (NIH) oversees numerous clinical data repositories within its data archive (https://nda.nih.gov/) for which processes to facilitate researcher access and associated ethical concerns are currently under consideration, with the aim of encouraging wider data sharing and the maximal use of collected datasets, while also ensuring data protection and appropriate ethical conduct.[123] In the transition toward a translational and transdiagnostic approach to psychiatry, it is feasible that some of the initial clinical translational applications would simply involve the use of current treatments, and/or enriching recruitment in clinical trials, as well as adding objective target measure outcomes that correlate to RDoC domains in the development of novel therapies. From this perspective, there may not be any obvious health risks introduced, but rather the opportunity to help select currently approved treatments, and/or to complement current trial recruitment criteria and outcome endpoints with measures that expand beyond diagnostic group and symptom scales.

It is also important to consider the potential health risks associated with a lack of access to precision medicine for psychiatric patients. The failure to optimize treatments for patients with these chronic debilitating disorders may itself contribute to inadequate response to treatments, adverse effects of treatments, and nonadherence to medications over time.[124,125] It is also essential to consider the patient perspective when administering mainstay treatments for psychiatric disorders that often do not address symptoms at an individual level. Clinicians have an ethical obligation to seek out the best possible treatments for individual patients, particularly in disorders such as schizophrenia and psychotic disorders where considerable variation exists in the course of illness and symptom presentation from patient to patient. There is a need

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to expand clinical guidelines to assist clinicians in best-practice processes of incorporating emerging new evidence relating to biomarkers for diagnosis and treatment. Guidance on communicating the principles and processes associated with precision medicine to the patient is also essential to ensure consistency of approach and transparency in the decision-making process.

When considering the inclusion of genomics and digitally collected health data in precision psychiatry in future clinical studies and in clinical practice, regulations to protect personal data while ensuring transparency in the collection and use of individual patient data are essential.[126] It is also important to consider that despite the significant contribution digital health tools provide in addressing the unmet needs of patients with technological know-how, they may not be accessible to many individuals who do not possess or cannot afford smartphones or the expertise to use them.[126-128] Current initiatives for digital app regulation include: the US FDA formal guidelines on its approach to regulating "Mobile Medical Apps"[129]; NIH-funded projects[130]; and the APA app evaluation framework[126] and the International Digital Mental Health Network (IDMHN),[131] which are both supplemented with publicly available self-certification checklists (where developers answer questions derived from the APA evaluation framework about their apps).

Aligning the RDoC with DSM/ICD nosologies

In its inception, the RDoC framework was intended to concentrate on constructs identified on the basis of solid scientific evidence to serve as a platform for ongoing research and does not claim to include all of the psychopathology listed in the DSM and ICD nosologies.[36] The RDoC matrix outlines these constructs as a basis for operationalizing ongoing assessments and does not "prescribe" which measures are pre-determined for each construct or subconstruct. Consequently, there is not necessarily a direct mapping between RDoC constructs and assessments developed from a different tradition, such as in neuropsychology; in clinical settings, existing assessments may lack sensitivity to the specific cognitive-emotional constructs that are key to the RDoC domains.[132] In addition, as the RDoC domains are also not aligned with DSM diagnoses, some reconfiguration and reorganization may be required, for example, the Positive Valence Systems Scale, a measure of the Positive Valence Systems domain of the NIMH's RDoC, has demonstrated validity in identifying reward-related abnormalities in depression,[133] which may also translate to related disorders. Future developments of the RDoC framework should include the creation of new rating scales that are specific to discrete domains, thereby avoiding overlap.[57,132] Thus, in future years, neuroscience-led efforts to optimize measures that more specifically operationalize RDoC constructs may eventually lead to their utilization in informing classification and diagnosis within future revisions of the DSM/ICD classification systems. Although the RDoC were not established with a specific goal of informing treatment choices and outcomes, ongoing refinement of the RDoC domains might also address the current gap between gold-standard diagnostic criteria and diagnosis-focused clinical scales that are used to measure therapeutic benefit and the domains of function studied under RDoC. The lack of correspondence between RDoC constructs and gold-standard therapeutic outcome measures makes it difficult to mine large clinical and biological datasets generated over decades of DSM-based research.[132] Other domains of clinical outcome, such as self-perception and response biases that are associated with functional outcomes and suicidal ideation, are also not captured in the RDoC as yet.[132,134]

Future opportunities

Given that traditional diagnostic criteria emphasize the impact of capacity for functioning in multiple domains, including social and occupational, RDoC are well positioned to inform the development of outcome measures that link brain and behavior to function. Since their inception, RDoC have incorporated cross-cutting dimensions such as neurodevelopment, and the integration of neurodevelopmentally based tools for clinical decision-making that may also enrich RDoC's real-world impact.[135] The initial step of establishing quantifiable and assessable biomarkers in real-world settings that can operate in parallel with existing psychiatric decision models, and then identifying where new emerging biological data and candidate biomarkers might be of value, is required to fast-track this transition.[136] The strength of the RDoC is that they are framed so that they can constantly evolve with scientific developments, and can be adapted and optimized according to the most recent data with the aim of meeting diagnostic and therapeutic goals and informing the design of future clinical trials.[35] It is only through the continuous refinement of RDoC using the enormous wealth of data yielded by these investigations that a progressive path can be carved toward a more concrete model for precision psychiatry. This evolving framework would permit closer linkages to be made between assessment/diagnosis and treatment/prevention in psychiatric disorders.

Another opportunity presented by the incorporation of RDoC into clinical research and practice derives from the facilitation of examining psychiatric disorders along neurodevelopmental spectra, rather than supporting the traditional dichotomy of a diagnosis of illness or health. As it is increasingly recognized in the case of psychosis, there are various degrees of psychopathology, usually presenting in a progressive manner; from at-risk mental state, ultra-high risk for the psychosis prodrome, to first-episode psychosis and later schizophrenia/schizoaffective disorders. Diverse manifestations are consistently characterized by deficits in RDoC domains, such as cognition.[137] In addition, the concept of vulnerable periods of psychopathology, when environmental risk factors may impact more permanently on brain and behavior, is more accessible when using a dimensional outlook as outlined in the RDoC, combining analysis from continuous biological data provided by mobile sensors, passive monitoring, and ecological momentary assessments.[123] Studying these periods are key to understanding how the timing of events can impact risk for atypical development.

Providing training and guidance on RDoC approaches to clinicians

The evidence to date suggests there is potential for precision psychiatry using an RDoC approach to influence clinical development in the short and long term by providing a bridge into clinical practice. However, there is a need to raise awareness and educate newly qualified clinicians about RDoC. To address this need, the Discovery Clinic at Stanford University was established in 2013. Its main goal was to initiate an understanding of the clinical utility of the RDoC approach and involved a unique partnership between a community mental health center encompassing clinics and clinical training for mood and anxiety issues and a technology-enabled healthcare company integrating mental health with primary care.[26]

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Within this initiative, 51 feedback sessions were conducted to discuss and refine the processes and didactic sessions for clinic trainees, and clinicians provided qualitative feedback on the patients' experiences.[26] Two valuable insights emerged from both the clinician and patient perspectives: from the clinicians' point of view, having access to multiple sources of medical data relating to the patient that is not always provided in the clinical interview process (eg, evidence of cognitive impairment, or extreme anhedonia even in the absence of overall severity of symptoms and knowledge of neural circuit dysfunction) was beneficial; from the patient perspective, having access to their individualized report information had the effect of destigmatizing and demystifying the clinical process.[26] It was evident from these findings that presenting patients with a shared model of understanding of RDoC diagnostic/treatment processes and explaining how the underlying biology is modifiable through medical interventions improves the patient experience by potentially diminishing shame and self-blame.[26]

Subsequently, a clinical translational program to incorporate feedback and develop structured case examples for clinical training programs was initiated and led to the launch of the Stanford Translational Precision Mental Health Clinic in 2021. This clinic aims to customize treatments for patients with mood and/or anxiety disorders who are not responsive to existing therapies by identifying biological subtypes through cutting-edge, multimodal assessment.[26] Further initiatives of this nature that promote the implementation of precision medicine in clinical settings within other domains of psychiatry are essential. However, one of the challenges to integrating ongoing research developments directly with clinical practice can be the geographical location of research and clinical sites, generating obstacles for information exchange and opportunities for clinical training. Precision psychiatry research involving neurobiological and other pathobiological measurements is typically undertaken in dedicated research settings where study design, outcomes, and data dissemination are largely driven by clinical research goals as opposed to real-world clinical application. Consequently, communication of potentially important pathobiological assessments and biomarkers that may support actionable diagnostic and treatment decisions is impeded, and opportunities to test the generalizability of findings into real-world evidence settings are missed. Facilitating the integration of research outputs with clinical practice may allow clinical training programs to unfold more naturally. The current lack of opportunities to train clinical residents and other prescribing and treating clinicians, such as nurse practitioners and physician assistants, in the use of new measurement techniques and application of the diverse biological outputs from these methods hinders the potential to incorporate new and more precise assessments and treatments in the clinic. Clinical training programs informed by the experiences of neuroscientists, clinicians, and patients during the course of translational research programs would accelerate the transition to precision psychiatry and provide a clinical toolkit that is equivalent to that of cardiology.[138]

Conclusion

Despite the highly complex nature of the brain and the obvious challenges associated with the implementation of precision medicine in heterogeneous psychiatric disorders, remarkable advancements have been made in recent years. Continued progress relies on ensuring that advances in the neurobiological understanding of the pathology, treatment, and disease progression of psychiatric disorders are mapped onto an understanding of clinical outcomes and treatment responses and inform future treatment development.

As an initial step forward, deeper insights into the links between brain and behavior, integrating theoretical and computational approaches, will allow patients to be grouped according to domains that are coherent across neurobiology and psychiatric symptoms and increase the accuracy of matching patients with efficacious medications and interventions. RDoC offer a framework for extending data-driven approaches in the identification of new clinical phenotypes in psychiatry, leveraging advancements in AI and computational neuroscience (see Figure 3).

Secondly, a translational and transdiagnostic research culture that encourages the complementary use of RDoC alongside current DSM/ICD nosology is important in the immediate future to enhance clinical trial outputs. RDoC can function within current DSM/ICD diagnoses, enriching current clinical trials and making significant contributions to our understanding of the biological correlates of clinical phenotypes through the mining of existing clinical and biological datasets.

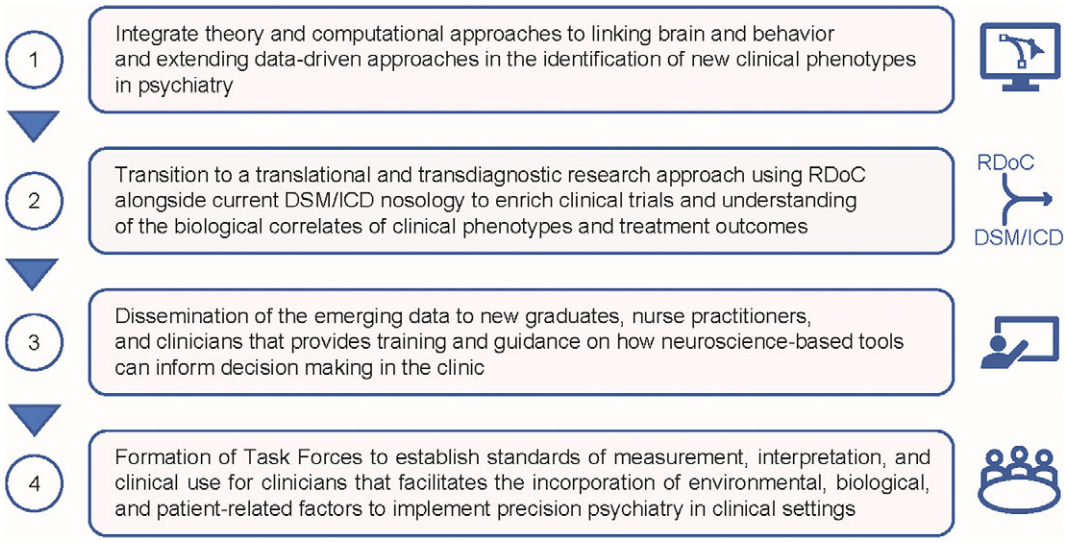

Figure 3. Proposed steps in the implementation of precision psychiatry.

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Thirdly, the growing knowledge base of the biological constructs of psychopathology generated using frameworks such as the RDoC, and the benefits for diagnosis, treatment, and prevention of psychiatric disorders, should be incorporated into clinical training programs. Dissemination of the emerging data in this fast-evolving field would prepare graduates, nurse practitioners, physician assistants, and other clinicians on how neuroscience-based tools can inform decision-making in the clinic.

Finally, these concerted efforts should aim to develop and optimize a clear set of guidelines and a clinical toolkit for clinicians that examines environmental and biological factors, in combination with individual self-report assessments, to facilitate the implementation of precision psychiatry in clinical settings. It is important that the precision approach allows insights from neuroscience to directly translate into clinically actionable tools. This will bring the field of psychiatry in line with recent initiatives to implement precision medicine in other clinical fields. Ultimately, the aim of precision psychiatry is to improve the quality of life of patients with psychiatric disorders and possibly even identify opportunities to intervene to prevent psychopathology.

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