Global mental health has emerged as an important specialty. It has drawn attention to the burden of mental illness and to the relative gap in mental health research and services around the world. Global mental health has raised the question of whether this gap is a developmental issue, a health issue, a human rights issue, or a combination of these issues—and it has raised awareness of the need to develop new approaches for building capacity, mobilising resources, and closing the research and treatment gap. Translational neuroscience has also advanced. It comprises an important conceptual approach to understanding the neurocircuitry and molecular basis of mental disorders, to rethinking how best to undertake research on the aetiology, assessment, and treatment of these disorders, with the ultimate aim to develop entirely new approaches to prevention and intervention. Some apparent contrasts exist between these fields; global mental health emphasises knowledge translation, moving away from the bedside to a focus on health systems, whereas translational neuroscience emphasises molecular neuroscience, focusing on transitions between the bench and bedside. Meanwhile, important opportunities exist for synergy between the two paradigms, to ensure that present opportunities in mental health research and services are maximised. Here, we review the approaches of global mental health and clinical neuroscience to diagnosis, pathogenesis, and intervention, and make recommendations for facilitating an integration of these two approaches.

Introduction

The field of global mental health has emerged in response to growing awareness of the considerable contribution of mental disorders to disease burden in both developed and developing countries, the relative lack of resources for mental disorder interventions worldwide, and the need for more research on how best to provide mental health services in low-resourced settings. Several key perspectives from the global mental health literature include the argument that mental health services is a human rights issue. Global mental health has raised the question of whether this gap is a developmental issue, a health issue, a human rights issue, or a combination of these issues—and it has raised awareness of the need to develop new approaches for building capacity, mobilising resources, and closing the research and treatment gap. Translational neuroscience has also advanced. It comprises an important conceptual approach to understanding the neurocircuitry and molecular basis of mental disorders, to rethinking how best to undertake research on the aetiology, assessment, and treatment of these disorders, with the ultimate aim to develop entirely new approaches to prevention and intervention. Some apparent contrasts exist between these fields; global mental health emphasises knowledge translation, moving away from the bedside to a focus on health systems, whereas translational neuroscience emphasises molecular neuroscience, focusing on transitions between the bench and bedside. Meanwhile, important opportunities exist for synergy between the two paradigms, to ensure that present opportunities in mental health research and services are maximised. Here, we review the approaches of global mental health and clinical neuroscience to diagnosis, pathogenesis, and intervention, and make recommendations for facilitating an integration of these two approaches.

Psychiatric diagnosis

The WHO has had a leading role in developing global classification systems, including a nosology of mental disorders. An International Classification of Disease (ICD) diagnosis of a mental disorder comprises a key first clinical step in relevant WHO treatment packages. The forthcoming ICD-11 edition will focus on considerations such as clinical utility, use in primary care systems, and use by clinicians without specialised training in mental health. The ICD-11 relies on diagnostic guidelines to describe mental disorders, emphasising the distinction between disorders and disability, and highlights the importance of comorbidity between mental and physical disorders.

From an alternative perspective, the National Institute of Mental Health (NIMH) in the USA has established the Research Domain Criteria (RDoC) as a new conceptual framework for psychiatric assessment and future research. By contrast with the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM), which provides diagnostic criteria for mental disorders, RDoC focuses on broad domains (eg, negative affect, positive affect, and cognition) that cut
across a range of mental disorders. These broad domains are defined with the following units of analysis: components of circuits (genes, molecules, and cells), circuits, and circuit outputs (behaviour, physiological responses, and verbal reports or clinician-completed instruments), which provide a bio-behavioural signature for every individual. RDoC principles include an emphasis on a translational approach, on behavioural and physiological dimensions, and an equal focus on behaviour and neurocircuitry.15

In the area of diagnosis and assessment, the approaches of global mental health and clinical neuroscience have different emphases. Global mental health uses a few simple categorical diagnoses and relies mainly on the judgment of non-specialised clinicians, whereas clinical neuroscience encourages complex dimensional measures and uses sophisticated laboratory techniques. Translational neuroscientists tend to be optimistic that psychiatric diagnosis will ultimately use biomarkers,9 whereas public health practitioners are aware of the many societal factors that influence the diagnostic process and they tend to be less optimistic about the potential use of biomarkers.7,8 Biomarkers might be more easily identified for some neuropsychiatric disorders (eg, Alzheimer’s disease) than others (eg, depression and anxiety), although there is ongoing interest in population-level biomarkers for common mental disorders.19

Despite the differences highlighted above, the approaches of global mental health and clinical neuroscience also have potential synergies in the area of diagnosis and assessment. First, global mental health specialists and clinical neuroscientists are acutely aware of the limitations of present psychiatric classification systems, the challenge of delineating the spectrum of abnormality from health, and the need for improved approaches to diagnosis and assessment. Second, experts in both fields agree that present classification systems such as the DSM-5 and ICD-11 have value in particular clinical contexts, and that they do therefore play a key part in optimising care. Third, it is agreed that assessment of the individual and of the environment are important in clinical practice and research. Indeed, several advances in psychiatric diagnosis have included both global mental health and clinical neuroscience perspectives (table).

We provide a few recommendations from these considerations (panel). First, it is important to continue an iterative approach to the development of new diagnostic classifications and new assessment measures, with the goal of optimisation of diagnostic validity and clinical utility. How frequently such revisions should occur has been debated; however, the general consensus is that psychiatric nosologies should reflect accumulating research and in turn encourage new research. Each revision of the psychiatric nosology has raised concerns about the extent

<table>
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<tr>
<th>Diagnosis</th>
<th>Global mental health perspective</th>
<th>Clinical neuroscience perspective</th>
<th>Synergy</th>
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<tbody>
<tr>
<td>Diagnostic thresholds</td>
<td>Diagnostic thresholds differ across different contexts; for example, the diagnostic threshold of schizophrenia once differed between the USA and UK.</td>
<td>Narrowly defined schizophrenia has diagnostic validity, schizotypal personality disorder is genetically related.</td>
<td>Development of reliable operational criteria for the diagnosis of both schizophrenia and schizotypal personality disorder.</td>
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<tr>
<td>Responses to trauma</td>
<td>Responses to adversity are often characterised by resilience, and we should be wary of medicalising adaptive responses.</td>
<td>Narrowly defined PTSD has diagnostic validity, but the spectrum of responses to trauma includes adjustment disorder.</td>
<td>Development of reliable operational criteria for PTSD and adjustment disorders in a single DSM-5 chapter trauma and stressor related.</td>
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<tr>
<th>Pathogenesis</th>
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<tr>
<td>Early adversity</td>
<td>Early childhood adversity is a major global health issue, which could have long-term sequelae and substantial health costs.</td>
<td>Early adversity alters specific neurocircuitry and particular molecular patterns, which helps explain the chronic sequelae of early adversity.</td>
<td>Studies that have addressed the effects of early adversity on mental and physical health, drawing productively on data from different contexts.</td>
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<td>Resilience</td>
<td>Although the majority of the population is exposed to psychological trauma, most remain resilient, and a minority develops psychiatric disorder.</td>
<td>The neurobiology of the response to stressors is increasingly well understood, as is the neurobiology of the dysfunctional responses seen in PTSD.</td>
<td>Studies that have addressed resilience despite adversity, drawing productively on data from different contexts.</td>
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<th>Treatment</th>
<th>Global mental health perspective</th>
<th>Clinical neuroscience perspective</th>
<th>Synergy</th>
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<tr>
<td>Optimisation of interventions</td>
<td>There are insufficient psychiatrists and psychologists in low-income and middle-income countries to cover treatments for those with serious mental illness.</td>
<td>Serious mental illnesses such as schizophrenia respond to psychoeducation and use of antipsychotic agents.</td>
<td>Development of task-shifting and task-sharing strategies that empower non-specialised health-care workers to deliver interventions for disorders such as schizophrenia.</td>
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<tr>
<td>Preventive measures</td>
<td>Early childhood is an important time for intervention, given that early adversity and early onset of symptomatology are key risk factors for adult mental illness.</td>
<td>The neurobiology of the response to developmental stressors and to environmental enrichment is increasingly understood.</td>
<td>Interventions that promote early development and resilience, including improved care of women with maternal depression.</td>
</tr>
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PTSD=post-traumatic stress disorder.

Table: Case examples of synergies between global mental health and neuroscience.
Panel: Recommendations for strengthening the integration of global mental health and clinical neuroscience in research on psychiatric diagnosis, pathogenesis, and intervention

Diagnosis
- Adopt an iterative approach to development of new diagnostic classifications and new assessment measures, aiming for optimisation of diagnostic validity and utility
- Evaluate the extent to which dimensional assessments of bio-behavioural domains are reliable and feasible across multiple settings
- Incorporate measures that go beyond the individual and his or her immediate environment, to include also relevant structural factors (eg, economic inequality)

Pathogenesis
- Include a strong focus on the measurement of environment in genetic studies of mental disorders
- Incorporate a focus on cultural context in neuroscientific studies in general
- Employ more detailed assessments of the range of components that constitute the social environment in research on risk factors

Treatment
- Incorporate neuroscience predictors (eg, genetics) and endpoints (eg, brain imaging), or other aspects of the RDoC framework, into trials in low-income and middle-income settings
- Integrate multiple constructs (eg, both biological and social risks) into a range of randomised controlled trials, in different settings
- Take lessons (on both pharmacotherapy and psychotherapy) for high-income countries from low-income and middle-income research, and vice versa

Ethics
- Encourage neuroethics research at the intersection of global mental health and clinical neuroscience

to which changes are evidence based, however, such concerns should only encourage a more vigilant assessment of the relevant data. Indeed, there is an argument that psychiatry has made a significant contribution to medical nosology by establishing research methods on the assessment and revision of diagnostic criteria.

Second, as we develop more sophisticated dimensional assessments of bio-behavioural domains and underlying endophenotypes (ie, heritable traits associated with illness), it is important to assess the extent to which these assessments are reliable and feasible across multiple settings. Functional brain imaging, for example, is at present not accessible to most individuals with common mental disorders. However, self-ratings of constructs, such as negative affect or anxiety sensitivity, which might be particularly relevant in the assessment and treatment of mood and anxiety disorders, might be possible in primary care populations in many culturally diverse settings. With the advent of mobile technologies (eg, cell phones), it might be possible to capture a range of physiological and behavioural measures in a cost-efficient way in a wide variety of settings. In the future, a balance of traditional diagnostic approaches (as represented in ICD-11) and alternative measures (as represented by RDoC) could be used in non-specialist primary health-care clinics to evaluate a range of mental health disorders in various clinical settings.

Third, as we develop more sophisticated interventions in global mental health and clinical neuroscience, it will be relevant to include in our diagnostic classifications and assessment measures factors that go beyond the individual and his or her immediate environment. This will include more comprehensive assessments of structural factors or exophenotypes, such as levels of poverty and food insufficiency. The present focus of DSM-5, ICD-11, and RDoC is on mental illness in particular individuals. However, both the traditional and alternative approaches explicitly recognise the importance of the individual’s environment; for example, DSM-5 encourages a cultural formulation, whereas RDoC includes measures of environmental adversity. Diagnostic criteria that refer to environmental context are key in reducing false-positive diagnoses; such criteria include requiring that symptoms are disproportionate relative to the circumstances, that symptoms be developmentally inappropriate for childhood disorders, and that symptoms occur in several contexts.

A thorough assessment of environmental factors requires rigorous evaluation of variables that might affect mental health; these include income generation and education opportunities, housing and social services, and other social determinants of mental health.

Pathogenesis
The WHO’s comprehensive mental health action plan, adopted by the World Health Assembly in May, 2014, made several key points about risk for mental illness, drawing on earlier work such as that of the WHO Commission on Social Determinants of Health. Mental health is influenced not only by individual attributes but also by the social circumstances and environment. Some groups might be particularly susceptible, including households living in poverty, people with chronic health disorders, minority groups, and people exposed to or displaced by war or conflict. People with a mental disorder might have an additional set of vulnerabilities and risks, including an increased likelihood of experiencing disability and premature mortality, stigma and discrimination, social exclusion, and impoverishment.

Clinical neuroscientists have focused on several other risks for mental disorder. There has been a particularly strong research focus on the neurogenetics of mental disorder, and efforts to increase funding in this area are ongoing. A strong emphasis has been put on
neuropasticity and disruptions in neural circuitry, with ongoing research programmes promising to further explore the animal and human genome. As exemplified by the RDoC approach, clinical neuroscience aims to understand the relevant underlying mechanisms responsible for clinical symptoms; both genes and environments might affect such mechanisms.

Potential differences in the approach to pathogenesis between global mental health and clinical neuroscience are evident. The approach of global mental health focuses mainly on societal risks including structural factors, and often uses sociological, anthropological, and related constructs and methods. The approach of clinical neuroscience focuses on biological risk factors and the underlying endophenotype, relying on sophisticated genetic, imaging, and other neurobiological concepts and investigations. Nevertheless, authors of recent work on risk factors for mental disorders have suggested that it is time to move beyond over-simplified contrasts between functional and organic factors, towards an empirical pluralism that focuses on the complex and multilevel mechanisms involved in the pathogenesis of mental disorders.26 Kendler25 notes that a range of “difference-markers” (from molecular genetics to culture) influence disease, that the pathways from genes to psychiatric disorders are complex and probabilistic, and that humans can make decisions that affect the expression of their own genomes.

Despite the differences highlighted here, the approaches of global mental health and clinical neuroscience to the understanding of the pathogenesis of mental health disorders also present potential synergies. First, the opportunity exists for work on the contribution of genes, environments, and interactions between genes and environments to the aetiology of mental health disorders.24 Kendler notes that a range of “difference-markers” (from molecular genetics to culture) influence disease, that the pathways from genes to psychiatric disorders are complex and probabilistic, and that humans can make decisions that affect the expression of their own genomes.

Second, cultural neuroscience is an emerging specialty of interdisciplinary investigation that has highlighted the diversity of human genes and neurocircuitry, and the value of including not only studies on western, educated, rich, and industrialised regions27 but also the importance of studying psychobiological mechanisms in a broader range of contexts that better portray the world’s population.28 Third, understanding the effects on the brain of social and financial deprivation across a range of populations could give insight into both mechanisms and mitigating factors. There are potentially important synergies between global mental health and clinical neuroscience for the study of cognitive reserve, neuroplasticity, and resilience to mental disorders.29,30 Indeed, several advances in our understanding of pathogenesis have relied on both global mental health and clinical neuroscience perspectives (table).

We provide here a few recommendations from these considerations (panel). First, it would be useful if genetic studies of mental disorders included a strong focus on the measurement of environment. Developmental psychobiology has long recognised the importance of both nature and nurture, and the consequent need to investigate interaction between genes and environments rigorously.31 Genomic studies of serious mental illness have, however, often not included a specific focus on the role of early child adversity and subsequent life stressors. In view of the growing recognition of the importance of psychological trauma in serious mental disorders,32 and the availability of rigorous methods for studying gene–environment interactions,33 including epigenetic effects, more attention to this area would be useful. A particular need exists for longitudinal and multigenerational studies, to understand fully the role of interactions between genes and environments and epigenetic mechanisms over time.

Second, when appropriate to do so, a focus of neuroscientific studies on the cultural context might be useful.34 The psychiatric research community has long been aware of the need to test hypotheses developed in one part of the world in other regions; Kraepelin, for example, explored the application of his German classification system in the far east. Cross-cultural psychiatry subsequently developed into a rich multidisciplinary specialty at the intersection of psychiatry, anthropology, and sociology.35 More recently, interest in application of neuroscientific methods in diverse populations and contexts has led to the growth of specialties such as genetic epidemiology, social neuroscience, and cultural neuroscience. Such research could lead to a better understanding of the neuroscience of normal human diversity, but ultimately also of mechanisms contributing to variation in psychiatric disorders.

Third, the incorporation of more detailed assessments of the environment would be useful for research on mental disorders; mental symptoms might be influenced by the individual’s microsystem (the immediate environment), mesosystem (an intermediate level of influence—eg, the health system), and macrosystem (the broader context, whether socioeconomic, political, or cultural).36 Just as a thorough clinical assessment of the individual patient requires a consideration of a broad range of environmental factors, so a rigorous understanding of risk factors and of pathogenesis demands a full appreciation of the social system in which a mental disorder develops. A significant amount of psychiatric research has focused on the immediate environment of the individual (eg, the family), and epidemiological research has brought attention to the effect of broader socioeconomic variables (eg, poverty) on mental illness.37 However, scope exists for establishing greater synergy between neuroscience methods and the study of broader structural variables (eg, economic inequality, climate change).38
Series

Treatment

Global mental health practitioners have emphasised the underdiagnosis and undertreatment of mental disorders, and the few financial and human resources available for prevention and intervention efforts in mental health, particularly in low-income and middle-income countries. However, efficacy and cost-efficiency for mental health interventions has a large evidence-base, packages of care have been developed for use in primary care in a range of different settings, and the evidence for the value of task-shifting and scaling-up treatment is growing. Implementation science advances our understanding of how best to adapt effective interventions to local contexts, and how to ensure that they are sustainable.

Clinical neuroscientists have acknowledged these advances, but have also identified the important need to develop interventions with increased efficacy and effectiveness. Particularly, there is a need to improve the management of risk factors and prodromal states, to identify new molecular and clinical targets, and to further decrease morbidity and mortality. Unfortunately, the pharmaceutical industry has decreased its investment in research on psychiatric disorders. More efficient ways of developing new drugs and bringing them to market is crucial. In the future, as we better understand the pathophysiology of mental disorders, so we will be able to develop more personalised interventions for these disorders.

The contrasting emphases of global mental health and clinical neuroscience in the area of intervention follow from their different views of diagnosis, assessment, and risk factors. The focus for global mental health is to encourage adaptation of what is known to work to address pressing clinical needs, whereas the focus for clinical neuroscience is to encourage awareness of neuroscientific data that could lead to entirely new foci of treatment. Global mental health relies on feasible, standardised interventions that are scalable in general populations, whereas clinical neuroscience envisages personalised medicine for each individual and values research on treatments that although not yet practicable are important in providing proof-of-principle evidence that a novel mechanism can be targeted in the future.

As before, these contrasting perspectives also have potential synergies. Gaps in practice and adherence exist even in high-income countries; improved dissemination of clinical evidence and enhanced adherence to treatment worldwide are required. Furthermore, treatment response shows individual variation even in low-income and middle-income countries, and we need to better understand the pharmacogenetic factors and other factors underlying such variation worldwide. In view of the range of risks for mental disorder, a multilayered and multisectoral approach to prevention and treatment is required, including early recognition and prevention of emotional or behavioural problems, provision of living and working conditions that enable healthy psychosocial development, promotion of positive interactions within and between social groups, social protection for the poor, anti-discrimination laws and campaigns, and promotion of the rights of those with mental disorders.

Clinical neuroscience focuses on proximal mechanisms, but evolutionary biology has also highlighted the importance of understanding distal adaptive mechanisms. The understanding of evolutionary theory could be as important as the understanding of neuroscience for the decision of who and how to treat. Those interested in proximal mechanisms remain optimistic that biomarkers will guide treatment, whereas another possibility is that an improved functional or ecological understanding of the nature of symptoms, and their adaptive value, will be important in clinical practice. For some disorders, such as Alzheimer’s disease, future personalised treatment is entirely biomarker driven, whereas for other symptoms such as anxiety, where such biomarkers are less sensitive and specific, a different approach will be needed.

Several treatment advances have relied on both global mental health and neuroscience perspectives (table), and recommendations regarding future research on intervention are suggested below and summarised in the panel. First, researchers should consider whether trials in low-income and middle-income settings incorporate neuroscience predictors (eg, genetics) and endpoints (eg, brain imaging), or other aspects of the RDoC framework. To date, trials in low-income and middle-income settings have considered implementation science issues such as feasibility, acceptability, and effect on costs and symptomatic outcomes, with the aim of scaling-up of cost-effective interventions. More can be learned from these trials by including additional questions. Understanding the neuroscientific basis of the behavioural interventions that are central to global mental health would be a particularly useful goal.

Second, researchers should consider integrating several constructs (eg, considering both biological and social risks) into all trials. Very few psychopharmacological trials, for example, have assessed the effect of socioeconomic status on treatment outcomes. Similarly, how early and ongoing stressors can alter the response of participants in clinical trials is little understood. Conversely, neuroscientific knowledge could be used to improve the design of prevention and treatment trials worldwide; for example, it is relevant for child and adolescent interventions to consider present research on developmental neuroplasticity. A better understanding of heterogeneity of trial participants, including variation in their social environment, could contribute to a better understanding of treatment outcomes, such as the variability in response to placebo interventions, a phenomenon that has impeded drug discovery.

Third, as treatment research integrates experience from work in both global mental health and clinical neuroscience, there could be lessons learned (in pharmacotherapy and psychotherapy) for high-income
countries from low-income and middle-income countries. Of note, the developed world presents substantial cultural heterogeneity, and social determinants such as poverty, stigma, low mental health literacy, and other barriers to mental health care are found in populations within high-income countries as well as in low-income and middle-income countries. Progress in concepts and methods aimed at ensuring that psychiatric interventions are feasible and acceptable to different population groups, and can be scaled up in a cost-effective way, could have implications worldwide.

Conclusions
We have summarised some of the key constructs and methods of those working in global mental health and in clinical neuroscience. There is potential for differences between these two approaches, and a reductionistic position of mental disorders as either brain disorders or as social phenomena exacerbates such differences. Hopefully, this reductionist position will diminish as concepts and data continue to emphasise the value of a pluralistic approach to understanding psychiatric diagnosis, pathogenesis, and intervention. Indeed, from this integrative and synergistic perspective, the concerns of global mental health and of clinical neuroscience are complementary. Those working in global mental health and clinical neuroscience recognise that as economies increasingly rely on skilled workers, so mental disorders will consist of an increasingly important portion of the population and in certain key disorders (eg, substance use disorders, depression, and anxiety disorders) and susceptible populations. Both disciplines are invested in ensuring equity in mental health services and research, with better treatments for mental disorders and more research on these disorders, worldwide.

We have not focused here on the key issue of research prioritisation. However, recent consensus documents on research questions and priorities in mental health have included concepts and methods from both global mental health and clinical neuroscience, with both basic scientists and public mental health researchers often agreeing on specific priorities. Here, we have put forward several recommendations for strengthening the integration of global mental health and clinical neuroscience, and for further encouraging and facilitating translation of knowledge between these disciplines, in future research on psychiatric diagnosis, pathogenesis, and intervention (panel).

Neuroethics, which is at the intersection between global mental health and clinical neuroscience, is also important. On the one hand, neuroethics poses questions of whether and how new findings in neuroscience and in psychiatry shed light on long-standing questions in philosophy (ie, the neuroscience of ethics). On the other hand, neuroethics has addressed the ethical questions fostered by novel neuroscientific and psychiatric methods and their applications in research and medicine (ie, the ethics of neuroscience). Global mental health, clinical neuroscience, and neuroethics each have to grapple with long-standing conceptual questions about the nature of mental disorder, and with the bioethics of neuroscience and psychiatric methods and interventions. Key issues that arise at the intersection of global mental health, clinical neuroscience, and neuroethics, and that deserve further attention, include the nature of disease and wellness, the importance of social inclusion and patient empowerment.

It would be of value for those working in the global public health and clinical neuroscience communities to at times put themselves in another’s shoes; clinical neuroscientists could benefit from asking questions about the global health relevance of their work, and global mental health practitioners might benefit from keeping a close eye on advances in clinical neuroscience concepts and methods. Both disciplines, however, require further investment and scaling-up; there is a need for additional resources for more rapid translation from bench to bedside, and from bedside to beyond. There is also a need

Search strategy and selection criteria
We searched Medline from 2000 to September, 2013, for the terms “global mental health” and “clinical neuroscience”. We focused on recent overviews of these two broad areas, but also included individual studies to illustrate relevant points. Review articles and book chapters are cited to provide readers with more details and additional references.
for training programmes that ensure that clinicians and researchers are not only able to acquire skills within each of these approaches, but also that they are able to work at their intersection. Such capacity building should go hand in hand with appropriate research governance mechanisms, particularly in settings where these are underdeveloped. Ultimately, the interplay between focused, in-depth psychobiological studies and large-scale, innovative population studies should provide a richer understanding of the brain and mind in health and disease, and contribute to decreasing psychiatric morbidity and improving global wellbeing.

Contributors
DJS initiated the paper. YE, AP, BJS, JW, and VP were consulted about the arguments that should be made and the exemplars that should be provided. DJS collated all inputs into a first draft. All authors edited and revised the first and subsequent drafts.

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