1 Introduction

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Introduction

The essence of global health equity is the idea that something so precious as health might be viewed as a right.

Paul Farmer, Rx for Survival, Global Health Champions

Without mental health there can be no true physical health.

Brock Chisholm, first Director-General World Health Organization

The first edition of *Introduction to Psychiatry* is a textbook designed to reach medical students, house staff, primary care clinicians, and early-career mental health practitioners. It is the editors' hope that this text will enable its readers to understand the neuroscientific basis of psychiatry, best practices in the psychiatric assessment and treatment of the patient, the current understanding of core psychiatric diagnoses, and the important underlying issues of population health, public policy, and workforce recruitment and training that must be tackled to bring these advances to all.

Why create a textbook of psychiatry specifically for clinicians not trained for the mental health field? To answer this question, one must understand the troubling challenges facing the mental health workforce, the changing face of mental health care delivery, the enormous comorbidity between psychiatric illnesses and other health conditions, and the impact on non-psychiatric medical illnesses when a comorbid psychiatric disorder is present.

The Prevalence and Impact of Psychiatric Disorders

Across the globe, no category of human suffering equals that of mental illness. Mental disorders are highly prevalent, have their onset beginning in childhood through early adulthood, and are stubbornly chronic. One in five people annually have a diagnosable mental disorder, and a staggering one in two people will suffer from a mental illness during their lifetime. (Kessler, 2005; Steel et al., 2014). Though the prevalence of mental disorders is approximately equivalent among

non-Hispanic whites, Hispanics, and non-Hispanic blacks, access to treatment and treatment intensity is lower among Hispanics and non-Hispanic blacks, leading to poorer outcomes (Alegria et al., 2008; US Dept of HHS, 2001).

Suicide is a frequent outcome of the more severe presentations of the most serious mental illnesses and is the second most common cause of death globally in young adults (Arensman, et al., 2020). Ninety percent of suicides are associated with a diagnosable psychiatric disorder. Substance abuse and death by drug overdose are a worldwide scourge.

Psychiatric disorders hit the child and adolescent population especially hard. Meta-analyses have found that the worldwide prevalence of mental disorders in children and adolescents is 13 percent (Polancyzk, 2015). Approximately half of all serious psychiatric disorders encountered in adults have their onset in childhood. Psychiatric disorders that have their onset in childhood and become chronic have a myriad of serious sequelae, following these young people through development and thus impacting their emerging identity, ability to learn, social development, and overall health and life expectancy.

Psychiatric disorders impede access to medical care and worsen clinical outcomes of medical illness. Virtually all medical problems have a poorer prognosis when accompanied by a comorbid mental illness. Individuals with mental illness in the United States and globally have a severely shortened life expectancy due to the mental illnesses as well as the poor overall health that accompanies them.

In spite of these staggering realities, the majority of individuals with psychiatric illness do not receive care.

Why Is This the Case?

The global population is growing. In 2021, the US population is projected to grow by 2,000,000 people from a combination of new births and immigration United Nations World Population Prospects U.S. Population Growth Rate 1950–2021. www.macrotrends.net. Retrieved 2021-03-29. Given this growing population, it can be predicted that the number of people needing mental health treatment will continue to increase.

Yet this growing demand for mental health care is not being met.

There is a severe workforce shortage in mental health globally, and indeed, in many cases that shortage may be expected to increase. For example, between 2003 and 2013, while the US population grew, the number of practicing psychiatrists declined (Bishop et al., 2016). A novel study analyzing data from the Association of American Medical Colleges (AAMC), American Board of Psychiatry & Neurology (ABPN), and US Census Bureau projected the psychiatrist workforce through 2050 (Satiani, et al., 2018). The study concluded that this workforce will continue to contract through 2024 if no interventions are implemented. In the United States, these

shortfalls will continue to be felt most heavily in rural areas, among the poor and non-white population.

The shortfall of mental health clinicians who treat children and adolescents is especially severe. Most areas of the United States are in "severe shortage" for child and adolescent psychiatrists. Inequity worsens this lack of care and the shortfall is severe in the developing world (Shatkin, 2018; Bruckner et al. 2011).

What to Do

Integration of Primary Care and Behavioral Health

Traditionally, mental health and primary care have been isolated from one another, housed in separate clinical locations, often with no access to a shared medical record and with separate insurance and administrative/regulatory governance. A movement to integrate behavioral health care into primary care pediatric and internal medicine settings has gained momentum in recent years (Ramanuj, et al., 2019). The provision of behavioral health in these settings has a number of clear advantages over the current siloed approach, in which behavioral health care settings are institutionally separate from other medical settings. The evidence base for improved overall health outcomes when integrated mental health care is provided is growing. Integrated care allows for seamless transitions of care from the primary care provider (PCP) to the behavioral health provider (BHP); overall improvements in health care costs and the efficient leveraging of scarce psychiatric resources are additional benefits of this approach.

The significant global treatment gaps for mental health problems is another powerful rationale for the integration of mental health into the primary care setting. Integrated care improves access to care and overall health outcomes on both the individual and population scale.

The integrated care approach includes on-site collaborative models, as well as telepsychiatry. Telepsychiatry has been shown to be effective in settings where in-person access is limited, such as rural areas, high population urban areas, geographically difficult-to-reach areas, and in times of disaster when access is blocked.

Significant stigma accompanies a mental health diagnosis in most cultures. An advantage of the integration of mental health treatment into the primary care setting is the decreased isolation of patients being treated for mental health disorders. Eliminating this isolation will not only improve the care of the mentally ill, but also allow the larger medical community to increase their exposure to these patients, promoting greater understanding and, ideally, reducing stigma.

In addition to integrating behavioral health into primary care medical settings, integration of primary care medical services into mental health settings (sometimes referred to as "reverse integration") has also gained ground as an effective model, particularly for individuals with serious mental illness and substance use disorders

whose closest and most frequent health care contacts may be with mental health clinicians. In addition, such individuals often have difficulty navigating general medical settings in which clinicians may have less familiarity with evaluating and treating general medical illness in individuals with significant psychiatric conditions and complex psychiatric treatment regimens. It is hoped that behavioral health integration into primary care as well as primary care into mental health settings will help address the substantial health disparities related to mental illness and substance use disorders.

Future Directions in the Scientific Basis of Psychiatry

Genetics

The field of psychiatric genetics has made extraordinary progress over the past twenty-five years. For a number of years, it had been firmly established through family studies that genes contribute significantly to the risk for psychiatric disorders. Indeed, for some disorders, such as bipolar disorder, schizophrenia, autism, and attention deficit disorder, the "hereditability" (i.e., amount of risk for the disorder attributable to genes) is as high as 80 percent. However, the search for single genes underlying specific psychiatric conditions utilizing linkage analysis and association studies with candidate genes for specific psychiatric disorders has been largely disappointing. An exception has been autism, in which about 20 percent of cases may be related to attributable to an identifiable genetic variant. This early research made it increasingly clear that most psychiatric disorders are likely to be polygenic "complex disorders" in which multiple genes interacted with epigenetic processes and environmental risk factors to determine the final outcome, in this respect resembling most other health conditions such as hypertension and diabetes

In recent decades, the sequencing of the entire human genome, the formation of large international collaborative consortia, and the availability of powerful computing abilities able to analyze data sets of genome-wide single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) have revolutionized psychiatric genetic research. The International Genomics Consortium (PGC) is the largest of these centralized data banks (Sullivan et al., 2018). Progress has been made toward identifying risk loci for psychiatric disorders, including schizophrenia, bipolar disorder, autistic disorder, and ADHD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). The phenomenon of pleiotropy, in which many genes identified have been found to be shared across a number of disorders, is clearly a major genetic feature in psychiatric illness.

The emerging recognition that distinct psychiatric diagnoses may be associated with overlapping genetic risk has challenged the traditional categorical understanding of psychiatric diagnosis, which is the foundation of the Diagnostic

and Statistical Manual (DSM) system of categorization (American Psychiatric Association, DSM-5, 2013). It also strengthens our understanding that many psychiatric disorders are "spectrum" disorders, captures the wide variations seen in individuals sharing a common diagnosis, and allows a data-driven approach to the variations so commonly seen in psychiatric presentations (Cross Disorder Group of the Psychiatric Genomics Consortium, 2019). These advances are sure to lead to a deep understanding of the biology of psychiatric disorders, transforming our diagnostic understanding and early screening of these illnesses and powerfully advancing our ability to treat these devastating disorders.

Neuroimaging and the Identification of Neural Circuits

Unlike common neurological disorders such as stroke, tumors, and multiple sclerosis, where gross pathological findings on brain imaging have allowed for accurate diagnosis and therapeutic intervention, psychiatric disorders, though often severe, are rarely accompanied by gross pathology on neuroimaging.

Advances in the field of non-invasive, in vivo functional neuroimaging over the past thirty years have begun to transform the field of psychiatry. These techniques have contributed to an understanding of the function of specific brain areas in psychiatric illness, along with how these areas communicate with one another and form interacting circuits. Knowledge of these circuits in normal development, health, and disease will aid in improving diagnosis, allowing for targeted therapies that do not currently exist in psychiatric practice.

Structural and functional MRI are increasingly refined and safer, with the capacity for longer and more detailed task observations, as well as better image resolution and processing. The structural and functional MRI work has been enhanced by PET studies that reveal metabolic and neurochemical processes in greater detail. Utilizing healthy controls and cohorts of patients with psychiatric symptoms, neural circuitry dysfunction has been localized and characterized in a number of psychiatric disorders, including major depressive disorder, schizophrenia, obsessive-compulsive disorder, and post-traumatic stress disorder. Though these approaches have not yet translated into concrete practical tools for psychiatric practice, such as establishing a psychiatric diagnosis or the probability of responding to a given treatment in an individual patient, they are helping to shed light on brain regions and circuits most likely to be relevant to psychiatric disorders. The promise is great that this will be forthcoming and transformative of psychiatric practice.

The Classification of Mental Disorders: The Diagnostic System of the Future

Various classification systems exist in psychiatry. Currently, the primary systems are DSM-5 (American Psychiatric Association) and the International Statistical Classification of Diseases and Related Health Problems-10 (ICD10, The World Health

Organization). Both are based largely on differentiating psychiatric presentations into distinct disorders based on a constellation of symptoms, such as hallucinations, delusions, depressed or elevated mood, and disturbances in sleep, appetite, energy concentration, or memory. At the same time, the genetic and neuroimaging/neurocircuitry developments described here are providing the field with the much-needed scientific basis for understanding psychiatric symptoms and disorders. This, in turn, is fueling the paradigm shift from the DSM process of descriptive categorical diagnosis, which is related to symptoms but not necessarily to brain circuits or genes, to the more neuroscience-based, mechanistic Research Domain Criteria (RDoC) project proposed in 2008 by the National Institute of Mental Health. The RDoC approach is inherently translational. Rather than focusing on specific disorders such as major depressive disorder or generalized anxiety disorder, used in clinical psychiatry, it adopts the view that progress in research on the pathophysiology underlying these conditions may be greater if the focus is not on disorders as defined by DSM but rather upon particularly behavioral dimensions that may span multiple disorders. It further recommends assembling information from different levels of analysis – genes to behavior – in a matrix summarizing data about functional dimensions of behavior characterized by genes, molecules, cells, circuits, physiology, and behavior for each of the five domains that have been identified. The five current domains in the RDOc system are negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal/regulatory systems. These domains of behavior were chosen not as comprehensive but as starting points to be built upon based on evolving knowledge. The RDoC matrix also includes a column that identifies paradigms which already exist and are well-validated – for example, Pavlovian conditioning in positive reward behavior.

While clinical psychiatry still relies heavily upon the symptom-based diagnoses reflected in the DSM (and similar ICD-10) classifications, the transdiagnostic approach reflected in RDoC has offered a promising roadmap to elucidate the neurobiological underpinnings of psychiatric conditions and potential new avenues to better understanding their etiology and to developing novel treatments.

The future of the field holds great promise that these breakthroughs will lead to early identification of risk factors, early diagnosis of psychiatric disorders and their subtyping, and precision therapeutics that will revolutionize the treatment of our patients.

Conclusion

With the recognition that individuals with serious mental illness die up to twenty-five years earlier than other individuals, often from general medical conditions; that most major medical conditions are associated with significantly worse

outcome and higher health care costs when accompanied by untreated psychiatric conditions such as depression; and that major public health crises like the SARS-CoV-2 (COVID-19) pandemic are well known to have profound and enduring impacts on mental health, it is clear that mental health is an integral component of health and that a knowledge of psychiatry is a foundational aspect of health care. With steady advances in knowledge, the stigma associated with psychiatric conditions is gradually on the wane while the development of effective, evidence-based treatments with medications, psychotherapies, neuromodulation, and other approaches continues to expand. Worldwide, mental health is the most neglected aspect of health care.

Yet there is reason for optimism. The twenty-first century is witnessing explosive growth in the field of psychiatry and behavioral sciences. Paradigm-shifting scientific breakthroughs in the areas of psychiatric genetics, functional neuroimaging, psychoimmunology, and cognitive sciences are upon us. The emerging fields of optogenetics and functional neural connectivity promise new advances in the future. The NIMH RDoC system classifies mental illness based on behavioral and neurobiological measures, thus bringing about a revolutionary dimensional understanding of mental disorders, as revealed by advances in neuroscience. The field of psychiatry is moving rapidly toward integration with the clinical neurosciences. The range of evidence-based treatments for psychiatric disorders is growing. In a powerful parallel development, due to breakthroughs in basic science and clinical applications, psychiatry is becoming more closely allied with its related fields of neurology, neurosurgery, and neuroradiology. Finally, the integration of psychiatric knowledge and clinicians into the primary care setting has begun to address the enormous problem of inadequate access to mental health care. This enhancement of shared knowledge is fueling hope for significantly greater access to mental health care for people across the globe. People with medical illnesses and co-occurring mental health disorders will benefit from the growth of this shared knowledge and integrated clinical care among their providers.

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2 Clinical Neuroscience

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Introduction

Psychiatry draws widely upon insights from many realms ranging from public health, the social sciences, and the humanities. As psychiatric disorders affect mood, cognition, perception, emotion, and behavior, brain science is recognized as foundational to understanding their pathophysiology. Along with the disciplines of neurology, neurosurgery, and neuroradiology, psychiatry is often regarded as one of the clinical neurosciences.

Although the clinical interview and observation of behavior continue to remain the mainstay for diagnosis of psychiatric disorders, growing insights about the pathophysiology of psychiatric conditions are likely to inform the assessment, treatment, and classification of psychiatric disorders in the coming years. A circuit-based understanding of brain function, the establishment of biomarkers for early identification and intervention, and genetic tools to stratify an individual's risk of disease and predict response to different treatment modalities promise to become increasingly integral to clinical psychiatry. As the field of psychiatry moves away from inefficient "trial-and-error" based approaches, toward precision medicine grounded in knowledge about individual variation in brain biology, fluency in neuroscience will be essential preparation for clinical practice.

This chapter will provide a general overview of neuroscience relevant to psychiatry. As progress is rapid, our focus is on neuroscientific concepts relevant to psychiatry, as well as on current efforts to identify clues about the underlying causes of psychiatric disorders, and discover promising targets for novel treatments.

Historical Context

In contemporary Western medicine, the impetus to link specific clinical syndromes to pathology in the brain dates to nineteenth-century Europe. The then-nascent field of neurology, led by notable physician-scientists, including Jean-Martin Charcot, Joseph Babinsky, Paul Broca, and Karl Wernicke, began to associate speech, motor, and cognitive abnormalities with lesions in particular brain regions. Preliminary attempts to explain emotional phenomena in terms of brain function were also made by Benjamin Rush in the United States and Wilhelm Griesinger in Germany.

One prominent clinician who believed that psychiatric symptoms could be explained neurologically was Sigmund Freud. Though best known for developing the field of psychoanalysis, focused on unconscious impulses and fears driving emotions and behavior, Freud was trained as a neurophysiologist and neurologist and was confident that psychological processes had neurophysiologic correlates yet to be discovered. As psychoanalysis was further elaborated between the late 1800s through the mid-1900s, becoming a leading force in psychiatry, the field increasingly diverged from brain science, though in recent years clinical practitioners and researchers of psychoanalytically based psychotherapies have shown renewed interest in neuroimaging and other methods for revisiting Freud's earlier vision.

In the latter part of the twentieth century, the discovery of effective pharmacological treatments for major psychiatric disorders, including antipsychotics and antidepressants, also brought renewed interest in the biology of psychiatric disease. These medications targeted neurochemical systems, particularly the so-called monoamines – dopamine, serotonin, and norepinephrine – which were being actively mapped in the brain during this same period. Their efficacy led to the *monoamine hypothesis of psychiatric illness*, the idea that alterations involving the levels or function of this group of neurotransmitters caused specific symptoms (e.g., depressed mood, anxiety, and psychosis). But without direct access to the brain in living individuals, more comprehensive approaches to understand the biology of mental illness were not yet possible. Scientists turned to animal models in order to probe the inner workings of individual cells and circuits in awake and behaving organisms, though their translational relevance to human psychiatric illness remains a considerable limitation. The development of functional brain imaging techniques in the 1990s enabled for the first time the study of altered brain function in vivo, and in conjunction with other advances in translational neuroscience, which will be discussed later, has revolutionized our understanding of mental illness as underlying brain and even whole-body disorders.

A New Neuroscience-Based Framework for Nosology

While the Diagnostic and Statistical Manual (DSM) remains the gold standard for clinical diagnosis in psychiatry, efforts to recategorize psychiatric disorders using neuroscience may ultimately reshape the way we think about psychiatric assessment. One such initiative is the Research Domain Criteria (RDoC) framework, championed in 2011 by Tom Insel, a psychiatrist, neuroscientist, and then-director of the National Institute of Mental Health (NIMH). Rather than using the DSM's distinct categories and checklists of symptoms and symptom duration for mental disorders, RDoC uses six domains of psychological processes that show