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Neural circuitry and precision medicines for mental disorders: are they compatible?

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Abstract

Given the failure of psychiatry to develop clinically useful biomarkers for psychiatric disorders, and the concomitant failure to develop significant advances in diagnosis and treatment, the National Institute of Mental Health (NIMH) in 2010 launched the Research Domain Criteria (RDoC), a framework for research based on the assumption that mental disorders are disorders of identifiable brain neural circuits, with neural circuitry at the center of units of analysis ranging from genes, molecules, and cells to behavior, self-reports, and paradigms. These were to be integrated with five validated dimensional psychological constructs such as negative and positive valence systems. Four years later, the NIMH stated that the ultimate goal of RDoC is precision medicine for psychiatry, with the assumption that precision medications will normalize dysfunctional neural circuits. How this could be accomplished is not obvious, given that neural circuits are widely distributed, have unclear boundaries, and exhibit a significant degree of neuroplasticity, with multiple circuits present in any given disorder. Moreover, the early focus on neural circuitry has been criticized for its reductionism and neglect of the more recent RDoC emphasis on the integration and equivalence of biological and psychological phenomena. Yet this seems inconsistent with the priorities of the NIMH director, an advocate of the central role of neural circuitry and projects such as the Brain Initiative and the Human Connectome Project. Will such projects, at a cost of at least $10 billion, lead to precision medications for mental disorders, or further diminish funding for clinical care and research?

Introduction

The goal of precision medicine for mental disorders has its historical roots dating to the nineteenth century, when the early psychiatrists, or 'alienists,' found themselves isolated and often demeaned by their counterparts in medicine and surgery (Mitchell, 1984; Rollins, 2003). The alienists therefore began a quest for parity with other physicians, a quest that became intense with the discovery of the bacterial cause of infectious diseases such as tuberculosis, and, in 1913, with the discovery of treponema pallidum in the brains of patients with tertiary syphilis, who often became psychotic (Shorter, 1997). Here was evidence of linkage between specific causal agents and specific diseases, leading to the concept of a specific – or precise – treatment.

If this could be accomplished in medicine, why not psychiatry? Thus began the search for specificity of diagnosis and treatment in psychiatry, the history of which I have reviewed elsewhere (Dean, 2012, 2017). Despite the search for specificity, the field suffered through a long period wherein primitive therapies (blood-letting, forced injections of mercury and horse serum, tranquilizer chairs) were both damaging and imprecise (Scull, 1986; Valenstein, 1986).

Precision did not improve with the advent in the 1950s and 1960s of the first antipsychotics, antidepressants, and other psychotropics, despite a 1962 amendment to the Food, Drugs, and Cosmetics Act in the United States mandating that prescription drugs were to be used for the treatment of specific diseases (Shorter, 1997). Nevertheless, it became increasingly clear that the growing armamentarium of psychotropic drugs was not aimed at specific disorders. This is true today, where psychotropics are being used to treat a variety of symptoms found in a variety of disorders, which accounts, at least in part, for the 300% increase in the use of antidepressants during the decade starting in 1988, and a similar increase in the use of antipsychotics (Healy, 2002; Milea *et al.*, 2010; Alexander *et al.*, 2011).

Remarkably enough, the rapid growth of psychotropic agents and other treatment modalities has had little positive impact on the mortality rates and overall outcome of mental disorders. Instead, people with mental disorders have a mortality rate 2.2 times higher than the general population across 29 countries in six continents, with higher rates in more recent studies, particularly those with a baseline in the 1990s (Walker *et al.*, 2015). During the years 1980–2014, the over-all mortality rates associated with mental and substance use disorders rose by 188% across counties in the USA, and by as much as 1000% is some counties in

Editorial

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the southeast and midwest (Dwyer-Lindgren *et al.*, 2018). Of note, the late 1970s marked by beginning of a rapid rise in socioeconomic inequality (Piketty and Saez, 2014).

In schizophrenia, mortality rates have worsened since the 1970s, rising from a standardized mortality ratio (SMR) of 1.84–2.98 in the 1990s (Saha *et al.*, 2007), a marked contrast with the 43% decrease in the SMR found in the general population (Ma *et al.*, 2015). Other studies have confirmed a worsening SMR in the past three decades in Denmark (Nielsen *et al.*, 2013). Mortality rates have increased in first-contact psychotic patients (Dutta *et al.*, 2012; Simon *et al.*, 2018), in bipolar disorder (Hayes *et al.*, 2017), anxiety disorder (Meier *et al.*, 2016*a*), and obsessive disorder (Meier *et al.*, 2016*b*). More generally, the odds of any adverse outcome (self-harm, drug use criminality) in schizophrenia and related disorders increased during the years 1972–2009 (Fazel *et al.*, 2014), lending credence to evidence demonstrating that outcome in schizophrenia has worsened over the decades (Hegarty *et al.*, 1994).

Rates of depression (Compton *et al.*, 2006) and suicide in the United States have increased (Centers for Disease Control, 2013; Case and Deaton, 2015), but whether this is the case globally has been disputed (Baxter *et al.*, 2014; Patten *et al.*, 2015). Rates of suicide in the USA have risen by almost 30% since 1999, with 25 states reporting increases of at least 30% in the years 1999–2016 (Stone *et al.*, 2018). Contrary to the oft-cited relationship between major depression and suicide, 54% of decedents in 27 states in 2015 had no known mental health condition.

Why the lack of progress?

Unfortunately, psychiatry has underplayed the role of socioeconomic inequality and adversity in the genesis and maintenance of mental disorders, despite evidence of a close correlation between levels of inequality and mental illness, substance abuse, childhood well-being, and shorter life-spans (Wilkinson and Pickett, 2009; Dean, 2017). Not surprisingly, rates of disability have not improved (Insel, 2009; Angell, 2011). A study of 15 European countries examined the relationship between suicide mortality and socioeconomic inequality, and noted a doubling of mortality in the lowest educational group in 2001 compared with 1991 (Lorant *et al.*, 2018).

The efficacy of the newer antipsychotics has not improved significantly over the decades. A meta-analysis comparing chlorpromazine with 43 other antipsychotics found that several newer agents were superior, but there were significant methodological problems (Samara *et al.*, 2014). Unfortunately, efficacy continues to hover around 50% (Leucht *et al.*, 2017), although injectables and clozapine have been shown to significantly lower the risk of rehospitalization (Tiihonen *et al.*, 2017). Similarly, a recent meta-analysis of 21 antidepressants found that all were superior to placebo, but amitriptyline, marketed in 1961, demonstrated greater efficacy than the newer drugs, although it was less tolerable (Cipriani *et al.*, 2018).

Our failure to significantly advance treatment has not been due to a lack of effort, with investigators constantly moving toward ever-greater complexity in the attempt to clarify the mechanisms behind the actions of psychotropic agents, and whether those mechanisms are related to outcome in specific illnesses. After the 1960s, with its emphasis was on receptor blockade and catecholamines (Healy, 2002), attention moved to *n*-methyl D-aspartate receptors, followed by an emphasis on intracellular signaling systems, various peptides and proteins, and neurogenesis. In recent years we have seen papers on the interactions of psychotropics and epigenetics, and, more recently, on acid-sensing ion channels and sigma receptors (Dean, 2011).

In treatment-resistant depression, ketamine, transcranial magnetic stimulation, and other forms of brain stimulation have shown positive results (Morishita *et al.*, 2014; Sanacora *et al.*, 2017), while ketamine has shown promise in the rapid reduction of suicidality (Wilkinson *et al.*, 2017). There is growing interest in the use of psychedelic agents for depression and post-traumatic stress disorder (PTSD) (Pollan, 2015; Mithoefer *et al.*, 2018). Some have advocated the use of opioids for depression (Kosten, 2016), despite the opioid epidemic, as well as other novel therapies such as nitrous oxide (Nagele *et al.*, 2015), and anti-diabetic agents (Zeinoddini *et al.*, 2015).

Progress has been made as well in emphasizing the role of psychological therapies, including cognitive behavioral therapy, with many studies showing either equivalence with or superiority to antidepressants. Interpersonal psychotherapies, behavioral activation, and exercise, whether alone or in combination with medications have also been effective (Gartlehner *et al.*, 2016; Qaseem *et al.*, 2016). A number of psychological therapies have significant metabolic effects on brain systems associated with depression, anxiety, PTSD, and obsessive-compulsive disorder (Crocker *et al.*, 2013; Insel and Cuthbert, 2015).

Despite these efforts, Holtzheimer and Mayberg (2011) stated that treatments for depression 'are no more effective today than they were 70 years ago,' a position echoed by Akil *et al.* (2010), and Insel (2009), with regard to schizophrenia.

What to do? The transition to neural circuits via an evolving Research Diagnostic Criteria

Despite the gains made over the past five decades, it is clear that we must substantially improve the diagnosis and treatment of mental illnesses. To that end, the National Institute of Mental Health (NIMH) has moved to the Research Domain Criteria (RDoC), a dimensionally oriented framework for organizing research (Insel *et al.*, 2010), a clear change from the Diagnostic and Statistical Manual of Mental Disorders (DSM)-oriented categorical disease model. The early RDoC framework was based on the assumption that mental illnesses are brain disorders that stem from specific dysfunctional brain neural circuits (Insel, 2009). Implicit in this early approach was the concept that specific circuits of relevance to behavior will be identified, and that some biological components of the circuits will be amenable to therapeutic interventions aimed at those components (Gordon, 2016). Indeed, one goal of the RDoC has been the development precision medicines for mental disorders (Insel, 2014), achieved by identifying relationships between aberrant neural circuits and functional impairments (Cuthbert, 2014).

However, the early focus on neural circuits and precision medications did not exclude the possible therapeutic impact of other modalities on aberrant circuitry, including various forms of brain stimulation and targeted psychotherapy, particularly cognitive behavioral therapy (CBT) (Crocker *et al.*, 2013; Insel and Cuthbert, 2015). Indeed, the relevance of psychotherapy was implied by the observations of Insel *et al.* (2010) that all levels of the RDoC matrix affect the genesis of mental disorders, including the individual, the social context, and the family environment.

Nevertheless, neural circuitry was the early primary focus of RDoC (Insel *et al.*, 2010), leading some to note that this approach was in itself reductionistic (Fava, 2014; Parnas, 2014), and might

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result in the same reification of mental disorders found with the DSM (Hyman, 2010). In contrast, Kozak and Cuthbert (2016) not only emphasized the integration of psychological constructs and biological phenomena, but stressed that no measurement would take precedence over any other – a clear rejection of reductionism. Yet Cuthbert (2014) has also noted that the NIMH may allow for combinations of DSM-International Classification of Diseases (ICD) categories and RDoC constructs, or using RDoC constructs across diagnostic groups.

The more recent change in emphasis is consistent with the notion that the RDoC would continually evolve (Cuthbert, 2014; Insel, 2014), but we now find that the priorities of the director of the NIMH include a focus on neural circuitry (Wadman, 2016), a stance that seems inconsistent with Kozak and Cuthbert (2016). How this will be resolved is not clear.

In addition to problems with the DSM-oriented categorical disease model, the search for specificity, and the neglect of socioeconomic issues, another barrier to progress has been the neuron doctrine.

The neuron doctrine *v.* neural circuits

Simply put, the first 50 years of psychobiological research was based on a core concept holding that the neuron is the structural and functional unit of the nervous system (Yuste, 2015). It followed that psychotropic drugs would be viewed as actors affecting the neuron and its receptors, neurotransmitters, and associated signaling systems. It then followed that the origins of mental disorders should be viewed as alterations of the same system.

However, higher-order functions became increasingly difficult to explain if the single neuron was the basic functional and structural unit of the brain. Moreover, anatomical studies had found a remarkable degree of connectivity between neurons, with one pyramidal cell connecting to tens of thousands of other cells (Yuste, 2015). Indeed, a 1 mm^3 voxel contains at least 80 000 neurons and 4 million synapses, with 680 000 voxels in a functional magnetic resonance imaging (fMRI) brain scan (Insel *et al.*, 2013).

This complex system clearly is designed to maximize the distribution of information (Yuste, 2015), and is '…characteristic of physical systems that generate emergent properties.' By definition, these properties are not found in the individual elements (neurons) that make up the system. Indeed, *individual* neurons are not particularly relevant to the functions of distributed neural circuits – also known as neural networks or neural circuits.

The current status of neural circuitry in psychiatry

With regard to neural circuits, my search of Ovid Medline on 17 June 2018 found 315 citations in 2010, increasing to 1124 in 2017–2018, necessitating a limited review.

Depression

Multiple neural networks have been identified in depressive disorder. These include regions of the default mode network (DMN), and the frontal-thalamic-caudate regions, although there was no correlation between the network structural changes and clinical characteristics (Korgaonkar *et al.*, 2014). In an overview of depression, connectomics, and neuroimaging, Gong and He (2015) noted structural and functional changes in at least seven brain regions, and functional associations involving the DMN, the anterior-cingulate cortex (ACC), thalamus, the ACC-insula, and the prefrontal-limbic-thalamic areas, as well as four other areas. Both structural and functional connectivities were characterized by hubs that integrate information, with prominent hub abnormalities in the DMN and frontal-cortical networks.

In a study utilizing an RDoC approach, Luyten and Fonagy (2017) suggested an integrative model of child and adolescent depressive disorder based on three core domains of stress (negative valence, and arousal/regulatory systems), reward, and social cognition. Under each domain, the authors examined data on three units of analysis: neural circuitry and physiology, genetics, and behavior.

They concluded that childhood depression results from interacting impairments in stress systems that lead to problems with reward and cognition, and a reward deficiency syndrome. With regard to neural circuitry, however, we see a repetition of the same issues just noted, namely, a wide-spread and often overlapping system of circuits. For example, under reward (positive valence), we find reference to the mesocortical and mesolimbic pathways and their connections to the ventral striatum, nucleus accumbens, amygdala, hippocampus (HC), prefrontal cortex (PFC), and ACC, but these pathways also underlie the stress system.

The positive valence system was the subject of another integrative attempt, querying the RDoC using circuitry as entry points (Elmer *et al.*, 2016). The authors selected the lateral habenula, noting an annotation to the positive domain – reward expectation. The brain regions involved in this construct included the amygdala, dorsal AC, ventral striatum, basal ganglia, orbital-frontal cortex, and substantia nigra. However, a specific circuit could not be identified. Indeed, the authors stressed that the same anatomical structure may have a variety of connections, which, when activated, may lead to considerably different outcomes.

Psychosis

With regard to psychosis, we also find widespread circuit abnormalities, with a focus on connections from the ventral striatum to the orbitofrontal cortex, the ventromedial PFC, and the HC, amygdala, and thalamus (Haber and Knutson, 2010). In a study (Fornito *et al.*, 2013) utilizing resting-state fMRI to assess circuitry in 30 patients with first-episode psychosis (FEP), the authors found not only a significant degree of dysregulation of cortico-striatal systems, but a pronounced gradient, ranging from hypo-connectivity dorsally to hyperconnectivity ventrally. There was a significant association between symptom severity and functional connectivity in a circuit linking the dorsal caudate with regions in the dorsolateral PFC (DLPFC) and left medial PFC. The use of antipsychotics did not affect the circuit disturbances.

In line with the goals of the RDoC, a meta-analysis (McTeague *et al.*, 2017) of 283 studies involving cognitive control tasks across schizophrenia, bipolar or unipolar depression, anxiety disorders, and substance abuse, the authors found a common pattern of neural circuit disruptions, with abnormal activation in the left PFC, anterior insula, the right ventrolateral cortex, the right intraparietal sulcus and the mid-cingulate/presupplementary motor area. These findings seemed to represent a transdiagnostic phenotype.

In keeping with the move toward transdiagnostic studies Gong *et al.*, (2017) compared participants with FEP, major depression, PTSD, and healthy controls (all were treatment naïve), using resting state fMRI. The three groups were characterized by reduced

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connectivity in the ventral-medial PFC and the left posterior–inferior parietal cortex within the DMN, a notable transdiagnostic finding, since each condition is marked by cognitive dysfunction. On the other hand, the FEP group showed increased connectivity between the ACC and the central executive network (DLPFC and the posterior parietal cortex), an area involved in planning, attentional control, working memory, and decision-making.

Precision drugs from imprecise circuitry: what are the issues?

(1) Insel (2009) stressed the specificity of brain circuits as a guiding principle for understanding mental disorders, but quickly noted the 'remarkable plasticity of brain circuits,' noting that rapid reorganization occurs in the cortex in response to changing input. Indeed, Yuste (2015) has stressed that a given neural circuit may never be in the same state twice. Although neural plasticity is advantageous to survival and adaptation, could a psychotropic drug adapt to a constantly changing circuit? While there is evidence that synapses and transmitters can change their functions depending on context (Spitzer, 2012; Dulcis *et al*., 2013), could a therapeutic modality (drug or CBT) continue to yield positive results by altering a threshold in a circuit? However, an ongoing positive effect would seem to rest on a very high degree of linkage between a circuit and their associated circuit behaviors.

(2) Carandini (2012) has noted that the present gap between neural circuits and behaviors may be so wide as to preclude any therapeutic applications, given our lack of a computational understanding of large neuronal populations.

(3) Meta-analytic studies of neuroimaging have shown more neural similarities than differences between disorders, regardless of symptom differences (Goodkind *et al*., 2015; Etkin, 2017). Further, a broad range of cellular changes can converge on a neural circuit and lead to the same clinical diagnosis, regardless of the underlying stimulus (Akil *et al*., 2010).

(4) One task never activates a single neural circuit, nor is there evidence of a mental disorder associating with a single circuit (Barch and Carter, 2016; Etkin, 2017). Indeed, a study of bipolar disorder found 17 different neural pathways, with each pathway targeted by multiple genes (Nurnberger *et al*., 2014). Not surprisingly, pathways vary across studies (Phillips and Swartz, 2014). The heterogeneity of pathways found in bipolar disorder may be present in PTSD as well, where different circuits are associated with different symptom clusters (Tursich *et al*., 2015).

(5) The degree to which a neural circuit has clear-cut boundaries remains unclear. Buckner *et al*. (2013) have noted past work indicating 'fuzzy' transitions between areas, and 'patchy' projections. Unfortunately, these are more common in the evolutionary newer cortex, with association cortices having the highest degree of variation in fMRI coupling patterns – a problem when assessing complex mental disorders.

(6) Nevertheless, Finn *et al*. (2015), using fMRI, have found that patterns of functional connectivity profiles in individuals are distinctive enough to allow identification of an individual from others in the group, regardless of the task at hand. The frontoparietal network seemed to be the most distinctive and most predictive of cognitive behavior. However, this work was based on the comparison of fMRI profiles separated by only one day, leaving open the question of consistency over time.

(7) Patterns of neural circuits are influenced by respiration, cardiac rhythms, head motion, the current task, recent experience, and time. Unfortunately, longitudinal studies are rare. Another confound is the effect of psychotropic drugs. Making matters even more complex, functional correlations may be present in the absence of direct structural connections (Buckner *et al*., 2013)

(8) The degree to which neural circuit abnormalities correlate with clinical data is debatable. In a study of cortical association networks in schizophrenia, bipolar disorder, and schizoaffective disorder, the frontoparietal network was severely disrupted, but there was no correlation with clinical ratings, including educational variables (Baker *et al*., 2014). Others have made similar observations (Tromp *et al*., 2012; Korgaonkar *et al*., 2014; Phillips and Swartz, 2014), while some have found positive associations (Rotarska-Jagiela *et al*., 2010; Fornito *et al*., 2013; Tursich *et al*., 2015).

(9) In a study of major depression, pervasive hyperconnectivity correlated with positive mood induction in 81% of the subjects, but this was complicated by a similar finding in 50% of healthy controls (Price *et al*., 2016), a persistent finding in neuroimaging, where significant overlap of findings is common (Rotarska-Jagliela *et al*., 2010; Cohen, 2016; Fusar-Poli and Meyer-Lindenberg, 2016).

Megastudies: clarity or confusion?

Given the issues just described, it seems fair to ask if the coming wave of mega-studies aimed at brain mapping, genetics, and neuroimaging will provide more definitive answers to the role of neural circuits in advancing the quest for precision medicines, prediction, and definitive diagnoses, or will they further confuse matters by uncovering incidental findings (Kohane *et al*., 2006) and others of very small effect sizes. Many current imaging studies enroll <100 subjects, but the numbers should rise exponentially with the advent of the Precision Medicine Initiative (renamed 'All of Us'), with its one million participants, the Advancing Innovative Neurotechnologies (BRAIN) Initiative, the International Brain Initiative, the 21 Century Cures Act, the Korea Brain Project, the China Brain Science Project, and the 100 000 Genomes Project (Advisory Committee to the NIH Director, 2013; Huang and Luo, 2015; Grillner *et al*., 2016). Not to be outdone, Europe has funded the Human Brain project (Abbott and Schiemeier, 2013), aimed at a supercomputer simulation that will model 'all that is known' about brain structure and function.

Another project, The Enhancing Neuroimaging Genetics through Meta-analysis (ENIGMA) Consortium was founded in 2009, ' …with the goal of identifying genetic influences on brain structure,' as summarized by Bearden and Thompson (2017). Given the lack of power in many imaging and genetic studies, ENIGMA set out to develop methods of standardizing and analyzing MRI studies done in 35 countries, resulting in much large sample sizes, reaching 33 000 in a study of hippocampal volume. ENIGMA has found consistent patterns of hippocampal volume deficits in major depressive disorder (MDD), bipolar disorder, and schizophrenia, but greater deficits in bipolar disorder *v.* MDD, and even more so in schizophrenia.

The authors note that their data 'leaves no question that these illnesses [schizophrenia, ADHD, OCD]…are all, in fact, disorders of the brain…', a stance quite different from that espoused by Kozak and Cuthbert (2016). Their future goals include developing

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deep-learning methods aimed at uncovering latent patterns found in brain images and networks. Perna *et al.* (2018), in an editorial, have also emphasized machine learning in the development of new predictive algorithms derived from data collected from electronic medical records and real-time data collected from smart phones and other technologies, noting that such approaches have resulted in the prediction of remission, relapse, and suicidal ideation. However, clinical applications have been rare.

Clearly, psychiatry is now hoping that mega-science will provide definitive data to advance the development of precision medications and clinically useful biomarkers that will enable us to independently and objectively validate diagnoses. However, Frégnac (2017) has questioned the 'industrialization' of neuroscience as the pathway to understanding the brain, noting a gap between technology and our conceptual understanding of brain functions. Indeed, he notes that technology is now driving concepts, rather than the reverse.

Indeed, technology and big data are revealing 'a new world or randomness and diversity,' clearly the case in genetics, where the emphasis is on epigenetics, private mutations, and a dramatic increase in the numbers of risk loci (Kendler and O'Donovan, 2014). As many as 6000–10 000 independent single-nucleotide polymorphisms and 1000 genes may contribute to the risk for schizophrenia, but these numbers explain only one-third of the variance (Yan, 2013). Nevertheless, hope remains that combining clusters of genes – in a polygenic risk score – with data from neural circuitry will prove more definitive (Akil *et al.*, 2010). Yet despite the growing size of genetic studies in mental disorders, these have failed to uncover any common risk variants of even moderate effect size (McClellan and King, 2010) while others have concluded that risk prediction for an individual cannot be derived from large-scale GWAS (Klein *et al.*, 2012).

What is the future of clinical care and research?

From a patient viewpoint, how will a depressed patient respond to a diagnosis of a dysregulated prefrontal-limbic-thalamic circuit as opposed to a diagnosis of major depression? Will this approach increase or decrease stigma? Several recent studies have found that stigma increases with an emphasis on biological causation rather than the reverse (Angermeyer *et al.*, 2011; Schomerus *et al.*, 2012). Interestingly, a meta-analysis of controlled trials found that various interventions did reduce public stigma, but not self-stigma (Griffiths *et al.*, 2014).

Finally, many are concerned about the funding – at least $10 billion – aimed at these projects, with at least $5 billion going to the BRAIN Initiative alone by 2024 (Huang and Luo, 2015), and another $1 billion to the European Human Brain Project. The very high costs of these studies has led considerable criticism (Enserink and Kupferschmidt, 2014; Reardon, 2016), including the distinct possibility of siphoning funds away from clinical care and sociocultural research (Holmes *et al.*, 2014; Xie, 2014), areas already under considerable stress (Hogan, 2002; Luhrmann, 2012; Creswell, 2013). For example, data from ClinicalTrials.gov revealed a 24% decrease in the number of NIMH-sponsored during the years 2006–2014, although industry funded trials increased by 43% (Ehrhardt *et al.*, 2015). In 2016, over half of the NIH-funded extramural research was devoted to search terms that included genes, genome, stem cells, and regenerative medicine (Joyner *et al.*, 2016).

While these are areas subsumed under the levels of analysis in RDoC, one has to ask if the concentration on these areas and the connectome will overwhelm the integrative goals of the RDoC? Indeed, an examination of three recent reviews of psychiatric genomics (Sullivan *et al.*, 2018), polygenicity (Maier *et al.*, 2017), and precision health (Feero, 2017) failed to reveal any mention of RDoC, or psychological constructs, parity of those constructs with biological factors, or their integration.

Given the massive funding of these world-wide brain projects, it seems likely that clinicians will find themselves with even fewer resources to improve the lives of their patients, despite the opioid epidemic, increasing rates of suicide and depression, and rising mortality rates. Mental health professionals should become more active in promoting research into socio-cultural issues and the accelerating levels of income and social inequality (Piketty and Saez, 2014; Stewart, 2018), critical factors in the genesis and maintenance of mental disorders (Wilkinson and Pickett, 2009). Indeed, an editorialist in The Lancet [Editorial (2018)] has called for a shift from the 'biomedical bubble' toward more funding for the environmental, social, and behavioral determinants of health. However, it should be noted that many of the studies on mortality and adverse outcomes took place in the Nordic countries, where the social safety net is more encompassing compared with that found in the United States. Nevertheless, given the interplay of politics and socioeconomic inequality, mental health professionals also need to become much more active in the political arena.

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