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

Charles E. Dean

Mental Health Service Line, Minneapolis Veteran Administration Medical Center, One Veterans Drive, Minneapolis Minnesota, 55147, USA

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

the southeast and midwest (Dwyer-Lindgren *et al.*, 2018). Of note, the late 1970s marked by beginning of a rapid rise in socio-economic 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.*, 2016a), and obsessive disorder (Meier *et al.*, 2016b). 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

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 corticostriatal systems, but a pronounced gradient, ranging from hypoconnectivity 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

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-Jagiela 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

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.

Author ORCIDs. (iD) Charles E. Dean http://orcid.org/0000-0001-7005-7991

References

Abbott A and Schiemeier Q (2013) Research prize boost to Europe. *Nature* **493**, 585–586.

Advisory Committee to the NIH Director (2013) Interim Report. Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Working Group. 16 September 2013.

Akil H, Brenner S, Kandel E, Kendler KS, King M-C, Scolnick E, Watson JD and Zoghbi HY (2010) The future of psychiatric research: genomes and neural circuits. *Science* **327**, 1580–1581.

Alexander GD, Gallagher SA, Mascola A, Moloney RM and Stafford RS (2011) Increasing use of off-label antipsychotic medication in the United States, 1999–2008. *Pharmacoepidemiology and Drug Safety* **20**, 177–184.

Angell M (2011) The epidemic of mental illness: why? *The New York Review of Books*, 23 July.

Angermeyer MC, Holzinger A, Carta MG and Schomerus G (2011) Biogenic explanations and public acceptance of mental illness: systematic review of population studies. *British Journal of Psychiatry* **199**, 367–372.

Baker JT, Holmes AJ, Masters GA, Yeo BTT, Krienen F, Buckner L and Öngür D (2014) Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. *JAMA Psychiatry* **71**, 109–118.

Barch D and Carter CS (2016) Functional and structural brain connectivity in psychopathology. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* **1**, 196–198.

Baxter AJ, Scott KM, Ferrari AJ, Norman RE, Vos T and Whiteford HA (2014) Challenging the myth of an "epidemic" of common mental disorders: trends in the global prevalence of anxiety and depressive disorder. *Depression & Anxiety* **31**, 506–514.

Bearden CE and Thompson PM (2017) Emerging global initiatives in neurogenetics: the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium. *Neuron.* doi: http://dx.doi.10.1016/j.neuron.2017.03.033.

Buckner RL, Krienen FM and Yeo BTT (2013) Opportunities and limitations of intrinsic functional connectivity MRI. *Nature Neuroscience* **16**, 832–837.

Carandini M (2012) From circuits to behavior: a bridge too far? *Nature Neuroscience* **15**, 507–509.

Case A and Deaton A (2015) Rising morbidity and mortality in midlife among white-non-Hispanic-Americans in the 21st century. *Proceedings of the National Academy of Sciences of the United States of America* **112**, 15078–15083.

Centers for Disease Control (2013) Suicide among adults aged 35–64 years-United States, 1999–2012. *Morbidity and Mortality Weekly Report* **62**, 321.

Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayaska Y, Imau H, Shinohara K and Tajika A (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. doi: http://dx.doi.org/10.1016/50140-6736(17)32802-7.

Cohen B (2016). Embracing complexity in psychiatric diagnoses, treatment, and research. *JAMA Psychiatry*, published online, 9 November 2016. Available at http://jamanetwork.com.

Compton WM, Conway KP, Stinson FS and Grant BF (2006) Changes in the prevalence of major depression and substance abuse in the United States between 1991–1992 and 2001–2002. *American Journal of Psychiatry* **163**, 2147–2151.

Creswell J (2013) Costs for mentally ill soar, and hospitals seek a better way. *The New York Times*, 26 December. https://nytimes.com/2013/12/26/health/er-costs-for-mentally-ill-soar-and-hospitals-seek-a-better-way.html

Crocker LD, Heller W, Warren SL, O'Hare AJ, Infantolino ZP and Miller GA (2013) Relationships among cognition, emotion, and motivation: implications for interventions and neuroplasticity in psychopathology. *Frontiers in Human Neuroscience* **7**, 261.

Cuthbert BN (2014) The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry* **13**, 28–35.

Dean CE (2011) Psychopharmacology: a house divided. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **35**, 1–10.

Dean CE (2012) The death of specificity in psychiatry: cheers or tears? *Perspectives in Biology & Medicine* **55**, 443–460.

Dean CE (2017) Social inequality scientific inequality, and the future of mental illness. *Philosophy, Ethics, and Humanities in Medicine* **12**, 10.

Dulcis D, Jamshidi P, Leutgeb S and Spitzer NC (2013) Neurotransmitter switching in the adult brain regulates behavior. *Science* **340**, 449–453.

Dutta R, Murray RM, Allardyce J and Jones PB (2012) Mortality in first-contact psychosis patients in the UK: a cohort study. *Psychological Medicine* **42**, 1649–1661.

Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RS, Morozoff C, Shiude S, Unutzer J, Naghavi M, Mokdad AH and Murray CJL (2018) Trends and patterns of geographic mortality from substance use disorders and intentional injuries among US counties, 1980–2014. *Journal of the American Medical Association* **319**, 1013–1023.

Editorial (2018) UK life science research: time to burst the biomedical bubble. *The Lancet* **392**, 187.

Ehrhardt S, Appel LJ and Meinert CL (2015) Trends in national institutes of health funding for clinical trials registered in ClinicalTrials.gov. *Journal of the American Medical Association* **314**, 2566–2567.

Elmer GI, Brown PL and Shepard PD (2016) Engaging Research Domain Criteria (RDoC): neurocircuitry in search of meaning. *Schizophrenia Bulletin* **42**, 1090–1095.

Enserink M and Kupferschmidt K (2014) Conflict erupts over landmark E.U. neuroscience plan. *Science* **345**, 127.

Etkin A (2017) Addressing the causality gap in human psychiatric neuroscience. *JAMA Psychiatry*. doi: 10.1001/jamapsychiatry.2017.3610.

Fava GA (2014) Road to nowhere. *World Psychiatry* **13**, 49–50.

Fazel S, Wolf A, Pam C and Lichtenstein P (2014) Violent crime, suicide, and premature mortality in patients with schizophrenia and related disorders: a 38-year population study in Sweden. *The Lancet. Psychiatry* **1**, 44–54.

Feero WG (2107) Introducing "genomics and Precision Health". *JAMA* **317**, 1842–1843.

Finn E, Shen K, Scheinost D, Rosenberg MD, Huang J, Chun MM, Papademetris X and Constable RT (2015) Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. *Nature Neuroscience* **18**, 1664–1671.

Fornito A, Harrison BJ, Goodby E, Dean A, Ooi C, Nathan PJ, Lennox BR, Jones PB, Suckling J and Bullmor ET (2013) Functional dysconnectivity of corticostriatal circuitry as a risk phenotype for psychosis. *JAMA Psychiatry* **70**, 1143–1151.

Frégnac Y (2017) Big data and the industrialization of neuroscience: a safe roadmap for understanding the brain? *Science* **358**, 470–492.

Fusar-Poli P and Meyer-Lindenberg A (2016) Forty years of structural imaging in psychosis: promises and truth. *Acta Psychiatrica Scandinavica* **134**, 207–224.

Gartlehner G, Gaynes BN, Amick HR, Asher GN, Morgan LC, Coker-Schwimer E, Forneris C, Boland E, Lux LJ, Gaylord S, Bann C, Pierl B and Lohr KN (2016) Comparative benefits and harms of antidepressant, psychological, complementary, and exercise treatment for major depression: an evidence report for a clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine* **164**, 331–341.

Gong Q and He Y (2015) Depression, neuroimaging and connectomics: a selective overview. *Biological Psychiatry* **77**, 223–235.

Gong Q, Hu X, Pettersson-Yeo W, Xu X, Lui S, Crossley N, Wu M, Zhu H and Mechelli A (2017) Network-level dysconnectivity in drug-naïve first-episode psychosis: dissociating transdiagnostic and diagnosis-specific alterations. *Neuropsychopharmacology* **42**, 933–940.

Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hegata LB, Ortega BN, Zaiko YV, Roach EL, Korgaonkar MS, Grieve SM, Galatzer-Levy I, Fox PT and Etkin A (2015) Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry* **72**, 305–315.

Gordon J (2016) On being a circuit psychiatrist. *Nature Neuroscience* **19**, 1385–1386.

Griffiths KM, Carron-Arthur B, Parsons A and Reid R (2014) Effectiveness of programs for reducing the stigma associated with mental disorders. A meta-analysis of randomized controlled trials. *World Psychiatry* **13**, 161–175.

Grillner S, Ip N, Koch C, Koroshetz W, Okano H, Polachek M, Poo M and Sejnowski T (2016) World-wide initiatives to advance brain research. *Nature Neuroscience* **19**, 1118–1122.

Haber SN and Knutson B (2010) The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* **35**, 4–26.

Hayes JF, Marston L, Walters K, King WB and Osborn DPJ (2017) Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000–2014. *British Journal of Psychiatry* **211**, 175–181.

Healy D (2002) *The Creation of Psychopharmacology*. Cambridge: Harvard University Press.

Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C and Oepen G (1994) One hundred years of schizophrenia: a meta-analysis of the outcome literature. *American Journal of Psychiatry* **151**, 1409–1416.

Hogan MF (2002) Spending too much on mental illness in all the wrong places. *Psychiatric Services*. doi: https://doi.org.10.1176appi.ps.53.10.1251.

Holmes EA, Craske MG and Graybiel AM (2014) A call for mental health science. *Nature* **511**, 287–289.

Holtzheimer PE and Mayberg HS (2011) Stuck in a rut: rethinking depression and its treatment. *Trends in Neuroscience* **34**, 1–9.

Huang ZJ and Luo L (2015) It takes the world to understand the brain. *Science* **350**, 42–44.

Hyman SH (2010). The diagnosis of mental disorders. The problem of reification. *Annual Review of Clinical Psychology* **6**, 155–179.

Insel TR (2009) Translating scientific opportunity into public health impact. A strategic plan for research on mental illness. *Archives of General Psychiatry* **66**, 128–133.

Insel TR (2014) The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. *American Journal of Psychiatry* **171**, 395–397.

Insel TR and Cuthbert BN (2015) Brain disorders? Precisely. Precision medicine comes to psychiatry. *Science* **348**, 499–500.

Insel TR, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C and Wang P (2010) Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry* **167**, 748–751.

Insel TR, Landis SC and Collins FS (2013) The NIH Brain Initiative. *Science* **340**, 687–688.

Joyner MJ, Paneth N and Ioannidis JPA (2016) What happens when underperforming big ideas in research become entrenched? *Journal of the American Medical Association* **316**, 1355–1366.

Kendler KS and O'Donovan MCA (2014) Breakthrough in schizophrenia genetics. *JAMA Psychiatry* **71**, 1319–1320.

Klein C, Lohmann K and Ziegler A (2012) The promise and limitations of genome-wide association studies. *Journal of the American Medical Association* **308**, 1867–1868.

Kohane IS, Masys DR and Altman RB (2006) The incidentalome. A threat to genetic medicine. *Journal of the American Medical Association* **296**, 212–215.

Korgaonkar MS, Fornito A, Williams LM and Grieve SM (2014) Abnormal structural networks characterize major depressive disorder: a connectome analysis. *Biological Psychiatry*. doi: http://dx.doi/10.1016j.biopsych.2014.02.018.

Kosten TR (2016) An opioid for depression? *American Journal of Psychiatry* **173**, 446–447.

Kozak MJ and Cuthbert BN (2016) The NIMH Research Domain Criteria: background, issues, and pragmatics. *Psychophysiology* **53**, 286–297.

Leucht S, Leucht C, Huhn M, Chaimani A, Mavridis K, Helfer B, Samara M, Rabaioli M, Bächer S, Cipriani A, Geddes JR, Salanti G and Davis JM (2017) Sixty years of placebo-controlled antipsychotic drug trials in schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. *American Journal of Psychiatry* **174**, 927–942.

Lorant V, de Gelder R, Kapadia D and Borrell C (2018) Socioeconomic inequalities in suicide in Europe: the widening gap. *The British Journal of Psychiatry*. doi: https://doi.org/10.1192/bjp.2017.32.

Luhrmann TM (2012) Beyond the brain. *The Wilson Quarterly*. https://wilsonquarterly.com/quarterly-2012-american-vistas/beyond-the-brain.

Luyten P and Fonagy P (2017) The stress-reward-mentalizing model of depression: an integrative developmental cascade approach to child and adolescent depressive disorder based on the research domain criteria (RDoC) approach. *Child Psychology Review*. doi: http://dx.doi.org/10.1016/j.cpr.2017.09.008.

Ma J, Ward EM, Siegel RL and Jemal A (2015) Temporal trends in mortality in the United States 1969–2013. *Journal of the American Medical Association* **314**, 1731–1739.

Maier RM, Visscher PM, Robinson MR and Wray NR (2017) Embracing polygenicity: a review of methods and tools for psychiatric research. *Psychological Medicine* **48**, 1055–1067.

McClellan J and King M-A (2010) Genomic analysis of mental illness. A changing landscape. *Journal of the American Medical Association* **303**, 2523–2524.

McTeague LM, Huerner J, Carreon DM, Jiang Y, Eickoff SB and Etkin A (2017) Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *American Journal of Psychiatry* **174**, 676–685.

Meier SM, Mattheisen M, Mors L, Mortensen PB, Laursen M and Pennix BW (2016a) Increased mortality among people with anxiety disorders: total population study. *British Journal of Psychiatry* **209**, 216–221.

Meier SM, Mattheisen M, Schendel DE, Mortensen PB and Plessen KJ (2016b) Mortality among persons with obsessive-compulsive disorder in Denmark. *JAMA Psychiatry* **73**, 268–274.

Milea D, Verpillat P, Gueilfucci F, Toumi M and Lamure M (2010). Prescription patterns of antidepressants: findings from a U.S. claims data base. *Current Medical Research and Opinion* **26**, 1343–1353.

Mitchell SW (1984) Address before the fiftieth annual meeting of the American Medico-psychological Association held in Philadelphia Pennsylvania, May 16, 1894. *Journal of Nervous and Mental Disease* **21**, 413–447.

Mithoefer M, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, Holland J, Hamilton S, Yazar-Klosinski B, Emerson A and Doblin R (2018) 3,4-Methylenedioxymethamphetamine (MDMA) assisted psychotherapy for post-traumatic disorder in military veterans, firefighters, and police officers: a randomized, double-blind, dose-response, phase 2 clinical trial. *The Lancet*. doi: https://doi.org.1016/S2215-0366(18)30135-4.

Morishita T, Fayad SM, Higuchi M-A, Nestor KA and Foote KD (2014) Deep brain stimulation for treatment-resistant depression: systematic review of clinical outcomes. *Neurotherapeutics* **11**, 475–484.

Nagele P, Duma A, Kopec M, Gebara MA, Parsoei A, Walker M, Janski A, Panagopoulos VN, Cristancho P, Miller JP, Zorumski CF and Conway CR (2015) Nitrous oxide for treatment-resistant major depression: a proof-of-concept study. *Biological Psychiatry* **78**, 10–18.

Nielsen RE, Uggerby AS, Jensen SOW and McGrath JJ (2013) Increasing mortality gap for patients diagnosed with schizophrenia over the last decades – a Danish nationwide study from 1980–2010. *Schizophrenia Research* **146**, 22–27.

Nurnberger JI, Koller DL, Jung J, Edenberg HJ, Foroud T, Guella I, Vawter MP, Kelsoe JR and for the Psychiatric Genomes Consortium Bipolar Group (2014) Identification of pathways for bipolar disorder: a meta-analysis. *JAMA Psychiatry* **71**, 657–664.

Parnas J (2014) Psychiatry without the psyche? *World Psychiatry* **13**, 46–47.

Patten SB, Williams JVA, Lovorato DH, Fiest KM, Bulloch AGM and Wang J (2015) The prevalence of major depression is not changing. *Canadian Journal of Psychiatry* **60**, 31–34.

Perna G, Grassi M, Caldirola D and Nemeroff CB (2018) The revolution in personalized medicine: will technology make it happen? *Psychological Medicine* **48**, 705–713.

Phillips ML and Swartz HA (2014) A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. *American Journal of Psychiatry* **171**, 829–843.

Piketty T and Saez E (2014) Inequality in the long run. *Science* **344**, 838–843.

Pollan M (2015) The trip treatment. *The New Yorker*, 9 February 2015, **XCL** (2).

Price RB, Lane S, Gates K, Kraynak TE, Horner MS, Thase ME and Siegle GJ (2016) Parsing heterogeneity in the brain connectivity of depressed and healthy adults during positive mood. *Biological Psychiatry* **81**, 347–357.

Qaseem A, Barry MJ, Kansagara D and for the Clinical Guidelines Committee of the American College of Physicians (2016) Nonpharmacologic versus pharmacologic treatment of adults with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Annals Internal Medicine* **164**, 350–359.

Reardon S (2016) Worldwide brain-mapping project sparks excitement – and concern. *Nature* **537**, 597.

Rollins HR (2003) Psychiatry in Britain one hundred years ago. *British Journal of Psychiatry* **183**, 292–298.

Rotarska-Jagiela A, van de Ven V, Oertel-Knőchel V, Uhlhass PJ, Vogeley K and Linden DEJ (2010) Resting-state functional network correlates of psychotic symptoms. *Schizophrenia Research* **117**, 21–30.

Saha S, Chant D and McGrath JA (2007) Systematic review of mortality in schizophrenia: is the differential mortality rate worsening over time? *Archives of General Psychiatry* **64**, 1123–1131.

Samara MT, Cao H, Helfer B, Davis JM and Leucht S (2014) Chlorpromazine versus every other antipsychotic for schizophrenia: a systematic review and meta-analysis challenging the dogma of equal efficacy of antipsychotic drugs. *European Neuropsychopharmacology* **24**, 1046–1055.

Sanacora G, Frye M, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, Summergrad P, Nemeroff CB and for the American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments (2017) A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*. doi: 10.1001/jamapsychiatry.2017.0080.

Schomerus G, Schwahn C, Holzinger A, Corrigan PW, Grabe HJ, Carta MF and Angermeyer MC (2012) Evolution of public attitudes about mental illness: a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica* **125**, 440–452.

Scull A (1986) Desperate remedies: a gothic tale of madness and modern medicine. *Psychological Medicine* **17**, 561–577.

Shorter EA (1997). *A History of Psychiatry. From the age of the Asylum to the age of Prozac*. New York: John Wiley & Sons, Inc.

Simon GE, Stewart C, Yarborough BJ, Lynch F, Coleman KJ, Beck A, Operskalski BH, Penfold RB and Hunkeler EM (2018) Mortality rates after the first diagnosis of psychotic disorder in adolescents and young adult. *JAMA Psychiatry* **75**, 254–260.

Spitzer NC (2012) Activity-dependent neurotransmitter respecification. *Nature Reviews* **13**, 94–106.

Stewart M (2018) The birth of a new American aristocracy. *The Atlantic*, June, **321**, 48–63.

Stone DM, Simon TR, Fowler KA, Kegler SR, Yuan K, Holland KM, Ivey-Stephenson AZ, Crosby AE, (2018) Vital signs: trends in state suicide rates-United States, 1999–2016, and circumstances contributing to suicide rates-27 states, 2015. *MMRW Morbidity and Mortality Weekly Report* **67**, 617–624. doi: http://dx.doi.10.15585/mmwr.mm6722a1.

Sullivan PF, Agrawa A, Bulik CM, Andreassen OA, Bőrglum AD, Breen G, Cichon S, Edenberg HJ, Faraone SV, Gelenter J, Mathews CA, Nievergeit CM, Smoller JW and O'Donovan MC (2018) Psychiatric Genomics: an update and an agenda. *American Journal of Psychiatry* **175**, 15–27.

Tiihonen JM, Mittendorfer-Rutz E, Majak J, Hoti F, Jedenius E, Enkusson D, Leval A, Sermon J, Tanskanen A and Taipale H (2017) Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 832 patients with schizophrenia. *JAMA Psychiatry*. doi: 10.1001/jamapsychiatry.2017.1322.

Tromp DPM, Grupe DW, Oathes DJ, McFarlin DR, Hernandez PJ, Kral TRA, Lee JE, Adams M, Alexander AL and Nitschke JB (2012) Reduced structural connectivity of a major frontolimbic pathway in generalized anxiety disorder. *Archives of General Psychiatry* **69**, 925–934.

Tursich M, Ros T, Frewen PA, Kluetsch RC, Calhoun VD and Lanius RA (2015) Distinct intrinsic network connectivity patterns of post-traumatic stress disorder symptom clusters. *Acta Psychiatrica Scandinavica*. doi: 10.1111/acps.12387.

Valenstein ES (1986) *Great and Desperate Cures. The Rise and Decline of Psychosurgery and Other Radical Treatments*. New York: Basic Books, Inc.

Wadman M (2016) Mental health chief to stress neural circuits. *Science* **354**, 403.

Walker ER, McGee RE and Druss BG (2015) Mortality in mental disorders and global disease burden implications. A systematic review and meta-analysis. *JAMA Psychiatry* **72**, 334–441.

Wilkinson R and Pickett K (2009) *The Spirit Level: Why Greater Equality Makes Societies Stronger*. New York: Bloomsbury Press, pp. 15–87.

Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, Feder A, Sos P, Wang G, Zarate Jr CA and Sanacora G (2017) The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *American Journal of Psychiatry in Advance*. doi: 10.1176/appi.ajp.2017.17040472.

Xie Y (2014) "Undemocracy": inequalities in science. *Science* **344**, 809–810.

Yan J (2013) New data adds to evidence for genetic causes of schizophrenia. Interview in *Psychiatric News*. doi: https://doi.org.10.1176/appi.pn.2013.10a.21.

Yuste R (2015) From the neuron doctrine to neural networks. *Nature Reviews Neuroscience* **16**, 487–497.

Zeinoddini A, Sorayani M, Hassanzadeh E, Arabi M, Farokhnia M, Salimi S, Ghaleiha A and Akhondzadeh S (2015) Pioglitazone adjunctive therapy for depressive episode of bipolar disorder: a randomized, double-blind, placebo-controlled trial. *Depression Anxiety* **32**, 167–173.