Challenges and Opportunities in Psychiatric Neuroscience

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Psychiatry faces a number of challenges as a field. These include the high individual and societal costs of mental illnesses, overlapping and heterogeneous diagnoses, a complete lack of biomarkers, and treatments that, although efficacious for some, leave many without adequate relief. On the other hand, scientific and technical advances present considerable opportunities, especially in genomics, computational and theoretical approaches, and neural circuit technologies. The National Institute of Mental Health is committed to taking advantage of these opportunities to address the challenges of psychiatry, in the service of achieving our mission of transforming the understanding and treatment of mental illnesses.

The mission of the National Institute of Mental Health (NIMH) is to transform the understanding and treatment of mental illnesses, paving the way for prevention, recovery, and cure. This is an ambitious mission, especially when considering the tremendous complexity of the brain, the principal organ in which mental illnesses are expressed. Psychiatric research faces a number of challenges in attempting to accomplish this mission, yet modern neuroscience offers considerable potential for future progress. In particular, advances in three areas—genetics, computational psychiatry, and neural circuits—present unique opportunities to advance the state of understanding of mental illnesses. By dissecting the complexity of the brain, these opportunities hold promise to address the challenges faced by psychiatry, leading the way to novel clinical approaches to mental illnesses.

CHALLENGES OF PSYCHIATRY

The first challenge faced by psychiatry is the tremendous burden imposed by mental illnesses on individuals and society. In 2017, nearly one-fifth of all U.S. adults—an estimated 46.6 million people—had a mental illness diagnosis in the preceding year (Substance Abuse and Mental Health Services Administration 2018). Mental illnesses are indiscriminate; they affect males and females, young and old, and cut across race and ethnicity. The cost to the individual is often severe and functionally impairing. Individuals with mental illnesses are disproportionately represented among the homeless and incarcerated (Fazel et al. 2016). Serious mental illness is associated with personal loss of earnings (Kessler et al. 2008), and a variety of economic measures indicate that mental illnesses have a negative global financial impact (Bloom et al. 2011). In fact, mental illnesses are among the leading causes of disability and poor health worldwide (World Health Organization 2003).

A second challenge is that of diagnostics. Addressing the burden of mental illnesses begins with proper diagno-

sis, without which appropriate and effective treatments are elusive. For decades, psychiatric diagnoses have been determined by lists of symptoms codified in the Diagnostic and Statistical Manual of Mental Disorders, currently in its fifth iteration. Patients must meet a minimum number of criteria, over a specified duration, to receive a given diagnosis. To confirm the presence of patient-endorsed symptoms and to ensure those symptoms are clinically significant, clinicians—especially in research settings—conduct structured or semistructured interviews. This symptom-based diagnostic system has high inter-rater reliability and ensures that psychiatrists use the same terms in the same manner (Pies 2007). In this way, study results can be compared across research groups.

Although this classification system has high reliability, it falls short on validity. High rates of comorbidity occur across diagnostic categories, and a high degree of heterogeneity exists within categories. For example, some studies estimate that as many as 75% of patients with major depressive disorder are diagnosed with an anxiety disorder at some point during their lifetime (Lamers et al. 2011). A large-scale study of psychiatric disorders among youth revealed high rates of comorbidity among attention-deficit/hyperactivity disorder, mood disorders, anxiety disorders, as well as substance use (Abram et al. 2003). In addition, patients with a given diagnosis do not necessarily meet the exact same criteria, resulting in heterogeneity within the same diagnosis; for example, there are currently 636,120 different symptom combinations that can result in diagnosis of posttraumatic stress disorder (PTSD) (Galatzer-Levy and Bryant 2013). Further complicating the diagnostic picture is the “not otherwise specified (NOS)” designation for patients whose symptoms are indicative of, but do not clearly meet criteria for, a given disorder (e.g., depressive disorder, NOS). Because many patients do not meet the stringent criteria applied in research for “pure” diagnoses, it can be difficult for physicians to predict course of illness and treatment response. Notably, the current classification system relies solely on

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self-reported or observable symptoms without regard to underlying biological causes.

In most medical specialties, biomarkers—laboratory tests, objective clinical signs, etc.—help establish a diagnosis, guide treatment, and/or predict the future course of illness. This is the case even for much of neurology, which, like psychiatry, faces the challenging complexity of the human brain. For example, several neuroimaging and cerebrospinal fluid biomarkers must be present for diagnosis of Alzheimer's disease (Ritter and Cummings 2015). Laboratory and neuroimaging biomarkers inform treatment for acute stroke in which rapid administration of a targeted treatment is essential (Polivka et al. 2016). Yet, in the field of psychiatry, researchers have been unable to find biomarkers for psychiatric disorders based on traditional diagnostic categories. In early endeavors, researchers hypothesized dysregulation of the glucocorticoid system as a biological mechanism for major depressive disorder (Plotzky et al. 1998). Dexamethasone suppression tests were used to measure how cortisone levels change in response to an injection of the exogenous glucocorticoid, dexamethasone. Compared with controls, patients with depression showed a relative failure to down-regulate endogenous cortisone (Kalin et al. 1981; Hayes and Ettigi 1983). However, this paradigm had poor sensitivity and specificity, and was ultimately not informative for clinical practice (Arana et al. 1985; APA Task Force on Laboratory Tests in Psychiatry 1987). Similarly, neurophysiological and neurobehavioral biomarker studies for schizophrenia have proven either unreliable or nonspecific (Calkins and Iacono 2000; Rosen et al. 2015), and early genetic studies revealed nonspecific risk factors that typically predisposed individuals to multiple disorders (Kendler and Greenspan 2006; International Schizophrenia Consortium et al. 2009; Brandon and Sawa 2011). More recently, neuroimaging studies have been likewise unable to link biomarkers with traditional psychiatric diagnoses. For example, aberrant amygdala activation or hippocampal volume measures have been observed across a range of seemingly disparate psychiatric disorders (Videbech and Ravnkilde 2004; Smith 2005; Adriano et al. 2012; Gilpin et al. 2015). The failure of biomarker studies based on traditional diagnostic categories has left the field of psychiatry without a full biological understanding of psychiatric disorders or a clear path toward improved treatments. Further, because of the absence of biomarkers, many promising treatments have failed to prove effective in clinical testing after years of preliminary research; as a result, many of the major pharmaceutical companies have largely withdrawn from psychopharmacological development.

Although available treatments can be transformative for some patients, for many with psychiatric illnesses, current treatments are inadequate and have limited efficacy. Antidepressants, antipsychotics, mood stabilizers, and anxiolytics have successfully treated many psychiatric illnesses—yet a common theme in neuropsychopharmacology is that in real world situations, these drugs are only effective in some individuals. Reports of treatment response rates (50%–90%), remission rates (30%–60%), and relapse rates (as high as 90%), vary widely depending on the

population, medication, and disease condition (Stern et al. 2018). When comorbid conditions are introduced, the rates for response, remission, and relapse are even more profound. There still remains a great need to optimize the clinical benefits, reduce the number of side effects, and develop personalized treatment regimens that will positively impact and adequately treat all patients.

Despite the wide range and benefits of some treatments, adverse events related to drug tolerability and side effects can be disabling. Although reasons for treatment adherence can be complex, medication side effects, which can range from cardiovascular disturbances to motor dysfunction, may contribute to a lack of adherence (Hampton et al. 2014). In addition, the financial and emotional toll that can be expended by patients that are waiting for a treatment to take effect, can also be a barrier to treatment success (Farooq and Naeem 2014).

OPPORTUNITIES

Genetics

The discovery of single gene disorders like Huntington's disease left the field hopeful that genes for disorders like schizophrenia or depression could also be cloned. But this optimism gave way to disappointment over the ensuing decades with the failure to find reproducible linkages. It became clear that psychiatric disorders were quite different and did not likely result from a single gene or even a small number of genes. With the advent of genome-wide association studies (GWASs), the true genetic architecture of psychiatric illnesses has become apparent. These studies have identified hundreds of loci that are associated with the risk for psychiatric disorders such as schizophrenia, bipolar disorder, depression, and others (Fig. 1; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014; Smoller et al. 2018). Each of these loci confers only a very small amount of risk, meaning that causal explanations are not easily constructed. Moreover, for the vast majority of these loci, the precise genetic alteration that influences disease risk is not clear. Nonetheless, each locus represents a clue to the biology that underlies that disorder. Even more recently, large-scale sequencing efforts, including whole exome and whole genome sequencing, have revealed additional biological clues, this time in the form of rare gene variants that confer large amounts of risk particularly for autism and other neurodevelopmental disorders. Altogether, GWASs and sequencing efforts provide a rich array of opportunities for scientists to understand and potentially develop treatments for that disorder.

To help set priorities for genomics research, NIMH convened a workgroup that provided recommendations on advancing the field (National Advisory Mental Health Council Workgroup on Genomics 2018). The group addressed the need to ensure that gene discovery studies are well-powered and unbiased, and that they use rigorous and appropriate statistical methods and significance standards. The workgroup also highlighted the need to carefully choose and enrich experimental systems to address both common and rare gene variants, and to expand efforts

Figure 1. Schizophrenia risk loci. Schizophrenia risk loci (green diamonds) arranged in a Manhattan plot in which each point on the plot is a single-nucleotide polymorphism, the x -axis is chromosomal position, and the y -axis shows statistical significance ($-\log_{10}(P)$). The red line shows the genome-wide significance level (5×10^{-8}). (Reprinted from Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014, by permission from Springer Nature 2014.)

beyond current diagnostic classifications to include additional disorders and other psychiatrically relevant phenotypes. In addition, because most genetic samples are comprised of individuals from European populations, the workgroup recommended that future studies should aim to capture a greater spectrum of genetic and phenotypic variation across human populations. This concern is addressed in part through projects like the NIMH-funded Human Heredity and Health in Africa (H3-Africa) Initiative—which is investigating the genomics and epidemiology of African populations in partnership with African scientific institutions.

Computational and Theoretical Approaches

Computational and theoretical approaches may be useful across a wide range of basic and clinical science applications to address the challenges facing psychiatry. There are two complimentary approaches to computational psychiatry: data-driven and theory-driven. Data-driven approaches leverage large data sets and algorithms (e.g., machine learning) to model neural mechanisms across levels (e.g., genes to cells, cells to circuits, circuits to systems, systems to behavior) (Huys et al. 2016; Redish and Gordon 2016). Theory-driven approaches use models to test hypotheses of how observations may be explained by lower-level variables of analyses using a rigorous mathematical framework (Oquendo et al. 2012; Averbeck and Chafee 2016; Redish and Gordon 2016).

A particularly useful theory-driven computational approach is to create biophysically realistic models of the brain. Biophysically realistic models allow researchers to explore a hypothesis space, make predictions, and test their theories. For example, to better understand the link between synaptic and cellular properties of hippocampal theta and gamma oscillations, researchers genetically modified mice to ablate a key molecule necessary for synaptic inhibition in parvalbumin-positive (PV) interneurons (Wulff et al. 2009). In the mouse model, the researchers found that theta- and gamma-frequency oscillations were intact. However, whereas gamma oscillations normally occur only at specific phases of the theta oscillation, in the mouse model this relationship was disrupted. Next, the scientists showed that a biophysically realistic model of a simple neural circuit that included PV interneurons and pyramidal neurons could generate realistic oscillatory behavior which preserved the relationship between theta and gamma oscillations. Moreover, eliminating synaptic inhibition onto the PV interneurons in the model also resulted in a disrupted relationship between the two oscillations, explaining the alterations seen in the mouse. Biophysically realistic models are particularly useful for making these links across levels of analysis, in this case, the molecular (synaptic inhibition mediated by a specific molecule) and the circuit (generation of nested gamma and theta oscillations). In addition to testing links across levels of analyses, computational models can also address trajectories in neurodevelopment or clinical prediction by mod-

eling across time. They may even assist researchers to translate animal findings to humans by modeling across scales.

Another theory-driven approach involves computational phenotyping, which is an attempt to break down abstract behavioral concepts into specific functional components that can be described mathematically and used to explore brain–behavior–illness relationships. In one compelling example, researchers developed a computational model of happiness based on rewards and expectations (Rutledge et al. 2017). They validated the model using a large sample of study participants who rated their moment-to-moment happiness while playing a probabilistic reward game on a smartphone. Next, they showed they could map the reward- and expectation-related variables to specific brain circuits using functional magnetic resonance imaging (fMRI). Their findings show that breaking down the abstract concept of “happiness” into more specific and quantifiable parameters enables circuit-based explorations of mechanism. The researchers also hypothesized that individuals with depression might have differences in some of these specific parameters compared to healthy control subjects, but their data failed to find any such differences.

Finally, data-driven approaches have important roles to play in psychiatric research. Such approaches typically use clustering, factor analysis, and/or machine learning to extract ordered information from large data sets. They are particularly useful when one has no a priori hypothesis about which are the important data elements or how they might be combined to provide useful information. Take, for example, the question of whether there might be different subtypes of patients with depression. Attempts have been made to define subtypes based on symptoms, course, severity, etc., but these have been difficult to replicate and not definitively useful in the clinic. Recently, NIMH-funded researchers used a data-driven approach to ask whether neuroimaging could help define depression subtypes. The researchers measured functional connectivity with resting state fMRI in more than 1000 people with depression, creating individualized connectivity maps for each of them (Fig. 2; Drysdale et al. 2017). Using a clustering algorithm, the researchers then asked whether there were different types of connectivity maps; the algorithm suggested there were four types of maps, which they called “biotypes.” Intriguingly, individuals with the same bio-

Figure 2. Functional connectivity-based subtypes in depression. (A) For each subject, whole-brain functional connectivity was calculated by correlating time-varying activity between all regions of interest (colored dots), as in the example shown ($R^2 = 0.88$) for nodes in the dorsolateral (solid line) and posterior parietal cortices (dashed line). (B) An example functional connectivity map for one individual. (C) Hierarchical clustering analysis of the maps of all the individuals in the sample revealed four types of maps, termed “biotypes.” (D) Members of the four biotypes differed in their likelihood of responding to repetitive transcranial magnetic stimulation. (Reprinted and adapted from Drysdale et al. 2017, by permission from Springer Nature 2016.)

type had similar constellations of depression symptoms, whereas individuals with different biotypes tended to have different symptoms. Even more intriguing was the finding that treatment responses differed with the different groups: Individuals in one of the biotypes responded better to repetitive transcranial magnetic stimulation (rTMS), a noninvasive treatment for depression, than those in the other biotypes. This finding suggests functional connectivity maps could potentially serve as useful biomarkers to not only identify subsets of depression, but also predict treatment response.

Of course, theory- and data-driven approaches can be combined to address the challenges facing psychiatry. Take, for example, the need for improved diagnostics. NIMH's Research Domain Criteria (RDoC) framework is a major theoretical approach to better describe features of dysfunction in patients suffering from mental illnesses. RDoC is centered around dimensional psychological constructs to investigate the nature of mental illness in terms of varying degrees of dysfunctions in general psychological/biological systems. It is based on theoretical groupings of behavioral domains, such as affect and executive function. One could imagine combining this theory-driven approach with a data-driven approach to validate the RDoC domains, by assessing dimensional constructs in a large sample of people and measuring the degree to which performance in different constructs varies together. Weaker relationships between measurements of different constructs would suggest they measure truly different types of behavior, whereas stronger relationships between such measurements would suggest that the constructs are more closely related than previously thought. Ideally, this analysis would include computational phenotyping as well, such that the different domain assessments would correspond to quantifiable, parameterized behaviors, permitting the pursuit of their underlying circuitry. Approaches informed by both theory and data hold promise for uncovering mechanisms of illness, hopefully paving the way for novel treatments.

Neural Circuits

If neurons are the building blocks of the brain, neural circuits are its fundamental functional units. Neural circuits are small groups of interconnected neurons that act together to perform the calculations necessary to guide behavior. For example, in the primary visual cortex, circuits of interconnected excitatory and inhibitory neurons receive inputs from the retina and begin the task of constructing representations of the visual world from the simple pixelated input received from the eyes. Similarly, information representing complex visual patterns are combined with auditory, olfactory, and other information to construct representations of specific episodes—memories—by neural circuits in the hippocampus.

Neuroscience has undergone a revolution over the past decade with the advent of myriad technologies aimed at measuring and modulating the activity of specific circuits. By virtue of these technologies, such as optogenetics, chemogenetics, viral tracing, and high-resolution optical

imaging, scientists have learned a tremendous amount about the circuits that control behavior. This is particularly true of behavior relevant to psychiatry, including avoidance behavior, fear learning, repetitive behaviors, stress responses, reward processing, working memory, and other executive functions. Circuit technologies have revealed key roles for specific neuronal types in specific brain regions, as well as specific connections between them, in these and other behaviors. By activating or inhibiting these circuit elements, researchers can enhance motivation, prevent the negative effects of stress, and so on. At least, they can do so in mice.

Of course, to help those suffering from mental illnesses, it is not good enough to change behaviors in mice. To transform mental health care with novel therapies, circuit-based knowledge must be translated into circuit-focused therapies, using either a neurobiological or technological approach. Both approaches have the initial steps in common: First, one needs to identify the circuit element responsible for a given psychiatrically relevant behavior in a model organism and, second, verify that this circuit is similarly engaged in the behavior in humans. After these steps, the two approaches diverge.

Similar to traditional efforts at drug discovery, the neurobiological approach seeks to identify therapeutic targets expressed in these circuit elements that might be exploited. For example, neurons in the central nucleus of the amygdala, when inhibited, reduce the expression of learned fear behaviors (Calhoun and Tye 2015). Might there be some receptor expressed in these neurons that researchers could antagonize that would inhibit these neurons, reducing fear—and by extension—reducing PTSD symptomatology? Molecular characterization of these neurons could be pursued to identify such a potential drug target. The neurobiological approach could also be of benefit to designing other kinds of treatments. For example, physiological or anatomical characterization of these elements might reveal approaches to brain stimulation therapies that would preferentially affect their function. The neurobiological approach requires extensive characterization of neurons, brain regions and connections with causal relationships to psychiatrically relevant behavior, to exploit features of these circuit elements to design novel therapies.

The technological approach recognizes that for some circuits, and some debilitating symptoms, the neurobiological approach may not be sufficient. In such cases, one can imagine adapting the very same technologies that are so effective in mice for use in humans. Beyond identifying the relevant circuit elements in humans as noted above, the technological approach would require the development of vectors to deliver genetic payloads into the human brain, refinement of methods to direct expression to specific cell types, the ability to verify expression in the living brain, and methods to deliver the appropriate kinds of neuromodulation. One could imagine a noninvasive approach, whereby viral vectors are injected into the bloodstream, delivering genes encoding effector molecules to neurons after crossing the blood–brain barrier (Fig. 3; Gordon 2016). These effector molecules could be activated by designer drugs, focused ultrasound, or magnetic pulses,

Figure 3. A technological approach to circuit therapies. Genetic payloads with cell type–specific enhancers could be packaged into viruses that, when injected into the bloodstream, would find their way across the blood–brain barrier and infect brain cells. Subsequently, systemic administration of activator drugs could alter activity in specific types of neurons, as is currently done in model organisms such as mice and rats.

in order to alter the activity of neurons in precise ways. Much of this technology already exists and needs only to be modified and refined; such work is ongoing as part of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. The BRAIN initiative has simultaneously initiated a rigorous neuroethics research program to ensure ethical development and use of these technologies.

HARNESSING OPPORTUNITIES TO ADDRESS CHALLENGES

The opportunities presented by genetics, computational and theoretical approaches, and neural circuit technology have the potential to transform our knowledge of mental illnesses and the clinical practice of psychiatry. To do so, these opportunities need to be harnessed to address the principle challenges facing psychiatry.

Indeed, each of the challenges could be addressed by combining aspects of all three opportunities. One could imagine an improved diagnostic system that harnesses genetic characterization of risk, assessments of computationally derived phenotypes, and neuroimaging findings indicating specific circuits to define a multidimensional diagnosis for each individual. These phenotypes could further be used to identify, perhaps using data-driven approaches, clinically useful biomarkers that provide predictions regarding course of illness or treatment responsiveness. These biomarkers would improve the efficacy of existing treatments by targeting interventions to the individuals most likely to benefit from them, thereby shortening the time to clinically meaningful improvements in function. Finally, biophysically realistic modeling of genetic effects on neural circuits of relevance to behavior could lead the way to transformative novel treatments, aimed at traditional molecular targets or using novel circuit technologies.

Some of these advances may be right around the corner—data-driven approaches to neuroimaging biomarkers,

for example, has the potential to change practice in the near term. Others, such as redefining diagnostics or developing new treatments based on genetics, may be further off. Nonetheless, the opportunities presented by modern neuroscience are undeniable, and if harnessed correctly, offer the potential to reduce the burden of mental illness in the years to come.

REFERENCES

- Abram KM, Teplin LA, McClelland GM, Dulcan MK. 2003. Comorbid psychiatric disorders in youth in juvenile detention. *Arch Gen Psychiatry* **60**: 1097–1108. doi:10.1001/archpsyc.60.11.1097
- Adriano F, Caltagirone C, Spalletta G. 2012. Hippocampal volume reduction in first-episode and chronic schizophrenia: a review and meta-analysis. *Neuroscientist* **18**: 180–200. doi:10.1177/1073858410395147
- APA Task Force on Laboratory Tests in Psychiatry. 1987. The dexamethasone suppression test: an overview of its current status in psychiatry. *Am J Psychiatry* **144**: 1253–1262. doi:10.1176/ajp.144.10.1253
- Arana GW, Baldessarini RJ, Ornstein M. 1985. The dexamethasone suppression test for diagnosis and prognosis in psychiatry. Commentary and review. *Arch Gen Psychiatry* **42**: 1193–1204. doi:10.1001/archpsyc.1985.01790350067012
- Averbeck BB, Chafee MV. 2016. Using model systems to understand errant plasticity mechanisms in psychiatric disorders. *Nat Neurosci* **19**: 1418–1425. doi:10.1038/nn.4413
- Bloom DE, Cafiero ET, Jane-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, Feigl AB, Gaziano T, Mowafi M, Pandya A, et al. 2011. *The global economic burden of noncommunicable diseases*. World Economic Forum, Geneva.
- Brandon NJ, Sawa A. 2011. Linking neurodevelopmental and synaptic theories of mental illness through DISC1. *Nat Rev Neurosci* **12**: 707–722. doi:10.1038/nrn3120
- Calhoun GG, Tye KM. 2015. Resolving the neural circuits of anxiety. *Nat Neurosci* **18**: 1394–1404. doi:10.1038/nn.4101
- Calkins ME, Iacono WG. 2000. Eye movement dysfunction in schizophrenia: a heritable characteristic for enhancing phenotype definition. *Am J Med Genet* **97**: 72–76. doi:10.1002/(SICI)1096-8628(200021)97:1<72::AID-AJMG10>3.0.CO;2-L
- Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, Fetcho RN, Zebley B, Oathes DJ, Etkin A, et al. 2017.

- Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med* **23**: 28–38. doi:10.1038/nm.4246
- Farooq S, Naeem F. 2014. Tackling nonadherence in psychiatric disorders: current opinion. *Neuropsychiatr Dis Treat* **10**: 1069–1077. doi:10.2147/NDT.S40777
- Fazel S, Hayes AJ, Bartellas K, Clerici M, Trestman R. 2016. Mental health of prisoners: prevalence, adverse outcomes, and interventions. *Lancet Psychiatry* **3**: 871–881. doi:10.1016/S2215-0366(16)30142-0
- Galatzer-Levy IR, Bryant RA. 2013. 636,120 ways to have post-traumatic stress disorder. *Perspect Psychol Sci* **8**: 651–662. doi:10.1177/1745691613504115
- Gilpin NW, Herman MA, Roberto M. 2015. The central amygdala as an integrative hub for anxiety and alcohol use disorders. *Biol Psychiatry* **77**: 859–869. doi:10.1016/j.biopsych.2014.09.008
- Gordon JA. 2016. On being a circuit psychiatrist. *Nat Neurosci* **19**: 1385–1386. doi:10.1038/nn.4419
- Hampton LM, Daubresse M, Chang HY, Alexander GC, Budnitz DS. 2014. Emergency department visits by adults for psychiatric medication adverse events. *JAMA Psychiatry* **71**: 1006–1014. doi:10.1001/jamapsychiatry.2014.436
- Hayes PE, Ettigi P. 1983. Dexamethasone suppression test in diagnosis of depressive illness. *Clin Pharm* **2**: 538–545.
- Huys QJM, Maia TV, Frank MJ. 2016. Computational psychiatry as a bridge from neuroscience to clinical applications. *Nat Neurosci* **19**: 404–413. doi:10.1038/nn.4238
- International Schizophrenia Consortium, Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P. 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**: 748–752. doi:10.1038/nature08185
- Kalin NH, Cohen RM, Kraemer GW, Risch SC, Shelton S, Cohen M, McKinney WT, Murphy DL. 1981. The dexamethasone suppression test as a measure of hypothalamic-pituitary feedback sensitivity and its relationship to behavioral arousal. *Neuroendocrinology* **32**: 92–95. doi:10.1159/000123137
- Kendler KS, Greenspan RJ. 2006. The nature of genetic influences on behavior: lessons from “simpler” organisms. *Am J Psychiatry* **163**: 1683–1694. doi:10.1176/appi.2006.163.10.1683
- Kessler RC, Heeringa S, Lakoma MD, Petukhova M, Rupp AE, Schoenbaum M, Wang PS, Zaslavsky AM. 2008. Individual and societal effects of mental disorders on earnings in the United States: results from the national comorbidity survey replication. *Am J Psychiatry* **165**: 703–711. doi:10.1176/appi.ajp.2008.08010126
- Lamers F, van Oppen P, Comijs HC, Smit JH, Spinhoven P, van Balkom AJLM, Nolen WA, Zitman FG, Beekman ATF, Penninx BW. 2011. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA). *J Clin Psychiatry* **72**: 341–348. doi:10.4088/JCP.10m06176blu
- National Advisory Mental Health Council Workgroup on Genomics. 2018. *Opportunities and challenges of psychiatric genetics*. National Institute of Mental Health, Bethesda, MD.
- Oquendo MA, Baca-Garcia E, Artés-Rodríguez A, Perez-Cruz F, Galfalvy HC, Blasco-Fontecilla H, Madigan D, Duan N. 2012. Machine learning and data mining: strategies for hypothesis generation. *Mol Psychiatry* **17**: 956–959. doi:10.1038/mp.2011.173
- Pies R. 2007. How “objective” are psychiatric diagnoses? Guess again. *Psychiatry (Edmont)* **4**: 18–22.
- Plotsky PM, Owens MJ, Nemeroff CB. 1998. Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. *Psychiatr Clin North Am* **21**: 293–307. doi:10.1016/S0193-953X(05)70006-X
- Polivka J, Polivka J Jr, Krakorova K, Peterka M, Topolcan O. 2016. Current status of biomarker research in neurology. *EPMA J* **7**: 14. doi:10.1186/s13167-016-0063-5
- Redish AD, Gordon JA. 2016. *Computational psychiatry: new perspectives on mental illness*. The MIT Press, Cambridge, MA.
- Ritter A, Cummings J. 2015. Fluid biomarkers in clinical trials of Alzheimer's disease therapeutics. *Front Neurol* **6**: 186. doi:10.3389/fneur.2015.00186
- Rosen AM, Spellman T, Gordon JA. 2015. Electrophysiological endophenotypes in rodent models of schizophrenia and psychosis. *Biol Psychiatry* **77**: 1041–1049. doi:10.1016/j.biopsych.2015.03.021
- Rutledge RB, Moutoussis M, Smittenaar P, Zeidman P, Taylor T, Hryniewicz L, Lam J, Skandali N, Siegel JZ, Ousdal OT, et al. 2017. Association of neural and emotional impacts of reward prediction errors with major depression. *JAMA Psychiatry* **74**: 790–797. doi:10.1001/jamapsychiatry.2017.1713
- Schizophrenia Working Group of the Psychiatric Genomics Consortium. 2014. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**: 421–427. doi:10.1038/nature13595
- Smith ME. 2005. Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. *Hippocampus* **15**: 798–807. doi:10.1002/hipo.20102
- Smoller JW, Andreassen OA, Edenberg HJ, Faraone SV, Glatt SJ, Kendler KS. 2018. Psychiatric genetics and the structure of psychopathology. *Mol Psychiatry*. doi:10.1038/s41380-017-0010-4
- Stern S, Linker S, Vadodaria KC, Marchetto MC, Gage FH. 2018. Prediction of response to drug therapy in psychiatric disorders. *Open Biol* **8**: 180031. doi:10.1098/rsob.180031
- Substance Abuse and Mental Health Services Administration. 2018. *Key substance use and mental health indicators in the United States: results from the 2017 National Survey on Drug Use and Health*. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD.
- Videbech P, Ravnkilde B. 2004. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry* **161**: 1957–1966. doi:10.1176/appi.ajp.161.11.1957
- World Health Organization. 2003. *Investing in mental health*. Department of Mental Health and Substance Dependence, Noncommunicable Diseases and Mental Health, World Health Organization, Geneva.
- Wulff P, Ponomarenko AA, Bartos M, Korotkova TM, Fuchs EC, Bahner F, Both M, Tort AB, Kopell NJ, Wisden W, et al. 2009. Hippocampal θ rhythm and its coupling with γ oscillations require fast inhibition onto parvalbumin-positive interneurons. *Proc Natl Acad Sci* **106**: 3561–3566. doi:10.1073/pnas.0813176106

Cold Spring Harbor Symposia on Quantitative Biology

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Cold Spring Harb Symp Quant Biol 2018 83: 1-8 originally published online March 19, 2019
Access the most recent version at doi:[10.1101/sqb.2018.83.037523](https://doi.org/10.1101/sqb.2018.83.037523)

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