EDITORIAL

nature neuroscience

Focus on psychiatric disorders

***Nature Neuroscience* presents a Focus issue highlighting progress in basic and clinical sciences advancing mental health research.**

Psychiatric disorders present a major medical, societal and economic burden and are the leading cause of disability worldwide. Compared to other areas of medicine, psychiatric research faces unique biological, technological, clinical, regulatory and ethical challenges. To overcome these hurdles, this past spring *Nature Neuroscience* and *Nature Medicine,* in collaboration with the Volkswagen Foundation, convened the Herrenhausen Symposium on Psychiatric Disorders. We brought together leaders from academia and industry to discuss advances and limitations in our understanding of the etiology, development and neurobiology of psychiatric disorders as well as the use of animal models. Stemming from these and other discussions, this issue of *Nature Neuroscience* and a companion issue of *Nature Medicine* present a special joint focus with a collection of Commentaries, Perspectives, Reviews and primary research from leaders in the field that address basic and clinical issues in mental health research.

Fueled by new technology and collaborative efforts in team science, psychiatry is seeing an accelerated expansion in gene discovery. We have learned that common, rare, inherited and *de novo* gene variants contribute to neurodevelopmental and psychiatric disorders[1,2]. Yet, translating these findings into disease mechanisms and new therapies is a major obstacle. This is a particularly vexing problem for genome-wide association studies that identify genomic regions and not disease-causing variants[3]. Given the potentially hundreds to thousands of genes involved, genomics and systems biology have risen to the forefront as analytically rigorous approaches for understanding how genetic variants affect gene regulation and disease risk[3,4] and how they converge onto specific molecular networks and biological processes[5,6]. It is likely that as gene discovery advances, systems biology will play an increasing part in bridging the gap between genetics and neurobiology[3].

Advances in genetics are also set to halt the retreat of an industry embittered by failures in CNS drug discovery. Several factors have contributed to limited success, including deficiencies in clinical trial designs that intervene at the wrong moment, in the wrong patients, while measuring the wrong outcomes. One remedy is more refined phenotypic characterization of patients, including a return to careful descriptions of disease course and its developmental trajectory that may narrow down potential mechanisms and identify therapeutic windows[7]. In addition, there is a growing realization and acceptance that animal models make poor predictors of drug efficacy in humans[8]. This stark reality has led some in industry to instead leverage genetics and genomics for both target identification and validation[9] and to relegate animals to safety and toxicity screens[8]. This is in sharp contrast to the central role animal models continue to serve in preclinical academic research.

The limitations of animal models comprise well-trodden terrain in post-mortem analyses of translational failures. Unlike other medical conditions, psychiatric disorders are classified based on behavioral symptoms and not objective biomarkers. Yet we impose diagnostic labels such as 'schizophrenia-like' upon model systems meant to be experimentally more tractable. For far too long the field has focused on validating models in terms of face and construct validity rather than elucidating basic mechanisms[8]. For example, behavioral impairments in an animal model that, on the face of it, bears some semblance to human psychopathology may in fact be irrelevant for understanding human pathophysiology. This is a common error of reverse inference, given that pathogenesis may be driven by different cellular and circuit components in humans. Even in the best-case scenario, where there is a clear disease link with a genetic mutation or environmental exposure, these disease constructs are rarely fully penetrant or disorder-specific. Thus, applying terms such as 'autism-like' or 'depression-like' to animal models, while convenient short-hand, is scientifically misleading. This allure of branding more and more research as translational no doubt stems from competition for limited research funds and citations, but authors, funders and publishers all have a duty to responsibly and accurately present research and its implications for human disease.

That is why editorially we will ensure that preclinical and translational research related to mental health is judiciously represented in our pages. When characterizing the biology of a gene or impact of a mutation, we will closely evaluate the literature cited to support a genetic link to disease and temper any claims that do not meet current statistical standards in human genetics[3], and we will not allow any functional data, regardless of biological plausibility, to circumvent these standards. We will also restrict the usage of 'disease-like' terms as applied to animal models of psychiatric disease and ask that the particular construct(s) measured be described explicitly. That is not to say we cannot gain insights about human mental health and disease from animals[10,11]; after all, there is an evolutionary continuum that ensures our neurobiology and psychology share roots with other species[12]. Rather, we hope to shift the emphasis away from phenomenologically validating models so that they resemble a disease or disease phenotype and toward elucidating basic processes affected by disease risk factors, be they toxins, pathogens or mutations. Simply put, making disease models should be eschewed in favor of discovering disease mechanisms. This is not a mere matter of semantics; we hope to encourage a reconceptualization of how animals may most effectively be used in preclinical research.

As it stands, in a rush to advance translational research, we risk abandoning the basics learned at the bench. We are a long way from fully understanding the 'typical' development and function of the brain: the assembling of stereotyped circuits, the computations of different cell types, the interactions of internally and externally driven activity and the integration of cognitive processes and affective regulation that

underlie thought, mood and behavior. Lacking these fundamentals, our understanding of their dysregulation in disease will necessarily be incomplete. That is why basic research is indispensable for understanding psychiatric disorders, as it provides the appropriate biological context in which to interpret potential disease mechanisms. Animals are of course a crucial component of this endeavor but should be part of a larger set of model systems chosen based on the nature of the question being asked. For example, understanding neurodevelopment under high polygenic risk may require patient-derived organoids[3], deciphering errant plasticity after exposure to drugs of abuse may necessitate *ex vivo* interregotion[11] and elucidating the circuitry of affective modulation may call for behaving animals[13]. In some cases, when investigating the basic function of higher cognitive and social domains, nonhuman primates will be the only viable model system[12] and in other cases there will be no substitute for humans[14].

We are committed to doing our part in supporting research that will advance mental health and well-being including supporting diverse fields and approaches as evidenced by the papers in this issue. At the Herrenhausen Symposium it was readily apparent that geneticists, neuroscientists and clinicians still have far to go in taking full advantage of discoveries in each other's fields. There are, however, shared lessons. In human genetics, establishing reliable links between gene variants and disease was only possible in the context of cataloguing the full complement of normal human genetic variation. In neuroscience, we will only advance our understanding of brain function outside the healthy range by discerning the rich diversity and individual variation in normal brain function across species, including our own[14]. ■

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13. Gordon, J.A. *Nat. Neurosci.* **19**, 1385–1386 (2016).
14. Miller, K.L. *et al. Nat. Neurosci.* **19**, 1523–1536 (2016).