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Meeting Report: Can We Make Animal Models of Human Mental Illness?

Lisa M. Monteggia,

Department of Neuroscience, The University of Texas Southwestern Medical Center, Dallas, Texas;

Hakon Heimer, and

Banbury Center, Cold Spring Harbor Laboratory, Cold Spring Harbor,

Eric J. Nestler

Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York.

Abstract

Modeling aspects of the human condition in animals has provided invaluable information on the physiology of all organ systems and has assisted in the development of virtually all new therapeutics. Research in cardiovascular disease, cancer, immunology, and other disciplines has benefited substantially from the availability of animal models that capture aspects of specific human diseases and that have been used effectively to advance new treatments. By comparison, animal models for neurological and psychiatric disorders have faced several unique obstacles. This paper highlights topics covered in a recent Cold Spring Harbor Laboratory meeting charged with examining the status of animal models for mental illness. The consensus of the conference is that despite the difficulties inherent with modeling brain disorders in animals, when used judiciously—fully cognizant that models of specific behavioral or biological aspects cannot completely recapitulate the human disorder—animal research is crucial for advancing our understanding of neuropsychiatric disease.

Keywords

CRISPR; iPSCs; Neurological disorders; Nonhuman primates; Psychiatric disorders; Rodents

MODELS FOR PSYCHIATRIC DISEASE RESEARCH

The development of validated animal models of brain disorders offers several challenges that are unique for the field of psychiatric disease research. Major impediments for psychiatric disorders include limitations in recapitulating human-specific abnormalities in cognition, language, and emotion, as well as the complete absence of validated biological biomarkers

Address correspondence to Eric J. Nestler, M.D., Ph.D., Department of Neuroscience, Icahn School of Medicine at Mount Sinai, One Gustave Levy Place, Box 1065, New York, NY 10029; eric.nestler@mssm.edu.

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for these illnesses. The field of neurodegenerative disorders has faced additional challenges because of the limited lifespan of rodents, which might explain in part the difficulty in fully recapitulating the neurodegenerative and progressive nature of these disorders in animals. These limitations, combined with the limited success of the pharmaceutical industry—based on the best academic research—to significantly advance central nervous system therapeutics over the past half century have led some to question the utility of animal models for psychiatric syndromes.

Particularly in mental illness, it may be best to talk about models “for” disease research, rather than “of” a given disease, to eliminate the misconception that a model must recapitulate all or most features of the disease. The group at the Banbury Center (1) expressed the following understanding: A model is an experimental preparation developed to approximate specific aspects of a particular condition or phenomenon in a nonhuman species. The importance of using animal models is that they make it possible to establish the underlying biology—which is not possible in humans—by manipulating specific mechanisms and studying the molecular, cellular, circuit, and behavioral consequences under normal and pathological conditions.

GENETIC MODELS

Tremendous advances are being made in genomic research, and all major mental disorders have a significant genetic component. However, individual genes of strong effect and high penetrance have not been identified, with the exception of genetic mutations that underlie a small subset of autism spectrum disorders. Patients diagnosed with a given psychiatric disorder often display different behavioral phenotypes, highlighting the heterogeneity of these disorders and limitations in our current diagnostic schemes. This heterogeneity and diagnostic uncertainty, in turn, have made it difficult to identify the genetic factors that contribute to human mental disorders and by extension to elucidate the abnormalities in neural circuits and signaling that underlie their pathophysiology. Nonetheless, the small number of “causal” genes—those with strong effect and high penetrance—linked definitively to autism spectrum disorders have allowed the generation of animal models to establish mechanistic links between the genetic defect and consequent molecular, cellular, and circuit abnormalities in the brain responsible for the behavioral impairments.

An important example is the identification of loss of function mutations in the methyl-CpG binding protein 2 (*MECP2*) gene that cause the neurodevelopmental disorder Rett syndrome. This autism spectrum disorder has been extensively modeled in mice and other organisms (2,3). While Rett syndrome is a rare disorder, with estimates of 1 in 10,000 live female births, it affects more individuals than most other causal genes that have been linked to neurological or psychiatric disorders. Mutant *Mecp2* mice recapitulate several key phenotypes of Rett syndrome, though not all features, demonstrating clear limits to our ability to model even monogenic brain disorders in mice. However, the examination of several *Mecp2* mutant mouse models has revealed surprising roles for this gene in the regulation of transcriptional processes and synaptic function. Recent studies have generated nonhuman primate models with impaired MECP2 function that recapitulate several key

phenotypes that have the potential to contribute a more detailed understanding of the pathophysiology of this disorder and by extension lead to improved treatments.

Mutations in several other single genes that encode synaptic proteins (e.g., Shank-3, neuroligins, and neurexins) have been linked to autism spectrum disorders (4). All of these mutations are exceedingly rare, but they represent a starting point to examine whether there are common impairments, and potential points of convergence, in synaptic and circuit, or molecular, function that may ultimately underlie these disorders. For example, studies have shown that several of the rare mutations in synaptic protein-encoding genes lead to similar synaptic alterations that impact neuron function and ultimately behavior (5). The generation of animal models with these mutations, despite their rarity in humans, is an important endeavor that provides a type of Rosetta Stone to uncover mechanisms that contribute to the pathophysiology of the disorder.

In contrast to *MECP2* and other autism-linked genes, most genetic factors associated with a psychiatric syndrome are not causative but rather constitute risk factors. An example of a particularly strong risk factor is the ε4 allele of the apolipo-protein E gene, which increases an individual's risk for developing Alzheimer's disease (up to 10-fold in individuals with two copies of the allele) but is itself not a causative factor (6). In addition, none of the genetic risk factors identified to date for common psychiatric syndromes, including schizophrenia, bipolar disorder, depression, anxiety, and addiction, exert nearly as strong an effect as does the ε4 allele for Alzheimer's disease. Rather, heritable risk for these psychiatric syndromes is now thought to involve many hundreds of genetic variations in each affected individual (7). Consequently, placing such a genetic variant, which contributes much less than 1% to the total genetic risk of a syndrome, into an animal model is unlikely to recapitulate any appreciable aspect of that syndrome. However, such models could reveal more subtle changes in neural and behavioral function that might contribute to the larger syndrome. In addition, clustered regularly interspaced short palindromic repeats (CRISPR) and related gene editing tools open the possibility of placing mutations in numerous risk genes into the same animal and thus possibly recapitulating more of the syndrome.

The field has gained increased appreciation for the iterative role of genes and environment in shaping behavioral outcomes. Studies of epigenetics describe a range of highly complex mechanisms by which experience early in life—beginning in utero—and continuing for a lifetime shape the expression of genes in specific cell types in the brain. Such mechanisms include many types of histone modifications and DNA methylation among many other types of chromatin regulatory processes. Advances in epigenetics are making it possible to take advantage of gene-by-environmental interactions to generate far more complex animal models that better recapitulate the range of factors that ultimately contribute to a mental disorder in humans. As just one example, manipulation of a gene (e.g., *Nr3c1* or *Otx2*) early in life in the context of some behavioral challenge can render an animal more vulnerable to stress or a drug of abuse later in life(8). Developmental models of disease vulnerability that take advantage of our growing knowledge of epigenetic regulation promise a new generation of more sophisticated animal models.

While most genetic disease research has focused on mice and, to a lesser extent, rats, nonvertebrate species such as *Drosophila melanogaster* and *Caenorhabditis elegans* have also advanced our understanding of biological regulation. In these instances, the species offer powerful models in which to study gene function but are less plausibly related to specific human behavioral outcomes. Recent technological advances (e.g., CRISPR) have also allowed for the generation of nonhuman primates with particular genetic manipulations to more closely mimic the human condition. There has been particular attention paid to the use of marmosets for this purpose, which, given their much smaller size, shorter interbirth intervals, larger litter size, and more rapid maturation rates are more amenable to such work than traditional nonhuman primate species such as macaques.

NEURAL CIRCUITS

The past decade has seen a strong focus on elucidating the neural circuitry that controls behavior. The development of optogenetics, designer receptors exclusively activated by designer drugs (DREADDs), and other approaches has enabled investigators to control the activity of specific neurons and projections in the brain and assess their impact on behavior. These methods have provided a new window into the brain with cellular, spatial, and temporal resolution that was not possible with older manipulations such as direct electrical stimulation or lesion or pharmacological studies. Optogenetics and related studies have been used to interrogate numerous neuronal populations and projections, providing a wealth of data with implications for a variety of brain disorders.

A limitation of these approaches is that the behavioral outcome of a specific brain circuit may be different between rodents and humans. Do the associated physiological and behavioral changes seen upon experimental stimulation or inhibition of a given circuit reliably predict the human condition? As mentioned above, there are also clear limitations to the behaviors that can be assessed. While rodents are useful models for examining certain types of behavior (for example, motor or reward learning), their value for examining higher-level function such as advanced cognition or emotion is less straightforward, and rodents are unlikely to be useful in studying hallucinations or suicidality. For this reason, there is renewed interest in the use of several nonhuman primate species (as stated above) for the exploration of the circuit basis of complex behavior, given that the brains of nonhuman primates are far more homologous to humans than rodent species and that such species exhibit far richer behavioral repertoires than rodents. The disadvantage with nonhuman primates is the challenge of using large numbers of animals in addition to their greater expense and regulatory burden. While we work to develop better animal models, it is essential to keep in mind what one can possibly learn from manipulating neural circuitry in each species and to use the species that is best suited to answer the experimental question under investigation.

ACKNOWLEDGING AND CAPTURING VARIABLES

Reproducibility has emerged as a major stumbling block throughout biomedical research, and variables such as sex differences, within- and between-strain differences in animals, circadian rhythms, and previous drug exposure in human illness can confound our ability to

replicate research on mental disorders. Capturing these and other variables such as peripheral metabolism, the immune system, gut function, and microbiomes and other nonneural contributions to psychiatric illness will not be straightforward, but the failure to do so risks delegitimizing large swaths of research.

Sex differences provide some instructive examples. Clinical data have shown that males and females present differently for many illnesses and respond differently to medications. Yet until relatively recently, clinical studies have largely focused on males, as has basic research in the field of neuroscience—and even when both sexes are included, only rarely have they been powered sufficiently to detect sex differences. For preclinical studies, males are often used to avoid potential confounds that can occur because of the estrous cycle in females. Indeed, sex hormones exert dramatic effects on neurotransmission, synaptic plasticity, and behavior, all of which can complicate data interpretation. Many studies of females in basic neuroscience research have used ovariectomized females with hormone replacement to control for the influence of endocrine factors. These studies have provided a crucial foundation for research but have largely left unanswered how a “normal” female may respond to an experimental situation (9). The recent initiative by the National Institutes of Health that requires sex to be considered as a biological variable should lead to a dramatic advance in our appreciation of sex differences if applied optimally. In particular, we may learn how rodent models used for decades in males can be modified for use in females. An example in point is the recent development of social defeat stress for female C57BL/6 mice (10,11), although social defeat has been used for years in other mouse species where females are more inherently aggressive (12).

CELLULAR MODELS OF HUMAN DISEASE

There has been an increased interest in cellular models of psychiatric syndromes in recent years, in particular the use of human induced pluripotent stem cells derived from patients and matched control subjects that carry an individual’s full genetic complement of risk (13). Advances are being made in generating “organoids” from such cells that show interesting patterns of intercellular organization. The theoretical advantages are clear: one can compare the effects of all the weakly acting genetic mutations in different neuronal, glial, or endothelial cell types between patients and control subjects. Moreover, the in vitro model offers the ability to study molecular and cellular mechanisms that associate with the genetic background of the disorder. Despite the promise, challenges remain. Variability in given molecular–cellular end points of interest across stem cell lines derived from a single human can be as great as those seen between diseased and control subjects. Also, the neuronal- and glial-like cells generated from human induced pluripotent stem cells are highly immature, displaying transcriptomic maps of embryonic cells, making it difficult to replicate age-dependent pathophysiology. Finally, because there are no known biomarkers of a psychiatric illness—no molecular or cellular abnormality that is pathognomonic or diagnostic for any given psychiatric diagnosis—how can one be confident that a molecular–cellular abnormality seen in patient-derived neurons or glia are related to the underlying pathophysiology of a disorder?

Similarly, there are limitations of cellular assays in drug development. It is inconceivable that a new medication, with a given cellular activity, will advance to the clinic without some demonstration of an efficacy-related end point in animals. The economics of drug discovery make it impossible to proceed to the clinic without the use of animal models far beyond their use in toxicology alone.

THE RIGHT MODEL FOR THE QUESTION

Animal models are too often used to infer information that they cannot offer or are interpreted in overly simplistic ways to address complex clinical phenomena. One example is the forced swim test, an assay in which antidepressants produce a change in a rodent's response to acute stress. The problem in the field is that it is used as an "animal model of depression," which it clearly is not. Perhaps it is not surprising that assaying drugs in this paradigm has not yielded clinically validated antidepressants with novel mechanisms of action. Another example is drug self-administration under fixed ratios of reinforcement, which offers highly consistent measures of the reinforcing properties of the drug and the animal's interest in obtaining it. Yet it cannot possibly model the complex human syndrome of addiction, which perhaps explains why numerous drugs that modify this relatively simple operant behavior have failed in clinical trials. To put it another way, the problem is not the animal models but rather the ways in which the field has often used them. The appropriate and productive way to pursue animal research is to recognize that there are different goals for different areas of animal research, ranging from basic biological mechanisms and variation in "normal" brain function and behavior to drug discovery and toxicology.

One way to promote this understanding is to foster crosstalk between clinical and basic research. To that end, the Banbury Center meeting participants pointed to the contentious rollout of the U.S. National Institute of Mental Health's Research Domain Criteria (RDoC) framework. The National Institute of Mental Health has stated that RDoC is not a substitute orthodoxy, that it will be responsive to new data, and that it will continually need to be reassessed against classification systems such as the DSM and ICD and, more importantly, a growing knowledge of the underlying biology of mental illnesses. However, some basic researchers have commented that RDoC's current behavioral domains are overly limiting, while some clinical researchers discuss the difficulty of incorporating RDoC-based research within a clinical world where DSM and ICD predominate. Better communication among extramural and intramural scientists would help promote a convergence of views. Cross-disciplinary workshops that bring researchers who focus on humans and animal models together in one venue would help, but there are many other opportunities across academic institutions, conferences, and funding organizations.

CONCLUSIONS

There are many challenges in the use of animal models for brain disorders that have been the subject of several recent reviews (14). Nevertheless, there was a clear consensus at the Banbury Center meeting that animal models are crucial in advancing our understanding of these disorders and developing more effective treatments, but that there needs to be greater attention to what can be learned from a given model and to designing new models that better

capture features of a human disease. Researchers must be judicious in their use of animal models, and not overpromise or overinterpret the findings. It is important to use as many complementary models as possible, and animal models must be continually validated against evolving genetic, molecular, and circuit findings from humans. Researchers must also be cognizant that models that incorporate more than one gene/environmental/developmental/sex influence will require larger sample sizes and greater attention to complexity and statistical challenges.

Despite the many challenges, there is also a tremendous amount of excitement within the field. The past decade has seen an unprecedented level of technological advances, including studying neural circuits in more specific ways than previously possible, the use of CRISPR technology to manipulate genes, and the ability to obtain complete transcriptome maps of single cell types and even individual cells, all geared toward advancing our understanding of human disorders. The use of these various approaches promises to bring new perspectives to the modeling of mental disorders.

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