Published in final edited form as:

Biol Psychiatry. 2016 January 1; 79(1): 4–6. doi:10.1016/j.biopsych.2015.02.009.

From Synapses to Behavior: What Rodent Models Can Tell Us About Neuropsychiatric Disease

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The pathophysiology of many neuropsychiatric disorders remains enigmatic for numerous reasons, including the lack of gross structural changes in the brains of affected individuals, the complexity of underlying genetic and environmental causes, and, above all, our relatively poor knowledge of how the brain normally functions to regulate behavior. Despite these obstacles, there is good reason to think that progress in understanding the pathophysiology of mental illness will come from elucidating how neural circuits—the cellular networks that result from connected neuronal populations with specific synaptic properties—mediate adaptive behaviors and how dysfunction in these circuits generates the major symptoms of mental illnesses (1). In particular, the plethora of synaptic genes and neuronal connectivity molecules implicated by human genetics studies has bolstered the theory that dysfunction in specific sets of synapses underlies the pathophysiology of mental illness (2). This suggestion should not be surprising because the diversity of synaptic connections likely evolved to allow for the higher order cognitive processing typically disrupted in neuropsychiatric disease.

Within this framework, we consider the utility of rodent models in understanding mental illness pathophysiology. Rodents, mice in particular, have been a key tool for modeling many genetic diseases. The hereditary nature of many neuropsychiatric illnesses and advances in understanding the genetic contributions to disorders such as schizophrenia and autism raised hopes that genetic manipulations in mice could provide an important foundation on which elucidation of pathophysiology can be built. However, endeavors to model human disease in mice have encountered several contentious issues: Can behavioral assays in mice faithfully mimic the human diseases we wish to study? Are the neural circuits in rodents sufficiently comparable to the circuits in humans such that studying rodent species can elucidate clinically relevant findings and principles? Can we learn anything of value at all about human brain function and dysfunction by studying rodents? These are reasonable questions because disease-modeling approaches in rodents garner significant funding. Here we argue that the explosion of molecular, genetic, imaging, and behavioral tools in rodents provides an unparalleled opportunity to examine how neuronal circuits

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Disclosures

MF and PR report no biomedical financial interests or potential conflicts of interest.

function to regulate behavior. The results of these experiments are a logical starting place for studying the pathogenesis of human brain disease, regardless of how precisely mouse behavioral phenotypes map onto human symptoms.

The assumptions underlying this view are that the molecular basis of circuit function has been robustly conserved over the evolution from rodent to human, as has the detailed connectivity of many critical behavioral circuits, dysfunctions in which mediate mental illness symptoms. Researchers using human and nonhuman primate subjects frequently point out limitations of these assumptions highlighting, for example, the expansion of the prefrontal cortex. However, for many of the circuits implicated in mental illnesses, such as corticostriatal and mesolimbic dopamine circuitry, there is scant evidence that the principles generated from work in rodents do not apply to the human brain. Imaging studies have repeatedly shown conservation in the function and connectivity of these types of circuits (3).

Recent technologic advances reveal the enormous potential of using mice to understand how neuronal circuits regulate behavior. The generation of well-annotated transgenic mouse strains has provided genetic access to a broad array of cell types. Together with viral and genetic technologies that allow for the control of neuronal activity over a range of time scales, the real-time interrogation of circuit function is currently possible. These experiments have begun to categorize the importance of specific neuronal circuits in regulating a range of behaviors, including motor output, motivated action, fear, and anxiety (4). Such “circuit mapping” bookends our quest to understand and ameliorate disease—it facilitates understanding of how specific circuits mediate behavior, while highlighting circuits whose modulation may serve to reduce symptoms. Although circuit-based studies illuminate the behavioral functions of specific neuronal networks, they do not directly address pathophysiology. A deeper exploration of why networks malfunction is required—that is, how environmental exposure interacts with genetic insult to alter neuronal physiology, connectivity, and communication. Because of the array of sophisticated tools available, rodent models provide an ideal substrate in which to identify disease-relevant circuits that are vulnerable to genetic or environmental insults.

More recent analyses in genetically modified mice illustrate the potential of rodent disease modeling for understanding and ameliorating brain dysfunction. A knockout mouse lacking the *SAPAP3* gene, which encodes a synaptic scaffolding protein highly expressed within the striatum and linked to obsessive grooming in humans, demonstrated repetitive behaviors and increased grooming along with altered striatal synaptic transmission (5). Viral replacement of wild-type *SAPAP3* within the striatum of adult knockout mice rescued the overgrooming phenotype, demonstrating the importance of striatal *SAPAP3* function for the behavioral phenotype. Further experiments demonstrated abnormalities in a grooming-based response-inhibition task, which was linked to deficits in striatal feedforward inhibition and could be corrected through optogenetic activation of orbitofrontal excitatory projections into the striatum (6). Similarly, a knockout mouse lacking the *CNTNAP4* gene, a synapse-associated protein linked to autism spectrum disorders and schizophrenia, highlighted the advantages of exploring mutation-related synaptic changes to guide appropriate pharmacologic interventions (7). These types of studies illustrate how a simple genetic perturbation in a

specific set of synapses can be correlated with pathologic behavioral output—a sophisticated conclusion that would be impractical to reach in any species other than mice.

Complementary approaches afforded by advances in rodent neuroscience relied on detailed genetic and circuit-level analyses of specific “endophenotypes”—basic, heritable behavioral units thought to be translatable to human disease (8,9). To explore the genetic and circuit abnormalities potentially underlying the repetitive behaviors associated with autism spectrum disorders, acquisition of a motor routine on the rotarod was assessed in two neuroligin-3 (*Nlgn3*) genetic models (8). Both mutant strains exhibited enhanced rotarod learning owing to more stereotyped movement patterns. Through viral and genetic manipulations, it was determined that removal of *Nlgn3* specifically within D₁ dopamine receptor-expressing medium spiny neurons of the nucleus accumbens was sufficient to produce the repetitive behavior seen in constitutive *Nlgn3* mutants. Detailed synaptic analyses revealed significant deficits in inhibitory transmission specifically onto the same D₁ dopamine receptor-expressing medium spiny neurons, providing a plausible synaptic mechanism for the more repetitive motor routines. Similar strategies were employed to examine the role of the oxytocin receptor, another autism spectrum disorder candidate gene, in the processing of social reward (9). Viral-mediated removal of oxytocin receptors from specific cell populations combined with a social place preference assay uncovered the dorsal raphe as a key circuit node in the acquisition of social reward mediated by oxytocin. This behavior involved a serotonin-mediated heterosynaptic regulation of excitatory transmission into the nucleus accumbens through oxytocinergic modulation of dorsal raphe afferent fibers. These studies highlight another strength of efforts to model neuropsychiatric diseases in mice—the ability to uncover critical circuit nodes that may be responsible for multiple disease symptoms.

A final example of the utility of rodent models comes from the large body of work using rodents to model drug addiction. For no other neuropsychiatric disorder does rodent behavior more accurately mimic the pathologic behavior of humans. Rodents self-administer drugs and exhibit drug-seeking behavior in response to drug-associated cues. The synaptic maladaptations caused by drugs of abuse have been extensively characterized in rodent models and may lead to the development of potential therapies. Current neural circuit-based hypotheses of addiction pathophysiology largely derive from work in rodents and have been confirmed in imaging studies of human drug addicts (10). Finally, the optogenetic reversal of drug-induced synaptic adaptations has been shown to reverse aspects of cocaine-seeking behavior (4). These findings elucidate the neural circuit modifications mediating relapse and provide a stellar exemplar of the utility of rodent models.

In conclusion, we believe there is a convincing case for using mouse models to understand neural circuit control of behavior and the ways genetic and environmental insults cause dysfunction in vulnerable circuits to mediate disease symptoms. However, the question remains: What do findings in rodents have to do with human behavior and disease? Debates over the parallels between mouse and human social behavior, executive function, or simple motor routines can continue endlessly and generate few testable hypotheses. More productive approaches will involve focusing on how best to employ the mechanistic information originating from rodent disease modeling to create coherent, testable hypotheses

for use in human imaging studies and the design of pharmacologic interventions. It seems clear that technologic advances in rodent systems have paved the way for a period of rapid progress in forging links between genes, circuits, and behavior. With additional technologic advances on the horizon, including imaging the activity of complex neuronal networks in vivo, it seems prudent to push ahead in this area and let the accrued data over the next decade address its relevance to human disease. At best, we will find valuable parallels between human and rodent brain disease leading to more sophisticated testing of pharmacologic and interventional therapies. At worst, we will increase our basic understanding of the divergence points between the control of rodent and human behavior and adjust our research directions accordingly.

Acknowledgments

This work was supported by the National Institute of Mental Health Grant Nos. K99 MH099243 and F32 MH096491 (MF, PR), National Institute on Drug Abuse Grant No. P01 DA008227 (RCM), and Simons Foundation Autism Research Initiative (RCM).

The authors apologize for the large number of relevant citations that were omitted because of space constraints.

RCM is a founder and on the scientific advisory board of Circuit Therapeutics, Inc., a biotech company using optogenetics to develop medical devices and novel drug discovery platforms.

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