How Animal Models Inform Child and Adolescent Psychiatry

Hanna E. Stevens, MD, PhD, AND Flora M. Vaccarino, MD

Objective: Every available approach should be used to advance the field of child and adolescent psychiatry. Biological systems are important for the behavioral problems of children. Close examination of nonhuman animals and the biology and behavior that they share with humans is an approach that must be used to advance the clinical work of child psychiatry.

Method: We review here how model systems are used to contribute to significant insights into childhood psychiatric disorders. Model systems have not only demonstrated causality of risk factors for psychiatric pathophysiology, but have also allowed child psychiatrists to think in different ways about risks for psychiatric disorders and multiple levels that might be the basis of recovery and prevention.

Results: We present examples of how animal systems are used to benefit child psychiatry, including through environmental, genetic, and acute biological manipulations. Animal model work has been essential in our current thinking about childhood disorders, including the importance of dose and timing of risk factors, specific features of risk factors that are significant, neurochemistry involved in brain functioning, molecular components of brain development, and the importance of cellular processes previously neglected in psychiatric theories.

Conclusion: Animal models have clear advantages and disadvantages that must be considered for these systems to be useful. Coupled with increasingly sophisticated methods for investigating human behavior and biology, animal model systems will continue to make essential contributions to our field.

Key Words: animal model, child psychiatry, development, genes, environment

J Am Acad Child Adolesc Psychiatry 2015;54(5):352–359.

Diagnosing, understanding, and treating child psychiatric illness pose special challenges, given the current limited understanding of the interconnection among brain function, mental processes, and behavior. Brain function and behavior are inseparable—spatially coordinated activity of billions of neurons self-assemble very complex structures over development, intrinsically linked to experiences and actions. The genome and the environment direct brain development, with risk factors in both domains identified for child psychiatric illness. However, the mechanisms that operate in development linking risk factors to deficits in children's functioning are often unknown. Basic mechanisms must be understood on the genetic or biological and environmental or behavioral levels in a unified manner, to target treatment and prevention to specific systems and developmental time points.

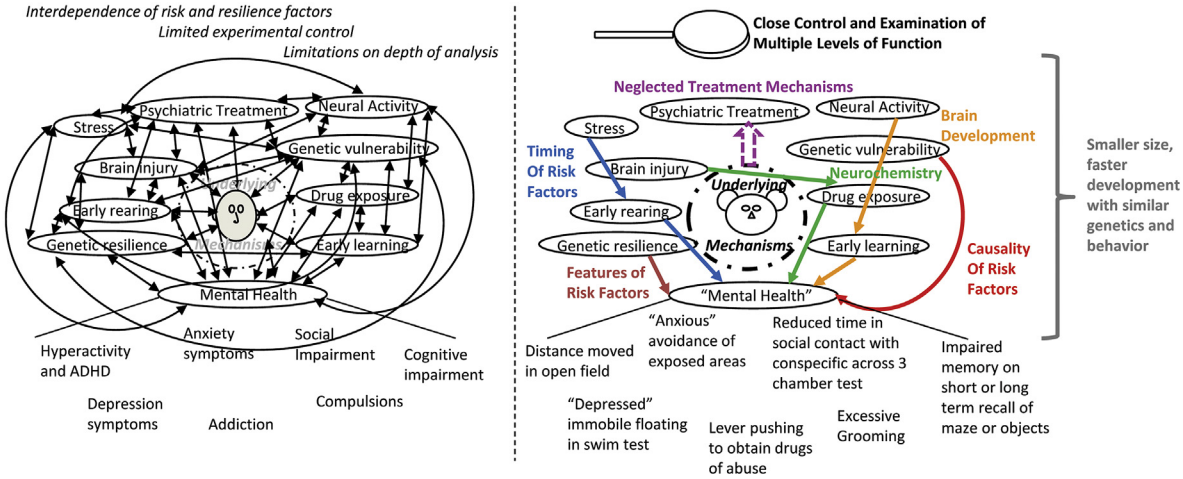
Our lack of pathophysiological knowledge arises from 3 significant challenges: severe limitations on closely examining the functioning human brain at the cellular, molecular, and systems levels because of potential harm to human participants and other reasons; even greater limitations in examining early human brain development when many processes occur in utero; and human diversity that arises from environmental and genetic backgrounds that limits causal inferences.

ANIMAL MODELS AND THEIR ADVANTAGES

One method to overcome these challenges is to use animal models alongside human research. The use of animal models for disorders that involve psychosocial domains appears unwarranted at times. However, the complex psychological and social human behavior of psychiatric disorders involves simpler behavioral and brain functioning that are also present in nonhuman species.

The benefits of using model animal systems are numerous (Figure 1). Importantly for childhood psychopathology, developmental relationships can be followed in real time. During early development, large-scale changes in gene expression are translated into a vast array of biological processes.[1] Being able to look at precisely selected time points in animal early development allows a detailed analysis of biological processes. In animal models, very close examination can also be made at all levels, looking from the level of genes and proteins to brain anatomy or whole brain physiological wave patterns, and finally, behavior. As an example, the observation in people that brain myelination increases through childhood has prompted studies in other mammals examining the molecular control of this process. In the reverse translational direction, detailed coding of animal social behavior (such as number of nose touches or licking between mothers and young) has prompted this same detailed coding of human social behavior (such as eye contact and stroking). This demonstrates how the close examination of nonhuman animals can lead to new insights about human social and cognitive development. Even knowledge discovery about humans has been facilitated by model system research. Two examples are neuroimaging approaches (e.g., magnetic resonance imaging

FIGURE 1 Schematic depiction of challenges of human research for child psychiatric disorders (left) and the benefits and discovery areas of animal model research (right). Note: ADHD = attention-deficit/hyperactivity disorder.



[MRI], electroencephalography [EEG]) and whole-genome sequencing advances that have depended on model systems for their development. When the details of any analytic level, molecules or behavior, are probed in a model system, it inspires the same questions to be asked in humans, pushing the boundaries of our knowledge and skills.

Research into child psychiatric disorders can take advantage of studying nonhuman species because much about fundamental processes of development is shared between species. First, 70% to 90% of genes are similar between humans and models such as mice and rats.[2,3] In fact, 99% of human genes have a corresponding gene in mice. The central nervous systems of all mammals and even invertebrates also have common elements—neurons and glia, proteins and lipids—which have similar biological roles. Conserved across vertebrates are also functional divisions between nervous system broad domains. For example, dorsal brain structures are responsible for creating patterns of behaviors (such as sensorimotor representations), and ventral brain structures are responsible for modulating behavior. These translate into core adaptive behaviors that are common across species including eating, reproduction, other social behavior, locomotion, avoidance of danger, and learning and memory.

From an experimental viewpoint, animal models have clear advantages over human studies. The ability to control experimental and background variables is much greater in animals, including genetics (Figure 1). Genetic and environmental control is especially high in laboratory rodents. The ability to manipulate a vast array of key factors makes model systems truly informative (Table 1). These manipulations cut across domains, from features of the environment to molecular and physiological factors and genetic manipulation.

The environment may be manipulated in many ways. Physiologically, the gas that is breathed or food provided can be changed.[4-6] Physical changes can be introduced in odors or in surrounding objects.[5,7] The social environment can be modified through maternal care or aggressive cage mates.[8,9] Behavioral experience is a complex form of manipulation that involves altered environments. Altered experience such as a more or less enriched environment or learning of other kinds is particularly important when considering development interaction.[7]

Genetic manipulation also plays a role in developing models for childhood psychiatric disorders. Historically, different animal strains have been produced from controlled breeding, with one "strain" having specific genes and behavior that define it.[10] More recently, genetic engineering has permitted the study of a gene's impact on an animal through eliminating, modifying, or turning on genes of interest in otherwise homogenous animals. Knock-out animals have a specific gene or gene part eliminated.[11] Knock-in and transgenic animals have extra genes either in the part of the genome corresponding to that gene or another random location. These manipulations can be used to determine a gene's role. This can be targeted to specific times during development and places in the body.[12] Genes can be engineered so that they are turned on or off only by very specific cellular events or experimenter activation with a drug.[13] Beyond understanding the role of genes by their addition or elimination, transgenic animals may also have "reporters" (proteins that have or produce colors inside cells) of when and where a gene is turned on.[14] These genetically altered animals pass genetic changes to their offspring.

Models can also be created with the injection of various molecules. Endogenous molecules such as steroid hormones or growth factors can be administered to an animal in atypical levels, locations, or times to understand their roles.[15] Pharmacological molecules such as antidepressants or psychostimulants are of obvious interest.[16] Synthetic nucleic acids or nucleic acid analogues can be used that interfere within cells by binding to the messenger RNA transcribed from a specific gene.[17] This prevents the mRNA transcription into a protein and therefore eliminates or reduces gene expression without eliminating the gene—these include small hairpin RNA (shRNA), small interfering RNA