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How Animal Models Inform Child and Adolescent Psychiatry

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Abstract

Objective—Every available approach should be utilized to advance the field of child and adolescent psychiatry. Biological systems are important for the behavioral problems of children. Close examination of non-human animals and the biology and behavior 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 utilized 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 both 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.

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Keywords

animal model; child psychiatry; development; genes; environment

Introduction

Diagnosing, understanding, and treating child psychiatric illness pose special challenges given the current limited understanding of the interconnection between 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 level in a unified manner in order to target treatment and prevention to specific systems and developmental time points.

Our lack of pathophysiological knowledge arises from three significant challenges: 1) severe limitations on closely examining the functioning human brain at the cellular, molecular, and systems levels due to potential harm to human participants and other reasons; 2) even greater limitations in examining early human brain development when many processes occur in utero; 3) 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 also present in non-human 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 for 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 non-human 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 (magnetic resonance imaging [MRI], electroencephalography [EEG], etc.) 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 non-human species because much about fundamental processes of development is shared between species. First, 70–90% of genes are similar between humans and models like 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 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 like 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 analogs 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 (siRNA), and morpholinos (from its chemical structure), which have varying specificity and duration of effect. Nucleic acids can be transduced directly into cells around injection sites through non-disease-causing viruses as carriers or through electroporation, a process that uses an electrical gradient to push nucleic acids across cell membranes. These transductions can also be used to add genes to cells on an acute basis, much like a limited transgenic manipulation (as above).

Lastly, the functioning of individual or collections of cells can be altered. Electrical stimulation, as performed in electroconvulsive therapy (ECT) but on a much smaller level, can grossly activate a region or brain circuit with small electrodes.¹⁸ Chemicals that impact neuronal activity can also be applied in particular brain regions.¹⁹ In the last 10 years, another technique, optogenetics, has been developed to allow a specific wavelength of light, from an apparatus mounted on an animal's head, to activate or suppress a cell through genetically introduced ion channels.^{20,21} This approach can be used to turn on or off a certain kind of neuron in a certain region, even when an animal is awake and behaving. It provides the most accurate way to implicate brain regions and cells in specific behavioral functions.

In addition to these specific experimental uses, animals have general practical advantages. Almost in proportion to their size, animal models develop faster and can be more closely examined at a dramatically lower cost in a smaller amount of space.

The Ethics of Animal Models

The ethics of research with humans and non-human animals differ significantly. Interestingly, standards for the protection of animal subjects have risen on a time course in the last century similar to that for human participants.²² Over time, in human research, children have become protected by government and professional entities as a special population for whom standards are higher due to their vulnerability. From this standpoint, using animal models in an ethical way allows our field to understand development with less negative consequences for children. At the same time, there are strict guidelines that protect the welfare of research animals. These regulations ensure that animal welfare is not overshadowed by the pursuit of potential human health benefits.

Animal Models and Their Disadvantages

While the biological systems of animals are impressive tools, behavior of humans and non-human animals can be very different, both on the surface and in underlying functions. First, there is a range of interpretation of what a particular behavior, like anxious-appearing movement, means in different species.²³ Mice may avoid walking into the center of an open box or onto open, elevated platforms, both anxiety-like behaviors with relevance to their survival, but the similarity of this to ruminative worries in people is not clear. Second, other than EEG or functional imaging, analysis of brain functioning in animals typically depends on physical performance in behavioral tasks—for example, mice must move to demonstrate a preference. In people, both report and observed behavior allows for a broader range of brain functioning to be understood. Third, consciousness and special human cognitive abilities (i.e., language) are involved in psychiatric disorders and are lacking in non-human species.

The percent difference in genes may be small between humans, macaques, and even mice, but may be amplified through the transcription of DNA to RNA, translation of RNA into proteins, and post-translational modification of proteins to produce a wide range of variation in molecules and cells across species. The regions of the genome that are never translated into proteins—those nucleic acid sequences previously considered to be “junk DNA”—have even more differences between species than protein-coding genes (exons) themselves.²⁴ These sequences contain highly functional elements—places where chromosomes can interact or be acted upon by factors that regulate their transcription—and produce non-coding RNA that regulate mRNA translation like those experimental RNAs described earlier.²⁵ The amount of non-protein-coding DNA dwarfs that of exons in the genome and may be where some of the most substantial differences between species and cell types, particularly those of the CNS, and developmental stages reside. Much of the function impaired in psychiatric disorders is determined by forebrain regions which have vast differences in size and structural specialization in humans compared to other species.²⁶ Understanding these more human-specific aspects may be difficult in animals.

The speed at which animals develop is beneficial for research, but the biology of varied rates of development may be significantly different. Recent findings from human cells transplanted into mouse brains demonstrated that human cells develop on their own human schedule.²⁷ The time scale of development matters because environmental or social exposures may “accumulate” effects on learning, the brain, neural cells, and genomes for humans differently than in more rapidly developing animals. Also, more protracted development in humans is one reason that neuroanatomy and behavior can become more elaborated, leading to brain and functional specialization only present in humans.

Another important limitation is that inter-individual differences in human genomes do not exist in species bred for laboratory use. Genetic diversity in the human population is related to the occurrence and specific phenotypes of psychiatric problems.²⁸ It is unclear if non-human primate individuals have the genetic diversity found across human individuals. This may be significant for multiple reasons. For example, there are different behavioral consequences of specific gene deletions in mice with different genetic backgrounds,²⁹ and

gene mutations with deleterious consequences in humans can be harmless in other mammals.³⁰ Gene polymorphisms and gene-gene interactions can impact neural function and behavior.

Looking at another level of behavior entirely—that of culture and social context—shows clearly that animal models cannot reproduce the complexity of psychiatric disorders. Some aspects of social context—hierarchies of social status, early contact with primary caregivers,^{9,31} juvenile participation in peer play³²—can be examined across animal models. But a vast array of human experience with relevance to psychiatric disorders—occupational functioning, religious culture, artistic expression, and economic pressures—cannot be captured in animals.

Despite this, animal model systems can be helpful and provide insights into human health, not as one-to-one analogies for specific diseases or the human experience of disease, but as fundamental relationships between behavior, organs, cells, and genes in a developmental time scale involved in illness.

Specific Uses of Animal Models

Animal models are not meant to represent specific childhood psychiatric disorders like obsessive-compulsive disorder (OCD) or attention-deficit/hyperactivity disorder (ADHD). They are instead used to examine risk and causative factors (genetic and environmental), protective factors, and treatments (biological and environmental) for disorders (Table 2).

Models have been extremely useful for uncovering information about childhood psychiatric pathophysiology. First, they permit the hypothesized causality of risk factors to be demonstrated, and, second, they can deconstruct risks into essential components: specific features, the timing of the cause-effect relationship, and the dose of exposure. For example, work begun by Harry Harlow in the 1940's and continued by many of his colleagues^{33,34} using macaque monkeys reveals that there are causal impacts of early rearing disruptions on the brain and behavior. By manipulating how much typical rearing an infant has (a model shaped like a mother providing food and/or warmth or only same-age peer monkeys instead of a parent), Harlow and colleagues began the discovery that typical infant cognitive and emotional development depends on specific core features of the early maternal-offspring relationship, including warmth and physical comfort, facilitating offspring attachment to its mother. In the realm of genetic risks, a mouse model developed first in the early 1990's by the Dutch Belgian Fragile X Consortium allowed for the definitive demonstration that the Fragile X gene and protein caused cognitive deficits in Fragile X mental retardation.³⁵ This mouse model established a relationship between specific levels or dose of the gene and its protein on one hand and learning and memory deficits on the other.

In like manner, stress had been implicated in the development of depression in humans and demonstrated as a causal factor beginning in rats in the 1960's and 70's measuring depression-like immobility in swim tests and avoidance of lighted areas.^{36,37} Subsequently, with the development of knockout mice, stress was found to predispose to depression-like and anxiety-like behavior by interacting with genes, including the monoamine transporters and components of the hypothalamic–pituitary–adrenal (HPA) neuroendocrine system.^{38,39}

Also, models have shown that the timing of stress—chronic versus acute—elicits different behavioral and biological results.⁴⁰ Not only did these models confirm the causality of stress, but they validated methods for depression-like rodent phenotypes that have facilitated other risk and protective factors for depression being investigated.

Just over ten years ago, based on work from Michael Meaney's lab,⁸ the field developed insights into specific features of maternal care that are critical for offspring stress regulation, including the heritability of maternal care in a non-genomic manner.⁴¹ The demonstration that gene and histone methylation was altered by early maternal licking and grooming in rats, coded diligently by observation of mothers with different tendencies in the first few weeks of life, was a paradigm shift.⁴² This work has led to further insights into how specific genes such as glucocorticoids and methylating enzymes mediate the influence of early experience. Combined with work on allelic variation of genes like the short versus long alleles of the serotonin transporter, the discovery of early gene methylation allowed for a molecular-level understanding of why only some individuals may be affected by early exposures and experience.

Studies of the spontaneously hypertensive rat (SHR) as a model of ADHD have demonstrated how models can contribute to neurochemical understanding. The dopamine signaling dysregulation and reduced release of dopamine in response to stimuli in the SHR may be involved in its impaired memory and overly active behavior that resemble ADHD.^{10,43} Convergent with the association of ADHD with polymorphisms in the dopamine transporter (DAT) gene, DAT knockout mice display profound hyperactivity coupled with a persistent hyperdopaminergic state.^{18,44,45}

Molecular aspects of psychiatry clearly extend beyond neurotransmitter chemistry, particularly for brain development implicated in neuropsychiatric disorders.⁴⁶ For example, animal models have shown how growth factors, critical for the organization of cells during development,^{12,47} have a role in affective disorders. Brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF), among others, are altered following chronic stress.^{15,48} The specific causality^{49,50} of these growth factors for anxiety and depression has also been documented in rodent models.⁵¹ These models have had direct implications for designing treatments. For example, neurobiological studies of molecules that are downstream of growth factor activity suggest that signalling pathways such as protein kinase C (PKC)⁵² or mammalian target of rapamycin (mTOR)¹⁹ might be targeted to change mood states and relieve debilitating symptoms.

Animal models have also revealed that affective disorders involve other cell processes like adult neurogenesis and glial cell functioning. Work in primates and rodents using both depression models and antidepressant medication suggests that both of these specific domains could be causal for mood problems and their treatment.^{53,54} In both clinical populations and animal models, current treatments for depression have been shown to result in alterations in glia functioning and neurogenesis, making these the targets for new drug development.^{16,55}

The development of newer treatments for psychotic disorders also relies on animal models. Postmortem studies suggest that inhibitory, GABAergic neurons are central to pathophysiology in psychosis,^{56–58} and animal models suggest inhibitory neuron functioning as a potential causal mechanism. Animal models that have GABAergic deficits can be used to understand this relationship, including animals with decreased BDNF and its receptor TrkB,⁵⁹ deficiencies in fibroblast growth factor (FGF) receptors,^{4,60} and environmental perturbations like chronic hypoxia,^{4–6} prenatal stress,¹⁴ and optogenetically/genetic knockdown-driven deficiencies in parvalbumin neuron activity.^{17,20,21} Antipsychotic medication in rodents affects not only the traditional dopaminergic system but also inhibitory neuron functioning.⁶¹ Novel treatments for psychosis may target GABAergic cell development and functioning.

Manipulating and longitudinally observing animal systems from immature developmental stages is a part of understanding disorders that begin early. The onset of disorders in childhood is not simply due to stronger pathology that appears earlier. By the same token, psychiatric symptoms of children are not a linear extension of adult risks—depression in children and adults may have distinct illness-associated risk factors. Specific developmental stages of emotion, cognition, and neurobiology in childhood disorders can be studied in model systems.

Developmental insights from animal models

The genetic and environmental risk factors for psychiatric illness may play a distinct role in early development because of distinct biological processes. For example, prenatal stress results in different changes to behavior and neurobiology than stress in adulthood. Animal model experiments demonstrate that an early, smaller, three-day exposure to stress during embryonic development can have similar effects to a later, larger, 10-day exposure to stress in adulthood.⁶² Additionally, prenatal and chronic adult stress result in different behavioral changes, examined with tests that are relevant to rat behaviour, including exploring an open field (more consistently impaired by prenatal stress) and persistence in swimming (more consistently impaired by adult stress).^{63,64} These models may indicate that some behavior is more dependent on early developmental processes sensitive to early stress and that others arise from different targets later in life.¹⁴

One last developmental example is the relationship between anxiety and alterations in serotonin. The serotonin 1A receptor (5HT1A receptor) is required during early postnatal development, but not in adulthood, for establishing normal anxiety-like behavior.^{13,65,66} Transgenic mice in which the receptor gene was removed from the brain demonstrate more anxious-like behavior, like avoiding open spaces, as adults. However, transgenic re-expression of the 5HT1A receptor gene in these same mice or blocking of the receptor in normal mice using methods discussed earlier demonstrated that anxiety-like behavior critically depended on this receptor during adolescence, but not adulthood. These data have profound implications for understanding anxiety disorders in which developmental factors, such as serotonin and related behavior at specific life stages, may result in later occurrence of symptoms.

Development Revisited

These findings suggest that early mechanisms of constructing the brain, not repeated in mature animals, may be inaccessible to interventions in adulthood or after development is over. However, recent data may disagree. One example is the mechanisms involved in Rett syndrome. Rett syndrome is a developmental disorder that is caused by mutations in a gene that codes for MeCP2, a methyl CpG binding protein.⁶⁷ This protein facilitates developmental and experience-dependant alterations in gene methylation that allow for gene silencing. Mouse models have similar phenotypes to patients.¹¹ The mouse phenotype can be “rescued” by adding the normal gene to the brain through gene-transduction in a seemingly dose-dependent manner, even in mature animals.⁶⁸ Gene rescue cannot be implemented in humans as it is in animals, and we do not know if the “rescue” in mice would even be as meaningful in humans. However, this example demonstrates that developmental events may be influenced even after their normal timing has passed, opening therapeutic possibilities.

Sensitive periods in development have been carefully documented at the perceptual and neural level using animal models.^{69,70} Refining of sensory abilities by early experience has been shown to involve GABAergic modulation of cortical circuits, synaptic pruning, and the production of proteins around cells, called perineuronal nets, which then solidify these networks. The most specific example of this is visual acuity, for which visual experience must occur during an early sensitive window prior to “solidifying” the network. However, exciting new findings demonstrate that plasticity may be revived after this window closes by both genetic/molecular manipulations and alterations in the environment.⁷¹ While these findings primarily pertain to vision, human abilities like language and socialization may rely on common mechanisms and may be similarly malleable.^{72,73}

Similar conclusions have been supported with another model of syndromic autism. Mouse models of tuberous sclerosis based on the human *tsc1* gene have a similar phenotype as patients. In *tsc1* KO mice, an important mediator of intracellular signaling, mTOR, is mis-regulated and signals indiscriminately throughout development. Administering the immunosuppressant drug that targets mTOR, rapamycin, to adult *tsc1* KO mice and other autism models, has demonstrated normalizing of biochemical disruptions and learning and memory. Therefore, although *tsc1* abnormalities start early, the role of mTOR in the adult brain may underlie this “rescue”.⁷⁴

Lastly, Angelman syndrome is due to paternal imprinting of a large section of chromosome 15. In patients, the maternal copy of a gene within this section, *Ube3a*, is missing and the paternal copy is silenced by methylation. A class of cancer-treatment drugs called topoisomerase inhibitors can un-silence genes previously turned off. The use of these drugs in the Angelman mouse model has demonstrated a partial reversal of the phenotype at the molecular and behavioral levels when the *Ube3a* gene is reactivated.⁷⁵ In all of these cases, our new insight is that neuronal functioning and development can still occur outside of normal developmental timing if the right target is found.

Examining Human Neurobiology Up Close

Complex human abilities may not have a cellular or molecular substrate in the brains of animal models. Human neural cells grow larger, establish more inter-cell connectivity, and develop over a slower developmental time frame. The molecular underpinnings for these differences are still to be discovered, but may reside, as discussed earlier, in the extensive non-coding regions of the genome or post-translational variation in humans.²⁴

The recently developed induced pluripotent stem cell (iPSC) model represents a useful complement to animal model systems for the investigation of human neural development. Human skin cells are first reversed in their development to become similar to early stem cells and then guided to become neurons, allowing for studies comparing and contrasting typically-developing and diseased neurons. Human gene environment and gene-gene interactions can then be explored in culture, where neural development is recapitulated.^{27,76} This approach was only developed because extensive work in animals demonstrated key genes that allowed development to be reversed.⁷⁷ Limitations of this approach include possible epigenetic changes with culture manipulation and the lack of the larger level of brain patterning and circuitry. Therefore, this new human approach will produce the greatest insights together with increasingly sophisticated methods of animal model work, including optogenetics and the use of novel organisms such as zebrafish.^{20,78}

Conclusions

The examination and manipulation of whole animal systems has provided clear advances in linking specific aspects of physiology, neural circuitry, and behavior to precise genetic and environmental manipulation. While animal models are only one part of efforts in the field to understand child psychiatric disorders, they are an invaluable complement to human research. The primary advantages of animal models --the control and manipulation of variables across all levels of functioning and close examination of outcomes not possible in humans --will likely always be useful as our field advances. The field of child mental health can advance most rapidly when results from animal models are closely integrated with clinical research and the experience of working with children and families to produce new insights. The best questions can be asked in research if all practitioners in our field understand the capacity of animal model research. This requires continued communication between all who are invested in the mental health of children.

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

Table 1

Types of Animal Models

Environmental Manipulation	Physiological environment
	Physical environment
	Social environment
	Behavioral experience
Genetic Manipulation	Strain differences
	Knock-out animals
	Transgenic animals
	Knock-in animals
Acute Manipulation	Neural cell control through optogenetic, electrical, or chemical stimulation
	Endogenous ligands
	Drugs
	shRNA, siRNA, morpholinos, gene transduction

Note: shRNA=short hair-pin RNA (ribonucleic acid), siRNA= small interfering RNA.

Table 2

Examples of Disease-Specific Models in Child Psychiatry

Disease-Specific Models		
Gene Disruptions or Genetic Risk	Dopamine transporter knockout or knockdown mice	ADHD
	Fragile X mental retardation protein mutant mouse	autism
	MeCP2 (Rett syndrome) mutant mouse	autism
	Pten (syndromal autism) mutant mouse	autism
	SAPAP3 (synaptic protein) mutant mouse	OCD
	Slitrk5 (transmembrane protein) knockout mouse	OCD
	Fibroblast growth factor mutant mice	depression and anxiety
	Serotonin receptor knockout or knockdown mice	depression and anxiety
	Spontaneous hypertensive rat (high-risk strain)	ADHD
Neurocircuitry Manipulation	Neonatal 6-hydroxydopamine-lesioned rat	ADHD
	Olfactory bulb disruption in rodents	depression and anxiety
Other Biological or Physiological Manipulation	Neonatal hypoxia/anoxia in rodents	ADHD
	In utero or early life exposures to alcohol, nicotine, valproic acid	various (autism, learning disabilities, etc.)
	Prenatal maternal immune activation	schizophrenia, autism
Environmental Manipulations	Chronic stress in rodents	depression and anxiety
	Macaque monkey peer-rearing, maternal variable foraging	juvenile and adult anxiety, addiction, depression
	Alterations in rodent maternal care (i.e. licking)	various

Note: ADHD= Attention-deficit/hyperactivity disorder; MeCP2= methyl CpG binding protein 2 gene; OCD = obsessive-compulsive disorder; pten=phosphatase and tensin homolog gene; SAPAP3=SAP90/PSD-95-associated protein 3; Slitrk5= SLIT and NTRK-like family, member 5.