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Animal models for neuropsychiatric disorders: prospects for circuit intervention

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Monogenic animal models for psychiatric diseases have enabled researchers to dissect the relationship between certain candidate genes, neural circuit abnormalities, and behavioral phenotypes along development. Early reports of phenotypic reversal after genetic restoration in mouse models sparked hope that genetic defects do not damage circuits irreversibly in early-onset disorders. However, further studies have suggested that only some circuits exhibit this plasticity, while many others require proper gene function during development. This review focuses on what we have learned from a few evolutionarily conserved circuit–phenotype relationships and their developmental windows to illustrate their importance when considering intervention strategies.

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Introduction

Recent surveys from 2010 determined that mental illness affects about 20% of all adolescents in the United States [1]. Treatments for these often debilitating conditions are limited to only a few available drugs that target the symptoms with moderate to low success, and attempts to develop more effective treatments have been largely disappointing. Many reasons have been proposed for the absence of breakthroughs, but most recognized is the lack of mechanistic knowledge of these disorders [2••,3•,4,5]. Currently, examining neurophysiology in human genetics-based monogenic animal models represents the clearest route to attaining mechanistic insight in a subset of disorders.

Research with these models not only revealed potentially targetable abnormalities in synaptic pathways and circuits, but also trajectories of abnormal brain development that identify opportune windows for intervention [6–9,10•,11••]. At the same time, tremendous progress in technology development has provided tools that allow the manipulation of genes and circuits [12,13,14•]. These tools, combined with the ongoing discovery of critical developmental periods for gene and circuit function, suggest exciting prospects of eventually applying gene-editing and circuit-manipulating technology to patients [15,16•]. Moving forward, increasingly sophisticated animal models will continue to be an integral part in linking circuit abnormalities to disorders and a platform to explore treatments using new technologies. This review highlights recent studies that revealed relevant circuit defects, discusses developmental windows of opportunity for intervention, and considers several future treatment strategies.

Emerging focus on circuits in monogenic models

To break down the complexity of neuropsychiatric disorders into more easily targetable units, researchers deconstruct the pathophysiology into circuit–phenotype relationships. Although discussing circuit defects in depth is beyond the scope of this review, three such relationships observed across different animal models exemplify the utility of this approach.

First, mice lacking the autism spectrum disorder (ASD)-linked synaptic scaffolding protein SHANK3 display a range of phenotypes including repetitive behavior [11••,17,18]. Repetitive behavior is also observed in mice lacking the cell-adhesion molecule Neuroligin-1 or the scaffolding protein SAPAP-3. Strikingly, electrophysiological examination of all three lines of mice revealed abnormal corticostriatal neurotransmission. Together with evidence from human patients and circuit-modulating studies in wildtype mice that causally link corticostriatal circuit dysfunction to repetitive behavior, these observations in the disease models suggest that abnormal function of this circuit is the neural substrate of manifestations of repetitive behavior regardless of the primary molecular insult [11••,19–21,22•,23,24].

Second, a recent study found that four genetically distinct mouse models for ASD display hypersensitivity to gentle touch and tactile stimuli. Elegant genetic dissection of the underlying circuits in two of the four models further

demonstrated that this defect most likely results from decreased inhibition of a somatosensory touch circuit in the spinal cord [25••]. Even more intriguingly, the exclusive dysfunction of this circuit and possibly ensuing inappropriate tactile sensations during development appear to contribute to abnormal social and anxiety behaviors observed in these mice.

Third, mice lacking the ASD-associated gene *Ptchd1* exhibit abnormal sleep and attention deficits [26••]. *Ptchd1* is highly enriched in the thalamic reticular nucleus (TRN), which regulates sleep spindles through thalamic burst modulation [27]. Electrophysiological examination of the TRN in *Ptchd1*-deficient mice revealed impaired bursting and decreased sleep spindles. Abnormal sleep spindles are also produced in mice lacking $Ca_V3.3$, which is a low-threshold calcium channel that is highly expressed in the TRN and genetically linked to several psychiatric disorders [28,29]. Together with the finding that the TRN is critical for selection of sensory stimuli in divided attention in wildtype mice, the evidence from the disease models indicates that TRN network dysfunction may underlie sleep abnormalities and attention deficits [30•].

Across disorders, these studies suggest a provisional framework of targetable circuits based on which aberrant corticostriatal activity drives repetitive behaviors. Also based on this concept, dysfunctional somatosensory neuron circuits in the spinal cord may underlie touch hypersensitivity in some cases, and possibly impaired social and anxiety behavior, whereas impaired TRN function may be a substrate of abnormal sleep and attention deficits.

Studying circuits beyond monogenic models

The aforementioned circuit studies in monogenic mouse models of neuropsychiatric disorders have greatly advanced mechanistic understanding. However, this strategy also faces several key challenges.

First, monogenic mouse models do not account for heterogeneous genetic backgrounds that modulate the effect of the modeled genetic variant. In fact, a recent study found that deletions of some genes only produce a phenotype in certain inbred mouse strains but not others, that is, the genotype–phenotype relationship depends on the particular genetic makeup outside the gene of interest [31••]. Second, only a fraction of disease is attributable to rare genomic variants that have large effects, while in the majority of cases risk is conveyed by many variants of small effect size that cumulatively confer susceptibility to disease. A large fraction of these variants map to non-coding regulatory regions, many of which are poorly conserved between species [32,36,37]. Third, many of the regions of interest, such as the prefrontal cortex display significant differences in gene expression and circuit architecture between rodents and primates (reviewed in Refs. [3•,38•]).

To overcome these challenges, investigators are attempting different strategies. One approach circumventing the need to dissect complex genetic underpinnings uses patient-derived induced pluripotent stem cells (iPS cells). This strategy has already revealed some preliminary signatures of abnormal neuronal connectivity, gene expression, and neurotransmitter secretion in schizophrenia [39–41]; and recent advances in brain organoid technology promise improved interrogation of simple circuit phenotypes using iPS cells (reviewed in Refs. [42]). However, to explore more complex circuits involving multiple brain regions and to identify circuit–behavior relationships, investigators may explore a second complex strategy with non-human primates in the future. Non-human primates are likely better models for the interrogation of defects in evolutionarily more divergent circuits [3•,38•]. In addition, these studies may leverage just emerging genome-editing technologies to introduce multiple non-conserved human loci to non-human primates. Studying high and low penetrance genetic variants and risk alleles in these humanized primate models could help understand how complex human genetic background differences shape different circuit–phenotype relationships.

Windows for interference with disease circuits

Researchers adopt animal models as powerful tools to establish circuit–phenotype relationships that are primarily caused by the lack of particular genes. Once such relationships have been identified, a critical question is whether there are time windows during which circuit defects and behaviors are malleable. The persistent defect in pathways regulated by these genes suggests that intervention at later points may ameliorate some aberrant behavior and physiology. Conversely, the early onset of neuropsychiatric diseases suggests that the genes are critical for certain aspects of circuit development during sensitive periods, and thus would cause irreversible deficits if not compensated for or restored before that developmental period. Longitudinal studies of animal models and the availability of new technology offer unique opportunities to parse these possibilities and better map out critical periods for particular genes and circuits.

Opportunities for late intervention

Supporting the possibility that normalization of a genetic defect after the completion of developmental milestones is effective, recent studies demonstrate profound reversibility of the pathology in mouse models for Rett syndrome, MeCP2 duplication syndrome, and SHANK3-linked ASD. In the vast amount of cases Rett syndrome is caused by mosaic expression of mutant and wildtype alleles of the epigenetic regulator MeCP2 in females.

Among other defects, a comparable genetic lesion in mice produces abnormal synaptic plasticity and behaviors such as inertia, irregular breathing, abnormal gait, and hindlimb clasping [46]. Asking whether this can be reversed in adulthood, Guy *et al.* conducted a pioneering study by engineering mice such that MeCP2 expression can be activated by tamoxifen-Cre-ER-mediated removal of a STOP-cassette in MeCP2. Four weeks after symptom onset, tamoxifen was administered for several weeks and endophenotypes assessed. Astonishingly, this late restoration of MeCP2 expression significantly improved the behavior and normalized synaptic plasticity, suggesting that most cellular and circuit defects associated with developmental lack of MeCP2 are reversible. Together with the finding that loss of MeCP2 in late developmental stages results in essentially the same gross defects as early loss [47], these results support a model of persistent requirement of normal MeCP2 function and suggest therapeutic opportunities for Rett syndrome throughout life. Interestingly, this possibility may generalize to the clinically distinct MeCP2 duplication syndrome. Mice carrying an extra copy of MeCP2 display hypoactivity, abnormal social, motor, and anxiety-related behaviors, as well as abnormal gene expression and synaptic plasticity. Simply normalizing the amount of MeCP2 in adult animals through tamoxifen-Cre-ER-mediated removal of one copy of MeCP2 rescued all deficits, which indicates that brains developing under the influence of excessive MeCP2 remain sufficiently intact to benefit from late interventions [48••].

Based on the evidence discussed above, defects associated with abnormal MeCP2 expression levels appear vastly reversible in adult mice, but an important question is whether this opportunity might generalize to other diseases with early developmental onset. Aiming to dissect the reversibility of abnormalities in SHANK3 mutant mice, Mei *et al.* devised a genetic model of SHANK3 deletion that allowed restoration of SHANK3 expression by tamoxifen-Cre-ER. Examination of mice lacking SHANK3 revealed reduced spine numbers, decreased expression of receptor proteins at synapses, impaired corticostriatal transmission, and behavioral abnormalities including anxiety, motor coordination deficits, excessive grooming, and reduced social behavior. Remarkably, animals with restored SHANK3 expression in adulthood displayed normalized striatal receptor expression, dendritic spine numbers and corticostriatal neurotransmission, as well as normalized grooming and social interactions [11••]. Together, these recent genetic studies highlight the potential to reverse circuit defects in some brain regions in adulthood.

Critical windows of opportunity

In the above example, genetic restoration of SHANK3 reverses dysfunction of the corticostriatal circuit and several behavioral problems. Other behaviors, however, such as anxiety and deficits in motor coordination were not rescued by adult re-expression of SHANK3, suggesting that other circuits irreversibly damaged during development are the substrate of these behavioral abnormalities. Indeed, restoration of SHANK3 at a much earlier time point at postnatal day 20 improved motor coordination and normalized anxiety. At this point, it is not fully understood how the lack of SHANK3 during development may contribute to irreversible phenotypes. One explanation could be that, in the absence of SHANK3, hyperactivity in the developing cortex derails developmental trajectories by driving precocious maturation as well as inappropriate, typically activity-dependent, circuit refinement [49•]. Several other recent examples encompassing studies on *MeCP2*, *Syngap1*, *Pten*, and 22q11.2 deletion syndrome also suggest a similar framework.

Elegant manipulation of *MeCP2* in somatosensory neurons at different points in development demonstrated that while both developmental and adult MeCP2 disruption cause abnormal tactile sensation, only the developmental deletion results in anxiety and social deficits. Consistently, only developmental, but not adult restoration of the gene in somatosensory neurons appears to protect the mice from developing signs of anxiety and abnormal sociability [25••].

In another study, Rumbaugh and co-workers observed that *Syngap1*$^{+/-}$ mice display abnormal synaptic physiology mostly between the second and third postnatal week. To dissect this further, the authors manipulated *Syngap1* expression at different developmental time points and revealed synaptic abnormalities for early developmental (P1-P15), but not late adolescent deletion of the gene [9,50]. Consistently, restoration of *Syngap1* to normal levels during adulthood failed to improve associated behavioral and electrophysiological defects except for an improvement in hippocampal plasticity [9]. Mechanistically, it is yet unclear how the reduction of *MeCP2* or *Syngap1* during early periods translates to long-lasting changes. Perhaps, similar to the precocious maturation of circuits and cortical hyper-excitability observed in *SHANK3B*$^{-/-}$ mice [49•], accelerated excitatory synapse maturation observed in *Syngap1*$^{+/-}$ or decreased inhibition of somatosensory neurons in *MeCP2*$^{-/y}$ mice may disrupt excitatory-inhibitory balance and thus experience-dependent circuit refinement during development.

The significance of sensitive periods is enormous, as transient treatment aimed to prevent abnormal brain development during that time may have lasting effects. This appears to be the case in exemplary studies on *Df(16)A*$^{+/-}$ mice, a model for the schizophrenia-associated 22q11.2 deletion. *Df(16)A*$^{+/-}$ mice display impaired hippocampal-prefrontal synchrony and encoding of spatial information, decreased axonal branching in the prefrontal cortex and working memory deficits [51,52,53••].

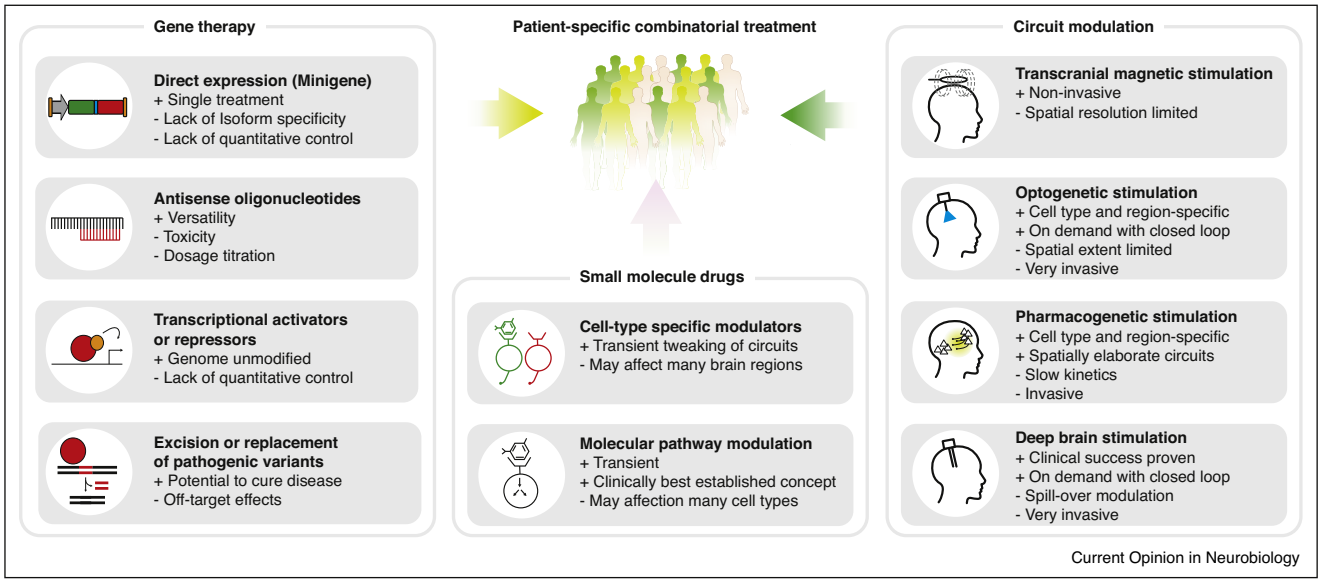
Intriguingly, *Df(16)A*$^{+/-}$ mice transiently treated with an inhibitor for GSK3 during development (P7-P28) displayed normal structural and functional connectivity and behavior in adulthood [53••]. Similar observations were made in *Pten*$^{+/-}$ mice, where excessive axonal branching of PFC to basolateral amygdala (BLA) connections and abnormal social behavior could be prevented by transiently antagonizing an underlying molecular substrate during development (P4-P14), but not later in life [10•]. Together, these studies highlight the value of early intervention before the development of abnormal circuits in the brain.

Avenues for normalizing circuits

The recent studies outlined above highlight the potential to improve patient outcomes in neuropsychiatric disorders. Currently, the three most actively explored treatment strategies in animal models are small molecule drugs, neural circuit modulators, and gene therapy (Figure 1). Testing of small molecule or peptide drugs in several rodent models shows promising results [18,26••,54–57], but successful translation has yet to be achieved. Moving forward, the candidates holding greatest promise will likely be those targeting stringently conserved pathways in well-stratified patient cohorts before critical periods close [10•,53••]. Once a sensitive period is closed and circuits incorrectly wired, circuit-modulating strategies, such as chemogenetics, optogenetics, or deep brain stimulation, may be used to overcome substantial circuit impairments. For example, a drug that rescues social deficits in *Pten*$^{+/-}$ neonates does not improve social function when administered to adult mice, but modulation of the underlying circuit using chemogenetics still does [10•]. Further supporting this idea, optogenetic activation of VTA neurons in adulthood can enhance social behavior in mice that engaged less in this behavior, likely as a result of inappropriate circuit development [57]. Deep brain stimulation (DBS) is another technique that can improve circuit function. This technique and other circuit modulators may be applied regardless of the underlying molecular defect, which renders them useful across disorders that share similar circuit defects [58,59••].

Contrasting these strengths, pharmacological and circuit-modulating treatments face challenges as their success may require the correction of multiple aberrant molecular pathways, cell-types, and circuits underlying a disorder. In such cases, restoring function on the genetic level may be a more attractive strategy, with several recently developed approaches holding great promise [11••,46,48••]. Approaches to normalize gene expression include antisense oligonucleotides [48••], transcriptional activators or repressors [14•,60•], direct expression of a gene or minigene-variant with split vectors for larger constructs [61,62], excision of pathogenic fragments [63], and in the future replacement of pathogenic variants with wild-type alleles through genome editing [64••].

Figure?1



Patients receive combinatorial treatments depending on the circuit defect and onset of intervention. Left: Several gene therapy strategies target the genetic defect directly. This strategy has great potential when early intervention is possible. Center: Small molecule drugs either target-specific molecular pathways or modulate the activity of cell types that participate in particular disease circuits. Right: Circuit modulators activate or inhibit abnormally active circuits. This strategy modulates the symptoms and has the potential to overcome abnormal circuit activity in adults.

Conclusion and outlook

Although animals cannot reflect all aspects of brain disorders, studies in monogenic models have revealed important neural circuit abnormalities, developmental trajectories, and windows of opportunity for intervention. Not surprisingly, there is not a singular mechanism underlying any given psychiatric disorder, but thanks to genetic tools, scientists have begun to deconstruct disorders into smaller, more modifiable disease units by parsing circuit–phenotype relationships. Regardless of the molecular defect, several lines of evidence suggest that disrupted cortico-striatal-thalamo-cortical circuit function underlies repetitive behavior, while aberrant tactile somatosensory circuit function during development contributes to abnormal social behavior in adulthood [11••,19,20,25••,65]. Presently, it is not completely understood how genetic defects lead to these circuit dysfunctions. Based on the evidence discussed here, the most conceivable theory is that some circuits depend on certain genes for their activity-dependent maturation and refinement during development while others require the genes to maintain proper synaptic function throughout life [9,11••,46,47,48••,49•,53••,66,67]. Inherently tied to this notion is the realization that interventions may be differentially effective depending on the time of their initiation [10•,11••,25••]. In mice, an opportune time to initiate pharmacological or gene therapy-based interventions appears to be during the first month of life. After this period, although still effective in some aspects, these interventions may fail to fully correct function of some abnormally matured circuits. Such circuits, however, could be further tuned with circuit-modulating technologies in a combinatorial strategy. Focusing on the translatability of these windows and interventions, ideally in organisms that closely parallel developmental trajectories of humans, such as non-human primates [38•,68], will be an exciting research focus that should greatly enhance the prospects of improving the lives of affected individuals.

Conflict of interest statement

TK and YZ report no biomedical financial interests or potential conflicts of interest. GF receives consulting fees from F. Hoffmann-La Roche and Taisho Pharmaceutical Co, Ltd, and has equity in Inscopix and Rugen Therapeutics (cofounder).

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