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Windows of opportunity: timing in neurodevelopmental disorders

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Developmental processes disrupted in neurodevelopmental disorders occur rapidly and with temporal precision. During development, individual gene activity can dynamically engage different signaling networks; thus genetic mutations can lead to different functional changes at different times. Interpretation of phenotypes can be further complicated if initial functional changes trigger compensatory mechanisms. Examining genetic mouse models of neurodevelopmental disorders reveals cellular phenotypes that change over the course of development and exist long before behavioral deficits are assessed. Correspondingly, earlier genetic interventions in these disorder models have often been more effective at improving behavioral deficits than late interventions. The restricted period of effective intervention demonstrates that identifying a target window is an essential component of treatment.

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Introduction

Neurodevelopmental disorders such as autism arise from the disruption of developmental processes, which are under precise temporal control. To develop treatments for neurodevelopmental disorders, it is critical to consider the circuit-specificity and timing of these developmental processes. For example, neuronal proliferation and migration, axon guidance, synaptogenesis, and activity-dependent refinement each occur at distinct times in different circuits during development. Moreover initial functional changes can be closely followed by homeostatic mechanisms which may confound analysis [1]. Thus expression of initial defects may only be obvious during specific time-periods in different circuits. Recent work with monogenic mouse models has supported the importance of timing in neurodevelopmental disorders [2,3]. Although our understanding remains incomplete, new models enabling temporally and spatially specific manipulations of autism-associated genes, including of Mecp2, Syngap1, Ube3a, FMRP, and Shank3, have allowed investigation of disease progression and reversibility. Careful mapping of the emergence of disease-related phenotypes in these models has revealed early and sometimes transient phenotypes, such as altered timing of synaptic maturation. Critically, only early interventions are able to effect later changes in behavior in many genetic models, suggesting treatment timing may need to be closely linked to the timing of deficit emergence and the underlying affected developmental process.

Neurodevelopmental disorder progression highlights sensitive windows in development

Examining developmental trajectories in mouse models of neurodevelopmental disorders shows that functional changes emerge during distinct periods of development. Phenotypes can include a shift in developmental timing or change over time, for instance from synaptic hypoactivity to hyperactivity. This speaks to changing gene activity and function at different stages as well as involvement of homeostatic or compensatory mechanisms, highlighting the importance of carefully cataloging deficits across development. For instance, several mouse models of loss-of-function genes found in autism show changing deficits that appear during the narrow developmental window of active synapse formation and refinement. Expression of Syngap1, a synaptic RasGAP (SynGAP) largely found in dendritic spines, peaks at postnatal day 14 (P14) in the mouse hippocampus and at this time point heterozygous loss of Syngap1 results in prematurely slowed dendritic spine dynamics and increased mEPSC amplitude [4••]. However, earlier in development at P9 no deficits are observed and later in development at P21 normalization to wildtype has occurred [4••]. A similar accelerated development following Syngap1 loss is seen in layer 5 of barrel cortex at the level of spine formation and pruning [5]. A phenotype that changes across development is also present in the striatum following homozygous loss of Shank3, a scaffolding protein of the postsynaptic density. Initial characterization of adult *Shank3B* mutants reported decreased cortical–striatal drive [6]. However, during the period when cortico-striatal activity emerges and stabilizes, at P14, Shank3 loss leads to

increased cortical–striatal drive [7••]. As the cortico-striatal circuit continues to mature, cortico-striatal drive in mutants plateaus so that by P30, control and mutant animals have similar mEPSC frequency. By P60, wildtype drive overtakes mutant [7••] congruent with original observations of *decreased* mEPSC frequency in adult Shank3b mutants [6]. Similarly, deletion of FMRP1, a translational regulator of many synapse-associated mRNAs, leads to multiple transitory deficits [8] including a different trajectory of synaptic potentiation between P4 and P10 at the thalamocortical synapse that normalizes by P14 [9] and short-term synaptic deficits at the cortical layer 4 to 3 synapse [10]. Although some of these early changes can seem impermanent, they nonetheless have important consequences for activity-dependent formation and refinement of neural circuits [5] and thus can have long-lasting impact, presenting as later behavioral phenotypes.

When taking a developmental approach to neurodevelopmental disorders, it is also necessary to investigate in a circuit — specific way. In different neural circuits, the same mutation can lead to emergence of neurodevelopment deficits at different times. The timing of deficits may reflect the different timing of developmental events, such as activity dependent maturation, or temporal regulation of gene expression in individual circuits. For instance, refinement of thalamic inputs in the barrel cortex occurs between P0 and P4, while cortical layer 2/3 development occurs between P13 and P16 [11]. Correspondingly, mEPSC synaptic deficits in layer 4 barrel cortex are observed between P4 and P7 in *Syngap1* mutant mice [12]. By contrast in layer 2/3 medial prefrontal cortex at P14, synaptic deficits are absent despite being present in adult *Syngap1* mutants [13•] while in layer 2/3 barrel cortex, enlarged spines are already observed [5]. Depending on the circuit, cortical region, and layer, phenotypes appear at different times in the same *Syngap1* mutant.

Neurodevelopmental disorders arising from different genetic mutations follow different developmental progressions; not all exhibit peak changes during circuit formation as described above. A different developmental progression is seen following loss of Mecp2. Mecp2 is an X-linked gene and is thought to act broadly throughout the genome regulating transcription of many genes, especially neuronal ones [14]. Loss of Mecp2 in girls leads to Rett syndrome, which shares features with autism such as stereotyped hand movements, and milder Mecp2 mutations have been associated with multiple psychiatric disorders [15]. At neonatal ages, Mecp2 is expressed at low levels only reaching maximum expression around 5 weeks of age in mice [16]. Correspondingly, in mouse models development proceeds relatively normally for about the first three weeks followed by regression with difficulties developing in multiple domains including motor dysfunction as measured by rotarod test, walking on a grid and nest building, as well as impaired fear conditioning, learning and memory and other deficits by 5 weeks of age [15,17,18]. The progressive behavioral deterioration seen in this disorder is also seen at the biochemical level; as the disorder progresses, transcriptional misregulation increases in severity [14]. Human baby girls show a similar trajectory with relatively normal early development, including learning to walk, until 6–18 months of age, when both mental and motor regression begins [15].

Experiments that induce mutations during specific time windows also support the existence of sensitive but limited time frames that are particularly affected by gene loss. The periods sensitive to gene perturbation reflect the trajectories of gene expression and functional importance. For instance, removal of Mecp2 after 4 months of age initiates multiple neurological symptoms with a similar time course to that of the full knockout, including early mortality in males [19–21]. By contrast, adult removal of Syngap1 has little effect at either the synaptic or behavioral level, consistent with its role in early synapse formation and circuit development [13•]. Using these developmental approaches to establish periods when deficits emerge and when gene activity is required can help predict windows of opportunity for effective treatment.

Limited windows for functional rescue revealed through controlled gene expression

Recent technical advances in genetic manipulations have led to some of the clearest demonstrations of the temporal limits for intervening in neurodevelopmental disorders by achieving temporally controlled reintroduction of genes. We focus here on genetic rather than pharmacological strategies due to the difficulties in interpreting the actions of drugs on a mechanistic level, particularly due to the notoriously promiscuous nature of drug activity [22]. Furthermore, ongoing development of safer and more efficient viral vectors means that gene therapy is becoming an increasingly viable therapeutic option [23]. In the meantime, new mouse genetic strategies have enabled restoration of endogenous gene function using Cre-induced removal of floxed stop cassettes [4••,24,25••] or re-orientation of double-floxed inverted exons [26••]. Achieving endogenous patterns and levels of gene expression is advantageous, considering many brain-specific genes show strong dosage effects; many disorders result from both deletions and duplications, as is the case with Mecp2 [15]. Approaches capable of restoring endogenous levels of isoform-specific gene expression in the correct cell types will therefore provide the best opportunity to rescue the phenotypes seen in neurodevelopmental disorders with minimal side effects.

Investigations using such novel genetic approaches are still at an early stage and may yet reveal further

gene-dependent variations; however increasing evidence suggests that late genetic rescue in adults can affect only a limited number of behaviors. Encouragingly, earlier interventions can improve behaviors even where adult intervention brings limited improvements. Thus, a restricted window of opportunity exists. Furthermore, the ability for some but not other abnormal behaviors in animal models to be normalized by adult manipulations suggests circuit and behavior-dependent limits of plasticity.

One of the earliest studies to undertake a gene re-expression strategy showed that adult re-expression of Mecp2 in mice as old as 3 months was able to improve overall condition as well as multiple motor deficits including gait and breathing. At a synaptic level, Mecp2 re-expression also reversed LTP deficits in the hippocampus [24]. However later, more quantitative, phenotypic assessment following Mecp2 re-expression revealed lingering behavioral and anatomical deficits [27]. In a model of Mecp2 overexpression, which shows similar phenotypes to Mecp2 loss, adult normalization of gene expression levels led to similar improvements [28]. The finding that even adult rescue is possible is consistent with findings from developmental deletion studies which suggest a requirement for Mecp2 in older animals. Supporting the possibility for eventual clinical treatments, systemic viral delivery of Mecp2 in adults also proved effective for behavioral improvement [29].

Unfortunately, in other genetic models of autism only intervention at relatively early time points of postnatal development has been able to affect adult phenotypes, including deficits in motor and anxiety-like behavior. For example, adult (2–4.5 month) reintroduction of Syngap1 [4••], Shank3 [26••], and Ube3a [25••,30] did not improve either motor deficits or anxiety-like behaviors as measured by rotarod, open field, and elevated plus maze tasks. Moreover, *Syngap1* mutants retained EPSC defects at cortical layer 2/3 after adult restoration of expression [13•]. On the other hand, earlier rescue around P21 in both the Ube3a [25••] and Shank3 [26••] models was able to rescue rotarod performance. This timing aligns with the emergence of neurodevelopmental deficits in Shank3 mutants [7••]. The potential for anxiety-like behaviors to be targeted at a younger age remains unclear, as they were rescued following re-expression at P21 of Shank3 [26••], but not Ube3a [25••] or Syngap1 [5]. However, 'anxiety' was measured using an elevated plus maze [5,26••] and rearing in open field [26••] for the Shank3 and Syngap1 models, while marble burying, nest building, and forced swim behaviors were used to evaluate the Ube3a model [25••]. Furthermore, it is important to note that most behaviors, even when measured using the same assay, involve the engagement of multiple circuits. Since a disturbance in a behavior could stem from disruptions of several different circuits, the differential ability of anxiety-like behaviors to be rescued in different models could stem from a difference in the underlying affected neural circuit.

Reintroduction of autism related genes in adult mouse models has been more successful at correcting cellular deficits in the striatum and hippocampus, as well as associated behavioral deficits in motor repetition and memory, respectively. For example, adult re-introduction of Shank3 restores spine number and morphology, synaptic properties, and levels of key synaptic proteins, including glutamate receptors, in the striatum. At a behavioral level, repetitive grooming and three chamber social interaction with preference to stranger mouse vs. object, behaviors associated with striatal function, are also improved [26••]. Although repetitive behaviors were not tested in the Syngap1 and Ube3a models, repetitive behaviors are present in mouse models of autism-associated transynaptic cell-adhesion molecules neurexin-1 [31] and neuroligin-1 [32]. Both repetitive grooming and three chamber social interaction deficits are present in a neuroligin-1β mutant mouse, generated by overexpression of a mutant neurexin-1 isoform that interferes with endogenous neurexin-1 signaling in the cortex and striatum. These deficits are rescued 14 days after halting mutant neurexin-1β expression either at approximately 3 months or 8 months of age [31]. A different type of repetitive motor behavior is present in the neuroligin-3 mouse model; knockout mice exhibit accelerated motor learning with more stereotyped behavior on rotarod performance [32]. As with the other rescues, re-expression of neuroligin-3 in 4-week old animals rescues this repetitive behavior. Furthermore, striatal circuitry was directly implicated in the rescue since neuroligin-3 expression was targeted specifically to D1-type medium spiny neurons of the nucleus acumbens using a viral approach [32]. Together these results suggest that stereotyped behaviors associated with deficits in striatal circuitry are more amenable to rescue at later ages. Similarly, hippocampal deficits have also been successfully targeted at adult stages. Adult reexpression of Ube3a and Syngap1 rescues hippocampal LTP [13•,30], along with contextual freezing in the Ube3a model [30]. Although freezing was not examined in the Syngap1 model, at the biochemical level, basal and stimulation-dependent changes in phospho-ERK were rescued, demonstrating the molecular plasticity of the hippocampal circuit [13•].

Altogether these examples suggest that across genetic models different circuits show different amenability for rescue. For many behavioral deficits, adult intervention is ineffective and earlier intervention is necessary. Some behaviors remain unchanged even following early postnatal genetic reactivation, perhaps requiring intervention *in utero*. Indeed intervention starting at P1 was able to rescue all measured Syngap1 behavioral deficits, including anxiety that was not rescued at P21 [5]. The developmental windows where reintroduction of genes leads to

rescue roughly align with times when postnatal phenotypes emerge, as described above for deficits in synaptic maturation following Syngap1 and Shank3 loss. The differential ability for different behaviors to be rescued perhaps corresponds to the inherent plasticity of the underlying circuits.

We have focused here largely on postnatal development, but there may be other sensitive periods in development, such as earlier periods of neuronal proliferation, migration, and morphogenesis. Neurodevelopmental disorder associated genes such as CHD8 [33], a chromatin remodeler, have been implicated in disrupting such earlier processes [34,35]. Furthermore, many implicated genes are pleotropic and can act at multiple stages in development. For instance, in additional to synaptic plasticity, Ube3a is also required in dendrite morphogenesis [36], while FMRP1 affects migration of newly born neurons in the cortex [37]. Indeed, an analysis of human cortical gene expression across fetal development revealed enrichment for gene networks implicated in autism in cortical layers midway through fetal development [38,39] as well as during a later window in development [38]. Deficits arising from disruption of such earlier processes would likely require correspondingly earlier treatments.

Conclusion

Moving forward, it will be important to have tools to determine critical windows both for autism and other neurodevelopmental disorders. For most disorders, interventions at the earliest timepoints, when deficits are first observed, are likely to be the most effective. However, these disorders are extremely heterogeneous and likely present with different trajectories and affected circuits in different individuals. Furthermore, critical windows of cellular and molecular dysfunction can precede overt phenotypes, making it difficult to provide therapeutic interventions at times when they are likely to be most effective. Thus, developing advanced diagnostic assays for humans that can be applied as early as possible will be critical [40]. In children with autism, several measures have been reported that have predictive power for deficits later in life. These include early behavioral deficits such as shifting of visual attention [41], and morphological changes in brain volume measured with MRI [42]. Electrophysiological differences, such as visual evoked potentials measured by EEG, have also been found and even share similarities between patient and mouse models [43]. In the future, the combination of multiple measures may be sufficient to assess the trajectory and circuit-based nature of disorders in individuals to indicate the windows for effective intervention.

Conflict of interest statement

None declared.

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