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Emerging Pharmacotherapies for Neurodevelopmental Disorders

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Abstract

A growing and interdisciplinary translational neuroscience research effort for neurodevelopmental disorders (NDDs) is investigating the mechanisms of dysfunction and testing effective treatment strategies in animal models and, when possible, in the clinic. NDDs with a genetic basis have received particular attention. Transgenic animals that mimic genetic insults responsible for disease in man have provided insight about mechanisms of dysfunction, and, surprisingly, have shown that cognitive deficits can be addressed in adult animals. This review will present recent translational research based on animal models of genetic NDDs, as well as pharmacotherapeutic strategies under development to address deficits of brain function for Down syndrome, fragile X syndrome, Rett syndrome, neurofibromatosis-1, tuberous sclerosis, and autism. Although these disorders vary in underlying causes and clinical presentation, common pathways and mechanisms for dysfunction have been observed. These include abnormal gene dosage, imbalance among neurotransmitter systems, and deficits in the development, maintenance and plasticity of neuronal circuits. NDDs affect multiple brain systems and behaviors that may be amenable to drug therapies that target distinct deficits. A primary goal of translational research is to replace symptomatic and supportive drug therapies with pharmacotherapies based on a principled understanding of the causes of dysfunction. Based on this principle, several recently developed therapeutic strategies offer clear promise for clinical development in man.

Key terms

neurodevelopmental disorders; pharmacotherapy; Down syndrome; fragile X syndrome; autism; neurofibromatosis-1; tuberous sclerosis; Rett syndrome

INTRODUCTION

Individuals affected with neurodevelopmental disorders (NDDs) exhibit mild to severe intellectual disabilities and may express maladaptive behaviors consistent with attention deficit hyperactivity disorder, obsessive-compulsive disorder, and autism spectrum disorders. Improved medical care, integrated educational opportunities, and symptomatic drug treatment have significantly increased the lifespan and improved daily living skills for individuals with NDDs. Drug therapies designed to address the disease state have been less successful. However, recent translational research in animal models for a number of NDDs show great promise for pharmacotherapy that targets pathology and cognitive deficits specific to these disorders.

The creation and characterization of animal models of NDDs have grown in the last decade, driving a number of promising translational research programs. Manipulating gene expression

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through transgenic, knockout, and knockin approaches in mice, flies, and worms permits study of the underlying anatomy, pathology, and physiology of disease. Mechanistic insights support the development of drug therapies to mitigate cognitive and behavioral deficits that could be life-changing. For example, pharmacotherapy that improves a child's capacity to learn should provide nonlinear improvements in cognitive abilities, social function, and independence. Despite recent progress, successful therapies for NDDs require significant additional basic and clinical research.

NDDs can be distinguished by genetic and environmental causes, the nature and site of dysfunction, and the time course of cognitive and behavioral deficits during development. In this review, we focus on NDDs with a known genetic basis. These disorders are easier to characterize with animal models, better defined in terms of mechanism, and most promising for the development of principled therapeutic targets. We will also restrict our discussion to NDDs for which abnormalities in the CNS are localized to individual cells, local circuits of neurons, or specific brain regions. Translational research in animal models has been fruitful for disorders that fit this profile such as Down syndrome, fragile X syndrome, Rett syndrome, neurofibromatosis type 1, tuberous sclerosis, and autism.

The extent of genetic insults and brain pathology underlying NDDs determine the potential for pharmacotherapy. For example, phenylketonuria is a disorder with straightforward genetics and dysfunction in a specific, well-understood molecular pathway [1]. Early intervention with dietary modification reduces or eliminates intellectual disability. Similar improvements in cognitive function are unlikely for other NDDs associated with severely underdeveloped brain regions or abnormal long-range projections such as fetal alcohol syndrome, microcephaly, and lissencephaly [2]. However, some improvements in cognitive function may be possible by addressing dysfunction in even severely malformed regions [3]. The prognosis of pharmacotherapy is better for NDDs caused by subtler changes that affect the function of local neural circuits. Translational research has identified pharmacological interventions that restore inhibitory-excitatory balance in neural circuits, compensate for dysfunctional molecular pathways, or address abnormal neurophysiology or synaptic plasticity. Therapies that address dysfunction in long-term plasticity, including both synapse strengthening via long-term potentiation (LTP) and weakening by long-term depression (LTD), are significant. These processes are generally recognized as the key substrate of learning and memory [4]. Individuals with different NDDs exhibit overlapping sets of deficits due to dysfunction in common brain regions. Pharmacotherapeutic strategies that address shared forms of dysfunction have the potential to mitigate symptoms in different NDDs.

Advances in translational research offer hope to both children and adults. Remarkably, recent findings have shown improvements in learning and memory in adult animals [5,6]. Mutations, deletions, or duplications of genes in NDDs may cause only modest changes in protein expression that shift the equilibrium of chemical reactions and signaling pathways. Thus, therapies that normalize function by either enhancing the activity of remaining proteins, disrupting mutant proteins, or modulating parallel and convergent pathways may improve abilities in individuals with NDDs.

The Translational Cycle

A primary goal of translational research in the field of neurodevelopmental disorders is to replace symptomatic and supportive drug therapies with pharmacotherapies based on a principled understanding of the causes of dysfunction. We define a model of this process as the Translational Cycle. Translational research starts with diagnostic, behavioral and genetic studies in man, moves to animal models and other reduced preparations for biological and neuroscientific study then progresses to drug development and clinical studies in man based on increased knowledge and therapeutic strategies.

We describe this Translational Cycle with seven multidisciplinary steps(Fig. 1):

1. *Human phenotype* – Characterization of the disease
2. *Human genotype* – Discovery of the underlying genetics
3. *Animal genotype* – Development of animal models that mimic the genetic etiology of human disease
4. *Animal phenotype* – Behavioral testing to probe cognitive, motor, and social behaviors; studies of underlying genetics, molecular biology, neurophysiology, and anatomy in animal models
5. *Therapeutic strategy* – Development of therapeutic strategies based on biological findings in animal models and optimization for safety and efficacy
6. *Drug development* – Optimization of lead compounds to improve drug-target specificity, bioavailability, or pharmacokinetics, as well as determination of appropriate dose, dosing strategy, and route of administration.
7. *Clinical trials* – Design and execution of clinical trials in man to address cognitive deficits

In the first step of the Translational Cycle, human disorders are identified as distinct from each other and the phenotypes are characterized (Fig. 1, step 1). The first NDDs described in this manner were common disorders with external traits including skin lesions and benign tumors in neurocutaneous syndromes such as tuberous sclerosis [7–9] and craniofacial abnormalities in Down syndrome [10]. Today, NDD diagnosis relies on detailed genetic and cognitive testing, behavioral phenotyping and, in some cases, neuroimaging. Improved characterization of NDDs to identify relative cognitive strengths and weaknesses (Fig. 1, step 1) has focused animal behavioral studies and determined brain regions of interest. For instance, human deficits in executive control and long-term memory implicate the frontal cortex and hippocampus, respectively.

Description of genetic causes of NDDs is a necessary step to enable the study of disease in animal models (Fig. 1, step 2). Down syndrome was the first disorder described on the basis of genetics due to the triplication of some or all of chromosome 21 [11]. Due to a revolution in human genetics, the genes, alleles, expression patterns, epigenetic factors, and patterns of inheritance that underlie various NDDs have been described.

Animal models form the foundation for detailed studies of the biology responsible for cognitive dysfunction in various NDDs (Fig. 1, step 3). Tools for genetically modifying mice and flies include addition or removal of genes, inducible expression of genes at particular developmental time points, and specificity of expression in cell types or tissues [12]. Studies in animal models reveal mechanisms of dysfunction and suggest therapies that target these pathways and systems. However, the value of transgenic animal models is limited by the correspondence of molecular, anatomical, physiological, and behavioral pathology in animals to that in man. Careful study of brain pathology and mouse behavior establishes how well an animal model represents human disease (Fig. 1, step 4). Therapeutic strategies are evaluated in animal models by measuring markers of dysfunction and performance in behavioral tasks (Fig. 1, step 5). A particular therapeutic strategy may address only a subset of cognitive functions, so multiple therapeutic strategies that target distinct deficits and brain areas are desirable.

Significant efforts are required to translate a viable therapeutic strategy into an approved drug. Drug development optimizes a therapeutic compound to improve drug-target specificity, reduce or eliminate dangerous side effects, and determine dose and route of administration (Fig. 1, step 6). Next, a lead compound enters clinical trials in man to test safety and efficacy

of therapeutic strategies discovered in animal models (Fig. 1, step7). For drugs intended to address intellectual deficits, trial design can be difficult due to relatively insensitive outcome measures such as cognitive tests. Moreover, outcome measures based on caretaker questionnaires are susceptible to bias, and the correspondence of improved outcome measures with higher functioning in daily living skills may not be straightforward. An approved pharmacotherapy for an NDD would reduce one or more cognitive deficits or maladaptive behaviors. Such a therapy completes the Translational Cycle by addressing the disease phenotype.

Important translational research challenges remain despite significant advances in the development of potential therapeutic strategies for NDDs. Animal models are often an imperfect representation of human disease or developmental disorders, and the differences between species may carry special significance for disease pathology. Moreover, higher cognitive functions in man such as language do not exist in mice or flies. Thus, improved characterization of animal models of NDDs requires better behavioral assays and physiological measurements. New animal models may improve the correspondence with human conditions. More specific and efficacious second-generation therapies require improved description of the mechanisms underlying successful pharmacotherapeutic intervention. A second set of challenges concern clinical development (Fig. 1, steps 5–7). Clinical development programs are expensive and low yield. Raising funds through government, philanthropic, and industry sources is challenging and slow.

In the following sections, we review translational research progress for several well-studied genetically-based childhood NDDs with an emphasis on research in animal models.

NEURODEVELOPMENTAL DISORDERS

Down syndrome

Down syndrome (DS) is caused by total or partial triplication of chromosome 21 (Hsa21) and occurs in approximately 1/700–1000 live births [13,14]. Most individuals with DS exhibit mild to severe intellectual disability. Medical conditions such as congenital heart disease, Alzheimer's disease, and epilepsy are common [15]. Individuals with DS have particular deficits in verbal skills [16] and cognitive tasks that depend on prefrontal, hippocampal, or cerebellar function [17,18]. Compared with previous decades, individuals with DS live longer and integrate more fully in social, family, and educational environments [19].

There are approximately 300–400 genes on Hsa21 [20–22], but not all genes are expressed at the expected 1.5-fold level, underscoring the complexity of epigenetic interactions [23] (Fig. 2C). Segmentally trisomic mouse models of DS enable studies of the combined effect of trisomy for many genes [20,24,25]. The well-studied Ts65Dn mouse is trisomic for about 100 genes on mouse chromosome 16 (Mmu16) that are homologous to those on Hsa21 [26]. The so-called 'Down syndrome critical region' (DSCR) on Mmu16 appears to be necessary for learning and plasticity deficits in mice [22], but there is conflicting evidence concerning whether the DSCR is sufficient to cause these phenotypes [27,28].

Despite trisomy for only a subset of Hsa21 genes, mouse models of DS exhibit learning and memory deficits and corresponding anatomical and physiological abnormalities [24]. Electron microscopy studies in Ts65Dnmice identified an excess of inhibitory synapses in the temporal cortex [29] and hippocampus [30] and enlarged dendritic spines in several brain regions [31]. Ts65Dn mice have enhanced long-term depression (LTD) and reduced NMDA receptor-dependent long-term plasticity (LTP) of synapses in the CA1 region of the hippocampus [27,32–38]. Signaling molecules involved in the induction of LTP are also disrupted in the hippocampus

of Ts65Dn mice [39]. Based on these anatomical and physiological studies, therapeutic strategies have been described that rescue LTP and deficits in hippocampal-dependent behavior.

Excessive activity of inhibitory neurons causes hippocampal LTP deficits in Ts65Dn mice, and drugs that reduce inhibition improve cognitive function in DS mice [3] (Fig. A–B). In slice studies, bath application of a $GABA_A$ receptor antagonist rescues LTP induction [34,36,37]. $GABA_A$ receptor antagonists have been used to enhance LTP since the first slice studies of plasticity [40], so the viability of this strategy *in vivo* required direct testing. In adult Ts65Dn mice, low daily doses of a $GABA_A$ antagonist such as pentylenetetrazole (PTZ) generated improvements in the induction of hippocampal LTP and learning that lasted for months after a two-week treatment regimen had ended [35,37]. $GABA_A$ antagonists can induce seizures at high doses and reduce the threshold for seizures via 'kindling' at moderate doses [41] but neither effect was observed at efficacious doses in mice (Garner et al., in preparation). Young DS children have increased susceptibility to seizures, so clinical development of $GABA_A$ drugs requires careful design and safety controls [3]. Beginning in the 1930s, PTZ was used clinically for 50 years for a variety of indications, including schizophrenia [42], senility [43], and some forms of intellectual disability [44], but the FDA revoked PTZ approval in 1982 due to absence of efficacy data. This long history of safe use in man makes PTZ a promising candidate for clinical development. Drugs that target specific $GABA_A$ receptor subtypes, such as those containing the α5 subunit, could provide a larger therapeutic window for treatment [45]. However, more work is required to develop safe α5-specific compounds [46].

Another mechanism that causes excessive inhibition in Ts65Dn mice is overexpression of G-protein-coupled inward rectifying potassium 2 (GIRK2) channels that are activated by $GABA_B$ receptors [47]. As a result, $GABA_B$ activation of GIRK2 channels enhanced inhibitory currents [48], and the $GABA_B$ antagonist CGP53432 improved LTP in Ts65Dn hippocampal slices [49]. Thus, drugs that target $GABA_B$ receptors offer an additional therapeutic target.

Neuromodulatory nuclei in the brainstem required for normal memory function degenerate in mouse models of DS, and drug therapies to enhance cholinergic and norepinephrinergic activity rescue behavioral deficits in DS mice. A third copy of the amyloid precursor protein (*APP*) gene disrupts retrograde transport of nerve growth factor (NGF), causes degeneration of basal forebrain cholinergic neurons [50,51] and may be linked to memory deficits [52]. In Ts65Dn mice, elevated levels of oxidative stress contribute to basal forebrain degeneration and memory impairment [53]. The cholinergic system also degrades in Alzheimer's disease (AD), and individuals with DS commonly show early onset of AD pathology and progressive cognitive impairment [54,55]. Approved AD drugs may help in DS. However, despite promising small, open-label trials, larger blinded studies have failed to find benefit of acetylcholinesterase inhibitor drugs approved for AD. The acetylcholinesterase inhibitor donepezil (Aricept™, Pfizer, New York, NY) is not efficacious in Ts65Dn mice [37] and its efficacy in man is inconclusive [56]. In contrast, acute injection of the noncompetitive NMDA receptor antagonist memantine (Namenda™, Forest Laboratories, New York, NY), an approved AD drug, improved performance in contextual fear conditioning in Ts65Dn mice [33,57] and a clinical trial is underway. Rivastigmine (Exelon™, Novartis, Basel, Switzerland), an approved drug for treatment of dementia in Alzheimer's disease and Parkinson's disease, is also being assessed in the clinic.

Norepinephrinergic cells in another brainstem nucleus important for memory, the locus coeruleus (LC), also degenerate in Ts65Dn mice [58]. Treatment with either a norepinephrine pro-drug approved to address neurogenic orthostatic hypotension, L-DOPS (Droxidopa™, Sumitomo Pharmaceuticals, Tokyo, Japan and Chelsea Therapeutics, Charlotte, NC), or xamoterol, a β-adrenergic partial agonist, improved performance in some behaviors [58]. Though promising, this therapeutic strategy requires more work due to the high doses of pro-drug used.

Several additional therapeutic strategies for DS have been proposed. Ts65Dn mice have reduced neurogenesis in the hippocampus, but this phenotype can be rescued with the approved selective serotonin reuptake inhibitor (SSRI) fluoxetine (Prozac™, Eli Lilly, Indianapolis, IN) [59]. Similar effects of fluoxetine on neurogenesis have been observed in rodent models of depression [60]. Ts65Dn mice exhibit reduced responses to the signaling molecule sonic hedgehog (SHH) during development, causing reduced cerebellar size and cell counts [61,62], as well as neural crest deficiencies that may underlie craniofacial abnormalities [63]. Delivery of SHH agonists to Ts65Dn mice during development rescued these deficits [62,63]. In man these developmental stages occur *in utero* and during infancy, so this therapeutic strategy will be difficult to translate.

There is a long history of nutraceutical trials for DS, but a meta-study of trials using dietary supplements for DS concluded these strategies are not effective for improving cognitive function [64]. Consistent with this finding, chronic administration of the nootropic piracetam, which reduces oxidative damage, did not improve cognitive function in Ts65Dn mice [65].

Fragile X syndrome

Fragile X syndrome (FXS) is the most common inherited form of intellectual disability with an incidence of ~1/3600 in males and ~1/8000 in females [66,67]. Individuals with FXS are generally anxious and hypersensitive to stimuli. They exhibit facial and ear abnormalities and enlarged testes. Common diagnoses include ASD, ADHD, sleeping disorders, and seizures [68,69]. Males with FXS have more severe cognitive deficits than females [70].

FXS is caused by expansion of a trinucleotide CGG repeat upstream of the fragile X mental retardation 1 gene (*FMR1*) [71]. If the number of repeats exceeds ~200, aberrant hypermethylation represses *FMR1* transcription [72,73]. *FMR1* encodes fragile X mental retardation protein (FMRP), an RNA binding protein that inhibits cytosolic translation [74] of various targets including those involved in the neuronal cytoskeleton such as MAP1B [75] and synapse structure e.g. PSD-95 [76,77] (Fig. 2G). Consistent with these mRNA targets, FXS is associated with a high density of dendritic spines and long, thin, tortuous spines in individuals with FXS [78] and *Fmr1*$^{-/-}$ knockout mice [79–84]. Zebrafish and *Drosophila* models of FXS confirm an evolutionarily conserved role in neuron structure and behavior [85–87].

Fmr1$^{-/-}$ knockout mice permit studies of brain dysfunction and tests of potential therapies to resolve these deficits [88]. The behavioral phenotype of *Fmr1*$^{-/-}$ mice is less severe relative to deficits in man, including mild and strain-dependent hippocampal deficits [89–92]. In contrast, anxiety and hypersensitivity phenotypes are robust in these mice [93–96]. Despite mixed findings in behavioral studies, introduction of functional *Fmr1* into KO animals has confirmed the role of FMRP in disease psychopathology [96,97].

Based on animal studies, the primary therapeutic strategies for FXS target excessive excitation with group 1 metabotropic glutamate receptor (mGluR5) antagonists [98] or $GABA_B$ receptor agonists [99]. Clinical development is underway for both strategies. FMRP normally inhibits translation near synapses, and some forms of plasticity are enhanced in *Fmr1*$^{-/-}$ mice [82,100] (Fig. 2G). The mGluR5 pathway drives activity-dependent translation of proteins that mediate LTD, and FMRP provides negative feedback on such translation [100,101]. Without this feedback, *Fmr1*$^{-/-}$ mice have enhanced mGluR5-dependent hippocampal [100,101] and cerebellar LTD [82]. Over-activation of mGluR5 receptors also increases seizure susceptibility [102,103]. Together these results support the mGluR theory of FXS and provide a framework for the development of new therapies [98] (Fig. 2G–H).

Antagonists of mGluR5's are a promising category of pharmacotherapies due to genetic and pharmacological rescue of disease phenotype in animal models. *Fmr1*$^{-/-}$ mice crossed with

Grm5 heterozygotes express 50% fewer mGluR5 receptors [104]. Reduced mGluR5 expression rescued increased spine density, reduced ocular dominance plasticity, enhanced inhibitory avoidance extinction, and sensitivity for seizures normally observed in *Fmr1*$^{-/-}$ mice [104]. Similarly, treatment with the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) rescued behavioral deficits in flies [105] and neurite branching in zebrafish [87]. In *Fmr1*$^{-/-}$ mice, MPEP rescued defective prepulse inhibition [106], audiogenic seizure, and anxiety phenotypes [107].

Clinical trials in FXS are underway with several compounds that target the mGluR pathway. No clinically adverse events occurred in a small open label, single dose study of fenobam (Neuropharm Group PLC, Surrey, UK), an mGluR5 antagonist, in adults with FXS [108]. Early stage trials are also underway for several other mGluR5 antagonists: STX107 (Seaside Therapeutics, Boston, MA), AFQ056(Novartis, Basel, Switzerland), and RO4917523(Roche, Basel, Switzerland). The mood stabilizer lithium carbonate (generic) is another therapeutic strategy to target overactive mGluR pathways that has shown some efficacy for improving cognition and irritability in an open-label trial in individuals with FXS (sponsored by the NIH and the FRAXA Research Foundation) [109]. However, an alternative strategy for increasing excitation via the AMPA receptoragonistCX516 (Cortex Pharmaceuticals, Irvine, CA) did not show benefit in a phase II trial [110].

Anatomical and neurophysiological aspects of the GABA system suggest it may be an alternative therapeutic target for FXS [99]. Expression of various $GABA_A$ receptor subunits is reduced in *Fmr1*$^{-/-}$ mice and *dfmr1* knockout flies [111,112], *Fmr1*$^{-/-}$ mice have reduced cortical density of GABAergic interneurons [113], and tonic GABA transmission is reduced in *Fmr1*$^{-/-}$ mice [114]. Based on these findings, a phase II trial in individuals with FXS using the $GABA_B$ agonist arbaclofen is underway (Seaside Therapeutics, Boston, MA). Ganaxolone (Marinus Pharmaceuticals, Branford, CT), a neuroactive steroid with positive allosteric activity at $GABA_A$ receptors, is in a phase II trial for epilepsy and migraine and may benefit FXS individuals with seizures [69,115].

Additional strategies have been evaluated in FXS animal models and may lead to clinically viable therapies in the future. For example, after treatment with the approved drug minocycline (generic), an antibiotic that also inhibits the metallopeptidase MMP-9 and reduces CNS inflammation, *Fmr1*$^{-/-}$ mice exhibited improved spine maturation and reduced anxiety [116]. Both open-label and placebo-controlled trials with minocycline in FXS are underway (trials sponsored by the Fragile X Research Foundation of Canada and The National Fragile X Foundation). In another study, brain derived neurotrophic factor (BDNF) rescued deficits in early forms of LTP in the hippocampus [117] indicating that modulating neurotrophin signaling could also be used to normalize synaptic plasticity mechanisms and circuit function.

Rett syndrome

Rett syndrome (RTT) is an X-linked disorder with an incidence of ~1/10,000 that predominantly affects females [118]. Individuals with RTT show progressive deficits beginning at ~6–18 months that include atrophy of verbal and skilled motor abilities, social withdrawal, hand wringing, respiratory difficulties, seizures, and autism spectrum behavior [119–122]. *De novo* mutations in the Methyl-CpG binding protein 2 (*MECP2*) gene [123] are generally responsible for RTT [124]. RTT symptoms are variable and depend on the pattern of X-chromosome inactivation (XCI) of the mutant allele [121,125–127], the nature of the *MECP2* mutation, and epigenetic factors [128]. MECP2 inhibits transcription by binding DNA methylated at CpG dinucleotides [129] and translation via direct interaction with RNA [130].

Several RTT mouse models have been created, including *Mecp2*-null mice(*Mecp2*$^{y/-}$ [131]) and mouse lines with truncated versions of *Mecp2* (*Mecp2*$^{308/y}$ [132] and *Mecp2*$^{R168X/y}$ [133]).

Constitutive and brain specific *Mecp2*-null mice exhibit neurological symptoms including motor impairments and respiratory issues [131], a delayed onset reduction in brain and neuron size [134], and deficits in hippocampal- and amygdalar-dependent tasks [135]. In contrast, *Mecp2*$^{308/y}$ mice that express a truncated version of the gene have a more mild and mixed phenotype. These mice exhibit a progressive decline in motor function, abnormal social behavior, and altered circadian activity patterns but perform normally in conditioned fear and Morris water maze tasks [132,136].

Studies in mouse models of RTT have revealed abnormalities that may be addressable with pharmacotherapy. RTT mouse models exhibit imbalances of inhibitory and excitatory activity, deficits in long-term plasticity, and abnormal spine anatomy [130]. *Mecp2*-null mice have reduced excitatory synaptic activity but no change in inhibitory synapses relative to wild-type mice in cultured hippocampal neurons [137] and layer V pyramidal cells in slice [138]. In contrast to studies in hippocampus and cortex, young *Mecp2*$^{y/-}$ mice have reduced GABAergic inhibition and increased excitation in the ventrolateral medulla [139]. Overexpression of *Mecp2* increases excitatory activity and synapse number [140].

MeCP2 couples neural activity to gene regulation, a process required for synaptic plasticity. Neural activity causes Ca^{2+} influx that drives phosphorylation of MeCP2 and releases transcriptional repression [141]. Consistent with this role, deficits have been observed in LTD and LTP in the hippocampus [142,143] and cortex [143]. In contrast, overexpression of *Mecp2* enhances plasticity in the hippocampus [144].

Deficits in *Mecp2* mutant mice are not purely neurodevelopmental, suggesting that drug therapy is possible in adults with RTT. The phenotype of *Mecp2* mutant mice can be rescued by introducing a wild-type copy of *Mecp2* in neurons [145,146] (but see [147] in which introduction of *Mecp2* into neurons failed to rescue the RTT phenotype) or inducing expression of functional *Mecp2* in young [148] or adult mice [149]. Unfortunately, such genetic manipulations are not transferable to humans. Moreover, therapies in humans will need to target downstream targets of *MECP2*, because *MECP2* gene dosage must be carefully regulated for proper brain function [131,134,144,146]. One such strategy increased lifespan and improved locomotion, breathing, and heart rate in *Mecp2*$^{y/-}$ mice with an active peptide fragment of the neurotrophic factor insulin-like growth factor 1 (IGF-1) [150]. IGF-1 is approved for the treatment of severe IGF-1 deficiency (mecasermin or Increlex™, Tercica, Brisbane, CA).

To date, therapeutic strategies for RTT have focused on mitigating specific symptoms. One strategy addresses heightened anxiety and stress in individuals with RTT [151]. *Mecp2*$^{y/-}$ mice over-express genes involved in glucocorticoid-mediated stress responses [152], and *Mecp2*$^{308/y}$ mice have high levels of corticotropin-releasing hormone (Crh) expression, enhanced stress responses, and elevated anxiety [153]. Crh receptor 1antagonists may improve these symptoms [130].

A second therapeutic strategy is focused on respiratory deficits in RTT. Cell-autonomous reductions in aminergic neurotransmitter levels due to *Mecp2* dysfunction occur in RTT individuals [154] and *Mecp2*$^{-/y}$ mice [155]. Moreover, reduced norepinephrine levels cause abnormal respiratory rhythms that are a common cause of mortality [155]. Desipramine (Norpramine™ or Pertofane™, Sanofi-Aventis, Paris, France), a norepinephrine reuptake inhibitor, improves respiration and extends lifespan in *Mecp2*-deficient mice [156,157]. A clinical trial using desipramine for RTT is underway. Another strategy improved respiratory function in *Mecp2*-null mice with an ampakine drug that increases excitatory activity via glutamatergic AMPA receptors and enhances BDNF secretion [158]. A third category of clinical development is targeting EEG abnormalities with dextromethorphan, an antagonist of NMDA receptors available as a component of over-the-counter cough suppressants.

Neurofibromatosis type 1

Neurofibromatosis type 1 (NF-1) is an autosomal dominant neurocutaneous disorder with a prevalence of approximately 1/2500–5000 [159]. NF-1 is caused by a mutation that inactivates the gene *NF1* [160], and *de novo* germline mutations are common [161]. In addition to a number of cutaneous abnormalities, individuals with NF-1 have IQs across a broad range with mean IQs in the low-average range [162]. Individuals with NF-1 express relative deficits in visual-spatial and visual-motor tasks, language, and executive function, and exhibit ADHD behavior and poor socialization [163,164].

NF1 encodes a protein, neurofibromin, that is highly expressed in the brain [165] and skin [166]. Neurofibromin is a Ras GTPase Activating Protein (RasGAP) that suppresses tumor formation and inhibits protein translation via the mammalian target of rapamycin (mTOR) pathway [167] (Fig. 2E). In the absence of neurofibromin, Ras is overactive and drives abnormal cell proliferation [168]. Neurofibromin also enhances the adenylyl-cyclase/cyclic AMP (AC/cAMP) pathway that couples neural activity to memory formation [169]. Both Ras and cAMP pathways are promising therapeutic targets for NF-1 based on studies in transgenic mouse and fly models.

In the absence of *NF1*, cAMP activity is reduced, causing reduced growth and memory impairment [169–171]. The small size phenotype of $Nf1^{-/-}$ flies can be rescued by cAMP activity [170], cAMP analogs [169], or the human *NF1* transgene [171]. Size rescue occurs in adult flies with inducible knockout of *Nf1*, confirming that the effect is not purely developmental [169,170]. Moreover, learning and memory processes mediated by the *Nf1*-dependent component of the AC/cAMP pathway are required for olfactory learning in *Drosophila* [172].

The RasGAP activity of neurofibromin and its role in inhibiting mTOR activation is an alternative pathway for drug therapy. $Nf1^{+/-}$ heterozygous mice have mild learning deficits in some tasks [168,173] and enhanced astrocyte proliferation but do not develop neurofibromas [174,175]. Homozygous deletion of *Nf1* exon 23a, which is responsible for RasGAP activity, caused learning deficits [176]. Moreover, spatial learning deficits in $Nf1^{+/-}$ mice can be rescued by crossing with $K\text{-}ras^{+/-}$ mice to reduce Ras pathway activity [177]. Enhanced Ras activity in $Nf1^{+/-}$ mice causes excess inhibition and LTP deficits in the hippocampus [177] that can be resolved by systemic application of picrotoxin, a broad-acting $GABA_A$ antagonist [178]. Thus, $GABA_A$ receptor antagonism is a potential therapeutic strategy for NF-1 based on reducing excessive inhibitory tone. Studies of neurofibromin RasGAP function suggest an additional therapeutic pathway but contrast with fly studies that showed learning deficits due to reduced AC/cAMP activity.

Drug therapies designed to reduce aberrant increased Ras/ERK signaling are in clinical development to address cognitive deficits in NF-1 [6]. The farnesyl-transferase inhibitor BMS 191563 (Bristol-Myers Squibb, New York, NY), rescues memory deficits in $Nf1^{+/-}$ mice by blocking post-translational modification of Ras [177]. Similarly, lovastatin (Altoprev™, Shionogi Pharma, Atlanta, GA and Mevacor™, Merck, Whitehouse Station, NJ), approved to treat hypercholesterolemia, reduces Ras pathway activation by inhibiting three-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase function and rescued plasticity and learning deficits in $Nf1^{+/-}$ mice [179]. A clinical trial with lovastatin (Altoprev™, Shionogi Pharma, Atlanta, GA and Mevacor™, Merck, Whitehouse Station, NJ), is being conducted in individuals with NF-1. Of note, there were no significant differences between treatment groups in a placebo-controlled three month trial in children with NF-1 using the lipophilic HMG-CoA reductase inhibitor simvastatin (Zocor™, Merck, Whitehouse Station, NJ) [180]. More work is required to determine if inhibitors of Ras activity will be effective in humans with NF-1. Rapamycin (Rapamune™ or sirolimus, Wyeth, Madison, NJ), an inhibitor of mTOR, a downstream component of the Ras-mediated translation activation pathway, has shown

promise in mouse models [181] and is approved as an immune suppressant for organ transplant and as a component in coronary stents(Fig. 2F).

Tuberous sclerosis

Tuberous sclerosis (TS) is an autosomal dominant disorder caused by a loss of function mutation in either *TSC1* [182] or *TSC2* [183]. The TS birth rate is ~1/6000 [184], and approximately two-thirds of cases result from a *de novo* mutation [185]. Individuals with TS develop benign growths called hamartomas in various organs [186] with CNS pathology of tubers, giant-cell tumors, and abnormal white matter [187]. Individuals with TS have deficits in memory, attention, and executive control [188,189] with frequent diagnoses of autism, attention deficit hyperactivity disorder, and sleep disorders [190]. Some individuals with TS are severely disabled (30–40 IQ) while others maintain a sub-average normal IQ [191]. Variability of cognitive function depends on the intensity of seizures during infancy [186,191] and the location of cortical tubers [192,193].

The proteins encoded by *TSC1* and *TSC2*, hamartin and tuberin, form a heterodimer that interacts with dozens of gene products [194,195] to affect protein translation, cell proliferation, and synaptic plasticity [195,196]. The complex functions as a GTPase activating protein (GAP) that reduces stimulation of the mammalian target of rapamycin (mTOR) pathway [197–199] (Fig. 2E). Inactivation of the *Tsc1/2* complex in *Drosophila* drives abnormal cell growth and proliferation via the mTOR pathway [200,201] or insulin signaling [202].

Mice with conditional knockout (CKO) of *Tsc1* mimic the loss-of-heterozygosity observed in hamartomas in some tissues in humans with TS, but these animals tend to have severe behavioral abnormalities [194]. Neuron-, forebrain-, and glia-specific CKO mice exhibit hyperexcitability, impaired hippocampal LTP, and memory deficits [203–207]. The severity of dysfunction in cells with no copies of *Tsc1* relative to heterozygous animals underscores the importance of gene dosage and loss-of-heterozygosity due to second hit mutations in TS.

Some cognitive deficits in TS mice are independent of developmental abnormalities, localized pathology, or seizures. Thus, the hamartin-tuberin complex plays a role in neural circuit dysfunction that may be addressable with pharmacotherapy [194]. Both $Tsc1^{+/-}$ and $Tsc2^{+/-}$ mice exhibit hippocampal-dependent learning deficits in the absence of pathology or seizures [203, 208]. Effects of *Tsc1/2* inactivation on synaptic plasticity appear more complex. $Tsc2^{+/-}$ mice have a reduced threshold for the late-phase of LTP in the hippocampus that requires protein translation [203]. Heterozygous “Eker rat” spontaneous *Tsc2* mutants have reduced LTP and LTD relative to wild type rats [209]. Young adult $Tsc2^{+/-}$ Eker rats are free of hamartomas and epilepsy yet exhibit a phenotype of enhanced long-term spatial memory, increased susceptibility to chemical kindling, and stronger cyclic AMP signaling [210].

Several drug therapies for TS are available or in clinical trials. Control of infantile spasms with currently approved drugs is an effective therapeutic strategy to reduce the likelihood of severe intellectual disability in individuals with TS. Vigabatrin (Sabril™, Lundbeck, Copenhagen, Denmark) is an approved inhibitor of GABA catabolism that resolves 80–100% of spasms in individuals with TS [211,212]. The approved anti-epileptic drug, levetiracetam (Keppra™, UCB Pharmaceuticals, Brussels, Belgium), is an effective secondary therapy for seizures in children and adolescents with TS [213].

The mTOR inhibitor, rapamycin (Rapamune™ or sirolimus, Wyeth, Madison, NJ), is a promising candidate for TS therapy that is approved in the US for organ rejection and coronary stents [214] (Fig. 2F). Studies in rodents support the efficacy of rapamycin for improving brain function and reducing tumor size in TS. Rapamycin rescues hippocampal learning deficits, abnormal LTP threshold, development abnormalities, and seizures [203,215]. Topical rapamycin improves survival [216] and reduces skin cancer growth in mice [217], and rapamycin therapy

prolongs survival by inhibiting tumor progression in the Eker rat [218]. Clinical trials are underway to test rapamycin in individuals with TS. Other mTOR inhibitors under development offer promise for TS, including the approved drugs CCI-779 (Torisel™ or temsirolimus, Wyeth, Madison, NJ), and RAD001 (Certican™, Afinitor™, or everolimus, Novartis, Basel, Switzerland) [219]. Exogenous interferon-gamma (IFN-γ) is an additional potential therapy based on promising mouse studies [219,220]. Intriguingly, in humans, a high-expressing IFN-γ allele corresponds to reduced disease severity [221].

Autism spectrum disorders

Autism spectrum disorders (ASD) are heterogeneous and include autistic disorder, Asperger syndrome, and pervasive developmental disorder-not otherwise specified (PDD-nos). ASD are diagnosed behaviorally on the basis of socialization deficits, impaired language and communication, and repetitive or restricted behaviors that generally present by age 3 (Diagnostic and Statistical Manual of Mental Disorders. 4th edition). A subset of children with autism have larger head circumference and total brain volume [222,223], and additional anatomical abnormalities are common, including an excess of local connectivity in the cerebral cortex and reduced long-distance cortico-cortical projections [224]. The prevalence of ASD has increased markedly in the last two decades with an estimated prevalence in the US of ~1/150 and higher rates of diagnosis in boys [225].

Currently, most cases of ASD are idiopathic, although a significant minority of cases is genetic in origin [226]. Twin and sibling studies observed high concordance rates indicating that ASD are highly heritable [227]. Monogenic causes–including those discussed above for Rett syndrome, fragile X, neurofibromatosis type 1, and tuberous sclerosis–are rare. Most ASD cases have polygenic causes with complex gene-gene [228–230] and gene-environment [231,232] relationships. Linkage analysis studies have identified autism susceptibility loci on most chromosomes [228, 233]. Microdeletions and microduplications cause copy number variation of genes in these regions that predispose to autism [226]. A comprehensive review of genetic associations with autism and the dozens of relevant mouse models is beyond the scope of this review [230,234–237]. Rather, we will discuss animal models for genes and pathways that have received recent attention in translational research.

Consistent with heterogeneous genetic and behavioral factors in ASD, several mechanisms of dysfunction have been identified: imbalanced excitation and inhibition, enhanced local neuronal connectivity, and abnormal levels of modulatory neurotransmitters such as serotonin [238]. The dozens of genes with potential links to ASD play roles in neurodevelopment and synaptic function. Putative autism genes include protein complexes that interact with the actin cytoskeleton at postsynaptic densities and mediate translation at synapses, including the genes *NF1* and *TSC1/2* that cause NF-1 and TS [229,235].

Postsynaptic neuroligins and presynaptic neurexins are cell-adhesion molecules that form a trans-synaptic signaling complex required for synapse formation and stability *in vitro* [239] and normal synaptic maturation and function *in vivo* [240,241]. Linkage studies in man [228,242–244] and neurobiological studies in mice [237,240,241] confirmed the role of this complex in some cases of autism. Neuroligins and neurexins interact with synaptic scaffolding proteins [241]. The neuroligin-neurexin complex promotes the formation of synapses that are subsequently pruned in an activity-dependent manner [240]. This function is consistent with abnormal brain growth in autism, and mutations in neurexin-1, neuroligin-3, and neuroligin-4 are associated with ASD [241]. Moreover, studies in mice with knockout of one or more neuroligin or neurexin support a role of these proteins in synapse maturation and function [237]. Neuroligin-1 and neuroligin-2 enhance post-synaptic currents at excitatory [245] and inhibitory synapses [246], respectively, and set the balance of excitation and inhibition in neural circuits [247–250]. Knockout mice for various

mouse orthologs of neuroligin have deficits in synaptic plasticity [251,252], spatial learning [251], vocalization, grooming, and some social behaviors [253].

ASD linkage studies identified additional genes that interact with neuroligins. SHANK3 (also known as ProSAP2) binds to the cytoskeleton and proteins, including neuroligins, at synapses [254]. As a key organizer of the postsynaptic density, it is not surprising that *SHANK3/ProSAP2* mutations have been identified in a small number of ASD individuals [255–257]. Moreover, *Shank1* knockout mice exhibit altered dendritic spine and synapse structure, weak synaptic transmission, anxiety, and impaired contextual fear memory [258]. The neurexin family gene Contactin Associated Protein-Like 2 (*CNTNAP2*) also associates with autism in linkage studies [259]. In summary, neuroligins and neurexins appear to play a central role in dysfunction associated with autism and drugs to target this complex and related pathways represent a potential therapeutic strategy.

Another therapeutic strategy targets the serotonergic system [260]. The serotonin transporter (5-HTT, *SLC6A4*) is associated with rigid-compulsive variants of autism [261,262], and circulating levels of serotonin are high in some individuals with ASD [263]. The melatonin production pathway begins with serotonin, and individuals with ASD exhibit both abnormal melatonin levels and sleep disturbances [264]. Drugs that target the serotonergic system may help children with ASD. However, clinical trials with SSRI antidepressants have had mixed results [265].

Various psychotropic drugs are prescribed to mitigate symptoms of ASD. Prescribed drugs include stimulants, antidepressants, adrenergic agonists, antipsychotics, antiepileptics, and drugs approved for Alzheimer's disease [266,267]. Two atypical antipsychotic drugs are FDA approved for irritability associated with autism: risperidone [268] (Risperdal™, Janssen Pharmaceutica, Beerse, Belgium) and aripiprazole [269] (Abilify™, Bristol-Myers Squibb, New York, NY and Otsuka America Pharmaceutical, Inc., Rockville, MD). Clinical development efforts for monogenic forms of autism, including Rett syndrome, fragile X syndrome, and tuberous sclerosis, may have benefits for some individuals with idiopathic autism. Additional clinical research is required to determine whether these drugs are safe and efficacious for some or all individuals with ASD.

CONCLUSION

Factors that affect amenability of pharmacotherapy

Several factors influence the potential for successful pharmacotherapy for neurodevelopmental disorders (NDDs). For instance, in some cases, effective therapy may require drugs to be given beginning in infants or young children, as is the case for phenylketonuria [1]. To do so requires timely diagnosis. Diseases with a simple form of inheritance and low rates of *de novo* mutations are easier to diagnosis prenatally or perinatally based on family history and genetic testing. The genes responsible for neurofibromatosis type 1 (NF-1) and tuberous sclerosis (TS) exhibit among the highest recorded rates of *de novo* mutations [161,185]. Children with these disorders generally do not have a family history of disease, and overt disease symptoms occur later in childhood or adolescence. If pharmacotherapies are developed that require early intervention, such as antiepileptics for infantile seizures [191], more widespread genetic testing for early diagnosis will be required.

The nature of genetic insult responsible for a particular NDD affects the ease with which a disease can be recreated in an animal model, characterized biologically, and addressed therapeutically. NDDs caused by monogenic disorders are generally easier to understand mechanistically and thus easier to treat. Monogenic disorders such as FXS and Rett syndrome (RTT) permit concentrated study of *FMR1* and *MECP2* genes, respectively. However, epigenetic factors may have a larger impact in man than for inbred mouse strains. Disorders

such as Down syndrome (DS) or autism in which many genes are affected require a more holistic approach for study and treatment due to the potential for complex interactions between numerous gene products.

The consistency of genetic mutation across tissues also affects the ease of translational research in animal models of NDDs. For animal studies that require comparison among a large number of animals for statistical power, random X chromosome inactivation (XCI) is unacceptable. Studies of animal models of FXS and RTT generally use males to ease comparison across subjects [270,271]. RTT occurs most commonly in females [66,118], so mouse studies must be considered with this caveat in mind.

A second consideration concerns the propensity for second-hit mutations that underlie hamartoma formation in TS and NF-1. Second hit mutations occur randomly, and the exact size, distribution, and developmental time-point of these mutations influence disease presentation. Mouse models of these disorders have used inducible and cell-type specific genetic constructs to consistently reproduce mutations in time and tissue. While this aids in comparison across subjects, any therapies developed for use in man must consider variability caused by second-hit mutations.

Pharmacotherapies that target disrupted equilibrium of neurotransmitter systems offer promise for NDDs. Drugs that counteract such imbalances affect ongoing neural circuit dynamics rather than established gross anatomical abnormalities. Therapeutic strategies in this category include GABA antagonists for DS [35] and NF-1 [178], mGluR antagonists for FXS [98], and norepinephrine reuptake inhibitors for RTT [156,157]. Functional homeostatic mechanisms may contribute to the rebalancing of neurotransmitter function after drug therapy [35].

Different therapeutic strategies for NDDs may be required at different stages of life. For example, infantile spasms in DS and TS are treated with antiepileptics [193,272]. If these treatments are unsuccessful, homeostatic mechanisms can be recruited that enhance inhibition to counteract the excitability responsible for spasms and lead to memory deficits [30,31]. Once neural circuits have stabilized with enhanced inhibition, drugs that reduce inhibition are more appropriate therapeutically [35]. As more is learned about the time-course of dysfunction in NDDs, targeting of therapies to the existing brain state may be improved. Moreover, individuals with NDDs have multiple cognitive and behavioral disabilities, and a particular drug therapy may improve only a subset of cognitive functions. Thus, a combination of complementary drugs may offer the most benefit by addressing deficits in attention, arousal, information processing, or depression.

Common mechanisms and therapeutic targets

The NDDs discussed here are phenotypically diverse yet linked by common mechanisms of dysfunction, including abnormal gene dosage, imbalance among neurotransmitter systems, and local protein translation (Fig. 2). A particular NDD can be caused by mutations in multiple genes, underscoring the convergence of dysfunction in key biochemical pathways.

Imbalances between excitatory and inhibitory networks are present in NDDs, as well as other psychiatric and neurodegenerative disorders (Fig 2A–B). Inhibitory networks dominate in DS [35], RTT [138,139] and NF-1 [173], while overexcitation occurs in FXS [98,273] and TS [274]. Moreover, imbalances of excitation and inhibition can shift during development. In DS and TS, infantile spasms are common, while inhibition dominates later in development. However, similar homeostatic mechanisms can be recruited in adult mice to rebalance circuit excitability [3]. Neurotransmitters such as norepinephrine, acetylcholine, and serotonin can modify the balance and effect of inhibition and excitation. Drugs that target these systems represent alternatives for resolving imbalances.

Altered gene dosage is a common theme in NDDs(Fig. 2C–D). Hundreds of genes are triplicated in DS [20], and microdeletions or microduplications of regions on a number of chromosomes affects susceptibility to autism [226]. Such copy number variation can increase or decrease the expression of genes, often in an unexpected or nonlinear fashion due to gene-gene interactions. For instance, many genes triplicated in DS are expressed at levels above or below the predicted 1.5-fold overexpression [23]. In NF-1 and TS, a single copy of a mutant gene appears to be insufficient to produce hamartoma growth, which requires loss-of-heterozygosity due to a second hit somatic mutation [8,275].

Abnormal translation of proteins near synapses is a third common cause of dysfunction in NDDs (Fig. 2E–H). Altered translation can cause abnormal cell proliferation, dendritic spine anatomy, and synaptic plasticity. For instance, fragile X mental retardation protein (FMRP) normally inhibits protein translation, so reduced FMRP function causes excessive translation responsible for enhanced plasticity in mouse models of FXS [276] (Fig. 2G–H). Similarly, loss-of-function of MeCP2 in RTT reduces activity-dependent local translation responsible for long-term plasticity [130]. Genes mutated in NF-1, TS, and some forms of autism affect translation, such as via the mammalian target of rapamycin (mTOR) cell proliferation pathway [8,274] (Fig. 2E–F). Thus, therapeutic strategies that recover normal levels of translation under appropriate circumstances are promising for several NDDs.

Translational cycle future directions

Discoveries about the molecular, genetic, anatomic, and neurophysiological mechanisms underlying NDDs have increased substantially in recent years. As our understanding of the neurobiology of NDDs grows, so does the spectrum of viable clinical strategies. NDDs reduce learning abilities during a period rich in intellectual, social, and emotional development, so even small improvements in cognitive function could provide significant benefits. There is still much more to learn about NDDs through each stage of the translational cycle. However, recent research findings suggest that new, effective, and principled therapies are possible for NDDs. Designing and executing clinical trials to test therapies will require significant effort and resources from government, philanthropic foundations, academic institutions, and the pharmaceutical and biotechnology industry. The repeated finding that cognitive function can be improved in adult animals in animal models of NDDs suggests that pharmacotherapies may help individuals with NDDs throughout their lives.

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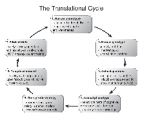

Figure 1. The Translational Cycle describes key events in the development of drug therapies for neurodevelopmental disorders (NDDs)

Characterization of the phenotype (1) and genotype (2) of an NDD in humans forms the basis for neuroscientific study. Creation of animal models based on the genetic causes of disease in humans (3) permits investigation of molecular, cellular, neurophysiological, and behavioral pathophysiology in mice, flies, or other organisms (4). Therapeutic strategies to address dysfunction in animal models (5) identify promising directions for drug development (6) and clinical trials (7) that quantify efficacy with endpoints that probe cognition, behavior, and quality-of-life. The primary goal of the Translational Cycle is to address the human phenotype (1). Abbreviations: X chromosome inactivation (XCI); pharmacokinetics (PK); neurodevelopmental disorder (NDD).

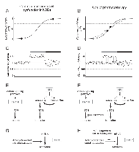

Figure 2. Neurodevelopmental disorders (NDDs) share common mechanisms of dysfunction amenable to similar therapeutic strategies

A: Imbalanced excitation and inhibition within neuronal circuits occurs in a number of NDDs. Schematic representation of excitatory-inhibitory ratio shows pathophysiologically high (black circle, upper right) or low (black circle, bottom left) levels that exceed a theoretical window of balanced activity (between horizontal dashed lines). Note near balanced ratios are essential for normal circuit and cognitive function. **B:** Pharmacotherapy to address excitatory-inhibitory imbalance modifies neural circuits to achieve a level of activity that supports normal brain function (black circles, center). **C:** Abnormal gene dosage underlies dysfunction in many NDDs. Schematic representation of expression for several dozen genes under conditions of normal expression (left, under open rectangle), increased gene dosage for a number of genes as expected to occur in Down syndrome (center, under grey rectangle), and pseudo-realistic variability caused by gene-gene interactions and other factors (right, under black rectangle). **D:** Pharmacotherapy to address abnormal gene dosage may achieve normalization of altered transcript levels (center and right, under grey and black rectangles, open circles with grey lines to indicate pre-treatment expression). Improved cognitive function may occur without modifying expression of some genes (black circles). **E:** Dysregulated control of protein translation at synapses occurs in several NDDs. In tuberous sclerosis (TS), loss-of-function of the TSC1/2complex reduces inhibition of mTOR and leads to high levels of protein translation (left). Similarly, loss-of-function of NF1 drives increased translation via reduced inactivation of Ras in neurofibromatosis type 1 (NF-1) (right). **F:** In both TS and NF-1, drugs that inhibit mTOR-mediated inhibition such as rapamycin (Rapamune™ or sirolimus, Wyeth, Madison, NJ) are used to reduce translation to normal levels. **G:** In fragile X syndrome (FXS) activity-dependent signaling cascades drive translation at the synapse that is normally controlled by negative feedback from fragile X mental retardation protein (FMRP). **H:** Potential therapeutic strategies for FXS may suppress activity-dependent signals to restore normal control of translation in the absence of FMRP. In panels **E–H**, arrows and T-bars indicate activation and inhibition of signaling pathways, respectively, arrow and T-bar thickness represent the strength of activation or inhibition, and boxed grey text corresponds to genes absent or mutated in specific NDDs. For brevity, many components of signaling cascades have been excluded. Moreover, it should be noted that Ras, mTOR, FMRP and mGluR signaling are not independent from each other, further supporting the concept that seemingly distinct genetic lesions in NDDs converge on critical regulatory pathways to alter synaptic, circuit and cognitive function. Abbreviations: mammalian target of rapamycin (mTOR); tuberous sclerosis gene products tuberin and hamartin (TSC1/2); neurofibromatosis type 1 gene product neurofibromin (NF1); group 1 metabotropic glutamate receptor (mGluR); GABA receptor (GABAR).