The promising trajectory of autism therapeutics discovery

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Pharmacological interventions for neurodevelopmental disorders are increasingly tractable. Autism is a neurodevelopmental disorder that affects approximately 1% of the population. Currently, the standard of care is early behavioral therapy. No approved medical treatments for the diagnostic symptoms are available. Strong evidence for genetic causes of autism implicates proteins that mediate synaptic transmission and structure. Mouse models with targeted mutations in these synaptic genes display behavioral symptoms relevant to the social communication abnormalities and repetitive behaviors that define autism spectrum disorder (ASD), along with biological abnormalities in synaptic physiology and morphology. As we discuss here, promising pharmacological targets, emerging from the mouse model studies, are now being pursued in early clinical trials. Thus, a high-prevalence disorder that was previously considered to be medically untreatable is now moving into the therapeutic arena.

Neurodevelopmental disorders were historically viewed as intractable to pharmacological interventions. The assumption was that abnormalities in brain development began prenatally, and were irreversible by the age of diagnosis. Recent discoveries implicate multiple genes in the causes of autism and related neurodevelopmental disorders. Many of these genes encode synaptic proteins that regulate the formation, maturation and strengthening of synaptic connections between neurons. Several genes encode neurotransmitter receptors that mediate excitatory and inhibitory synaptic transmission. Given that synaptic processes are ongoing in real time, synaptic transmission can be modified at any age and disease stage by available or novel pharmacological agents. New strategies focused on synaptic signaling targets indicate that compounds acting through signaling mechanisms could lead to efficacious pharmacotherapies for the diagnostic symptoms of autism.

Genetic advances
Single gene mutations are responsible for many neurodevelopmental disorders [1]. Fragile X syndrome, the major genetic cause of intellectual impairment, is produced by an expansion mutation in Fragile X mental retardation 1 (FMR1). The mutation causes loss of function of the translational repressor protein, Fem1, the Fragile X mental retardation protein. Rett syndrome is caused by a mutation in the gene encoding methyl-CpG-binding protein 2 (MECP2), which binds to methylated DNA and represses transcription. Tuberous sclerosis is caused by a mutation in a tumor suppressor gene, tuberous sclerosis (TSC), which regulates the mammalian target of rapamycin (mTOR) signaling. Many other examples of monogenic neurodevelopmental disorders with intellectual impairment are revealing biochemical mechanisms that appear to be amenable to therapeutic interventions derived from known mechanisms of action [2,3]. For example, increasing knowledge about the downstream proteins upregulated by the FMR1 mutation has led to the first clinical trials for Fragile X syndrome [4].

Autism is a particularly intriguing neurodevelopmental disorder, which is diagnosed uniquely and is often comorbid with other neurodevelopmental disorders. Autism is usually diagnosed when patients are 2–5 years old, based solely on two categories of behavioral symptoms: (i) persistent deficits in social interactions and social communication; and (ii) stereotyped and repetitive behaviors, with restricted interests and inflexibility [5]. Formally termed autism spectrum disorder (ASD), the syndrome encompasses considerable variability
Synaptic genes predict pharmacological targets for therapeutic interventions in autism. The synapse comprises the axon projecting from neuron 1, the dendrites extending from neuron 2 and the small spatial gap between axon and dendrite. Synapses form, mature and strengthen in response to activity-driven stimulation. Presynaptic neurexins, cadherins, contactin-associated proteins and other cell adhesion molecules bind to postsynaptic cell adhesion molecules, such as neurellins 1, 2, 3 and 4, to anchor the synapse. Neurotransmitters, such as glutamate, gamma-aminobutyric acid (GABA), serotonin, oxytocin and dopamine, are released from the axon terminal to cross the spatial gap. Receptors on the dendritic extension, such as the glutamatergic N-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and mGluRs, bind the neurotransmitter, initiating a cascade of postsynaptic events. Postsynaptic densities (PSD) thicken with newly synthesized proteins, forming a cytoarchitectural scaffold of proteins including SH3 and multiple ankyrin repeat domains (Shank) 1, 2 and 3. Downstream signaling molecules, such as phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinases (MAPK), extracellular signal-regulated kinases (ERK), phosphatase and tensin homolog (Pten), tuberous sclerosis (TSC) and mammalian target of rapamycin (mTOR), initiate biochemical events in neuron 2, to convert the activity-driven neurotransmitter signals emitted by neuron 1 into action events within neuron 2. Fragile X mental retardation protein (Fmr1) is a negative regulator of translation, inhibiting the synthesis of multiple downstream signaling proteins. Mutations in the genes encoding many of these synaptic elements in patients with autism and related neurodevelopmental disorders suggest therapeutics targets with known mechanisms of action. Existing compounds acting at these targets, including neurotransmitter receptors, allosteric receptor modulators, signaling elements and translation modifiers, offer repurposing opportunities to discover effective treatments for autism spectrum disorder.

FIGURE 1
Synaptic genes predict pharmacological targets for therapeutic interventions in autism.
TABLE 1
Examples of compounds under consideration for the treatment of ASD<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Mechanistic class</th>
<th>Compound</th>
<th>Phenotypes in mouse models, to evaluate treatment responses</th>
<th>Clinical indication and trial status</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine receptor antagonists</strong></td>
<td>Risperidone (Risperdal)</td>
<td><em>Fmr1</em>: sociability, protein synthesis, synaptic plasticity, cognition, seizures, hyperactivity, sensory gating and spine morphology</td>
<td>Autism: irritability, aggression and self-injury; FDA approved</td>
<td>[6]</td>
</tr>
<tr>
<td></td>
<td>Aripiprazole (Abilify)</td>
<td></td>
<td></td>
<td>[7,8]</td>
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<tr>
<td><strong>mGluR receptor-negative allosteric modulators</strong></td>
<td>AFQ056 (Mavogluant)</td>
<td><em>Shank2</em>: sociability</td>
<td>Fragile X syndrome: phase II and III clinical trials</td>
<td>[35,36]</td>
</tr>
<tr>
<td></td>
<td>CDPPB</td>
<td><em>Fmr1</em>: seizures, protein synthesis, synaptic plasticity, cognition, auditory sensitivity, spine morphology and activation patterns</td>
<td></td>
<td>[13]</td>
</tr>
<tr>
<td></td>
<td>CTEP</td>
<td><em>Fmr1</em>: seizures, hyperactivity, sensory gating, spine morphology and activation patterns</td>
<td></td>
<td>[20,34]</td>
</tr>
<tr>
<td></td>
<td>Fenobam</td>
<td><em>Fmr1</em>: spine morphology</td>
<td>Fragile X syndrome: open label trial</td>
<td>[4,19]</td>
</tr>
<tr>
<td></td>
<td>GRNS29</td>
<td>BTBR and CS8/J: repetitive behavior and sociability</td>
<td></td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td>JNJ16259685</td>
<td><em>Fmr1</em>: repetitive behavior</td>
<td></td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>MPEP</td>
<td><em>Fmr1</em>: seizures, hyperactivity, sensory gating, spine morphology and activation patterns</td>
<td></td>
<td>[18,19,24,32,33]</td>
</tr>
<tr>
<td></td>
<td>MTEP</td>
<td>BTBR: repetitive behavior</td>
<td>Fragile X syndrome: phase II clinical trials</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td>RO4917523 (NCT01474278, NCT01517698)</td>
<td>BTBR: repetitive behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NMDA glutamate modulation</strong></td>
<td>Memantine hydrochloride (Namenda)</td>
<td><em>Fmr1</em>: spine morphology</td>
<td>Fragile X syndrome: open label trial</td>
<td>[21,39]</td>
</tr>
<tr>
<td></td>
<td>d-Cycloserine</td>
<td><em>Shank2</em>: sociability</td>
<td>Autism: phase II clinical trials</td>
<td>[13]</td>
</tr>
<tr>
<td><strong>AMPA glutamate modulation</strong></td>
<td>CX546</td>
<td><em>Mecp2</em>: respiration</td>
<td></td>
<td>[26]</td>
</tr>
<tr>
<td></td>
<td>CX546, CX1837 and CX1739</td>
<td>BTBR: sociability and cognition</td>
<td></td>
<td>[37]</td>
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<tr>
<td></td>
<td>CX516 (Ampalex)</td>
<td>Briquet et al. (2014)</td>
<td>Autism and Fragile X syndrome: phase II clinical trial completed and closed</td>
<td>[38]</td>
</tr>
<tr>
<td><strong>GABA&lt;sub&gt;α&lt;/sub&gt; activation</strong></td>
<td>STX209 (Arbaclofen)</td>
<td><em>Fmr1</em>: protein synthesis, seizures and spine density</td>
<td>Fragile X syndrome and Autism: phase II and III clinical trials</td>
<td>[14,40]</td>
</tr>
<tr>
<td><strong>mTOR inhibitors</strong></td>
<td>Rapamycin (Sirolimus)</td>
<td><em>Pten</em>: macrocephaly, neuronal morphology, sociability and seizures</td>
<td>Tuberous sclerosis and Autism: phase II and III clinical trials</td>
<td>[15,27, 41–43]</td>
</tr>
<tr>
<td></td>
<td>RAD001 (Everolimus)</td>
<td><em>Tsc1</em>: survival rates, seizures, EEG, cognition and sociability</td>
<td></td>
<td>[43]</td>
</tr>
<tr>
<td><strong>Serotonin reuptake inhibitors</strong></td>
<td>Fluoxetine (Prozac)</td>
<td>BTBR: sociability</td>
<td>Autism: controlled trials completed and ongoing; FDA approved for pediatric use</td>
<td>[28,50]</td>
</tr>
<tr>
<td></td>
<td>Buspiron (Buspar)</td>
<td>BTBR: sociability</td>
<td></td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td>Citalopram (Celexa)</td>
<td></td>
<td></td>
<td>[53]</td>
</tr>
<tr>
<td><strong>Anti-inflammatory and Ras–Erk inhibition</strong></td>
<td>Lovastatin</td>
<td><em>NF1</em>: synaptic plasticity, cognition and attention</td>
<td>Neuropathogenesis: phase II clinical trials</td>
<td>[22,23]</td>
</tr>
<tr>
<td></td>
<td>Minocycline</td>
<td><em>Fmr1</em>: seizures and protein synthesis</td>
<td></td>
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</table>
domains (SHANK) 1, 2 and 3, Neuriligin (NLGN) 3 and 4, Neurexin (NRXN)-1, Contactin-associated protein-like (CNTNAP)-2 and Cadherin (CDH)-8 have been reported in individuals with autism. The SHANK family encodes scaffolding proteins that are integral to postsynaptic densities during synapse formation. Neuriligns and their neurexin binding partners, contactin-associated proteins and cadherins are cell adhesion molecules essential for connecting the presynaptic axon with the postsynaptic dendrite during synapse formation, maturation and strengthening. Point mutations and common genetic variants in the gamma-aminobutyric acid (GABA)-A receptor subunit β3, serotonin transporter, vasopressin 1a receptor and other components of synaptic transmission are associated with autism. Copy number variants, including deletions and duplications at chromosomal loci 7q11.13, 15q11–13, 16p11.2 and 22q13, appear in autism and in other neurodevelopmental disorders, such as Phelan–McDermid and Angelman syndromes. Genes within these loci include GABA receptor subunits, SHANK3, Ubiqutin 3A and signaling genes such as mitogen-activated protein kinase (MAPK) 3. Many of these proteins are constituents of activity-dependent signaling networks, which are modulated by experience and amenable to pharmacological manipulations. In addition, mutations associated with autism in genes regulating processes involved in brain development, including neurogenesis, the migration of neurons to cortical layers and the formation of long axon pathway connections, might be amenable to therapeutic interventions.

**Table 1 (Continued)**

<table>
<thead>
<tr>
<th>Mechanistic class</th>
<th>Compound</th>
<th>Phenotypes in mouse models, to evaluate treatment responses</th>
<th>Clinical indication and trial status</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Neuropeptide</td>
<td>Oxotocin</td>
<td>CS8/J: sociability * OT': social recognition * OTR': sociability, cognitive flexibility and seizure susceptibility</td>
<td>Autism: controlled trials complete and ongoing</td>
<td>[16,44–49]</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>OTR': sociability and cognitive flexibility</td>
<td>Autism: phase 1 clinical trials</td>
<td>[45,49]</td>
<td></td>
</tr>
</tbody>
</table>

* Examples illustrate the sequence of preclinical evaluation and clinical trials that are advancing the discovery of medical treatments for autism. Specific mechanistic classes of compound were identified from genetic studies of ASD and related neurodevelopmental disorders. Mutant lines of mice have been generated with targeted mutations in many of the homologous genes. Mouse phenotypes relevant to the diagnostic and associated behavioral symptoms of autism, and to the biological actions of the targeted genes, were evaluated using carefully defined behavioral and molecular assays. Strong phenotypic abnormalities were then used to evaluate several mechanistic targets. Promising proof-of-principle findings with compounds that effectively reversed phenotypes in the mouse models, taken together with clinical safety evidence and compelling hypotheses arising from the human genetics literature, led to the initiation of both open label and double-blind controlled clinical trials. Single gene mutation syndromes, such as Fragile X, Tuberous Sclerosis 1 and 2, and Neurofibromatosis 1 (NF1), which include a large percentage of patients also found to have autism, focused on defined populations for some of the first clinical investigations of potential therapeutics for ASD.

B Absence of a reference for a clinical trial indicates that the study is registered on clinicaltrials.gov but is currently unpublished.

First-generation drug targets

Several companies and academic investigators have begun the first clinical trials with various classes of compound, as described in Table 1. Strong evidence implicates the mGluR5 receptor in Fragile X syndrome. Mark Bear and co-workers at the Massachusetts Institute of Technology and Stephen Warren at Emory University discovered that Fmr1 inhibits the expression of approximately 100 other genes [17,30,31]. The Fmr1 mutation, which causes Fragile X syndrome, leads to overexpression of many of these proteins. One of the most highly investigated overexpressions is the glutamatergic mGluR5 receptor, which modulates excitatory neurotransmission. Breeding Fmr1-knockout mice with mGluRs-knockout mice rescued many of the aberrant phenotypes in the Fmr1 mutants. Based on these findings, prototypic mGluR5 receptor antagonists were tested in mouse models of Fragile X syndrome, with significant rescues reported [18,19,24,32,33]. Given that a high percentage of individuals with Fragile X syndrome meet the diagnostic criteria for autism, selective mGluR5 receptor antagonists and allosteric modulators were then tested in Fmr1 mutant mice and mouse models of autism [20,25,34]. Social abnormalities were reversed, and stereotyped and repetitive behaviors were reduced, in the Fmr1, BTRR, CS8 and Shanks2 mouse models [13,25,35]. Synaptic phenotypes were also rescued in the Fmr1 mouse model [36]. The first clinical trials of mGluRs compounds were conducted and are in progress for adolescents and adults with Fragile X syndrome. These include AFQ056 (Novartis, http://clinicaltrials.gov: NCT01443354, NCT01348087, NCT01253629, NCT01357239, NCT01482143, NCT00718341), Fenobam (FRAXA Research Foundation Consortium), and RO4917523 (Hoffman-LeRoche, http://clinicaltrials.gov: NCT01750957, NCT0117698).

A fundamental hypothesis in the autism literature focuses on dysregulation of the excitatory-inhibitory balance in the brain. This concept derives from the many electrophysiological and neuroanatomical studies in mouse models with mutations in risk genes for autism, which detected excessive glutamatergic excitatory neurotransmission, loss of inhibitory GABA interneurons, and/or impairments in synaptic plasticity, attributable to dysfunctions in the N-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and/or GABA receptor systems.
Pharmacological evidence emerged from mouse models with deletions in the synaptic genes Fmr1, Mecp2 and Shank2, and the BTBR inbred strain, which have shown beneficial results in some phenotypic domains from treatments with positive glutamatergic modulators, including d-cycloserine, amakipes and memantine hydrochloride [13,21,26,37]. Clinical studies of the AMPA-positive modulator, Ampalex (CX516), and Namenda (memantine hydrochloride), based on elevating glutamatergic neurotransmission, are of interest [38,39].

Seizures occur in approximately 30% of individuals with autism. This prevalence includes children with comorbid seizure disorders, such as tuberous sclerosis, chromosome 15q duplication syndrome (Dup15q), Angelman syndrome, Rett syndrome and Phelan–McDermid syndrome. Dialing down glutamatergic excitation, and/or elevating GABAergic inhibition, could normalize an excitatory–inhibitory imbalance. This attractive concept has been tested preclinically and clinically in Fragile X syndrome with the GABA-B agonist Arbaclofen [14,40]. In addition, the signaling pathway containing mTOR, which regulates cell proliferation in some cancers, lies downstream from risk genes implicated in autism, including Phosphatase and tensin homolog (PTEN) and TSC. Mouse models with mutations in these genes displayed pheno-typeic reversals after subchronic treatment with rapamycin [15,27,41–43]. Rapamycin has long been used to treat aspects of cancer. Rapamycin (Sirolimus) and its analogs (rapalogs), such as RAD001 (Everolimus) and Temsirolimus, are being repurposed in clinical trials to treat tuberous sclerosis and its associated autistic symptoms. By extension, rapalogs will be interesting to test directly in autism, particularly in cases that harbor mutations in PTEN and other genes upstream from mTOR. The first clinical trials with rapamycin compounds for tuberous sclerosis with associated autism are in progress (http://clinicaltrials.gov: NCT01730209, NCT01929642, NCT01289912).

Oxytocin is a neuropeptide in the brain that has been implicated in social affiliation in rodent studies [16,44,45], and in measures of social interaction and trust in human studies [46–48].

Although evidence for abnormalities in oxytocin or its receptor in autism is weak, the strategy of boosting levels of a neuropeptide that endogenously enhances social interactions is appealing. Peptides are quickly degraded by circulating peptidases, and cross the blood–brain barrier only minimally. An alternative workaround uses intranasal administration, to increase the first-pass concentration of peptide that reaches the brain. Intranasal oxytocin trials have produced beneficial effects in some reports, but no significant effects in others [46–49]. Given that oxytocin is readily available from nonpharmaceutical websites, off-label use is common, with variably positive anecdotal reports from parents. Nonapeptide compounds acting selectively at the oxytocin receptor present an attractive strategy for testing hypotheses about enhancement of social behaviors by oxytocin. Nearly 20 clinical trials are ongoing to evaluate oxytocin treatments in autism. Similarly, a new clinical trial by Hoffman-LaRoche is targeting vasoressin, a related neuropeptide system mediating social behaviors, with a vasopressin receptor antagonist RO5028442 (http://clinicaltrials.gov: NCT01474278, NCT01517698).

Novel therapeutic strategies have emerged from increasing knowledge of basic mechanisms and from the results of preclinical animal model studies. Table 1 describes current strategies that focus on: (i) serotonin reuptake inhibitors that might reduce repetitive behaviors, anxiety, depression, sleep disruption and other associated symptoms of autism, as well as potentially affecting brain development directly [28,29,50–53]; (ii) lovastatin [22,23] and (iii) minocycline [54–57], which are not only known for their anti-inflammatory and antibiotic actions, respectively, but also act on neuronal signaling pathways.

**Current caveats and future directions**

Preclinical findings from the mouse models literature suggest that treatments for ASD could include established and novel compounds acting through synaptic signaling mechanisms. Combining ongoing behavioral interventions with pharmacological medications could maximize synaptic synergy [58]. Similar to cancer, autism is grammatically described as a singular noun. In fact, the multiplicity of cancers arises from multiple biological and environmental causes. Proliferation is triggered by varying mechanisms. Treatments are diverse and increasingly tailored to subsets of molecular causes. Similarly, autism might be more correctly termed ‘autisms.’ Its heterogeneity of associated symptoms, variable severity of symptoms, comorbidities with other developmental disorders and range of implicated genes acting through different mechanisms, support the notion of a collection of related disorders. It may be possible to tailor pharmacological agents to the specific mutation identified in an individual with autism, using a personalized medicine strategy.

Animal models provide research tools to evaluate causal hypotheses and conduct preclinical pharmacological analyses. Robust mouse models further provide an opportunity to compare behavioral phenotypes with proposed biomarkers. Strong correlations between behavioral and biological abnormalities in robust rodent models could inform the choice of human biomarkers for ASD.

It is important to understand the strengths and the limitations of animal models. Findings in mice and rats suggest, but cannot definitively predict, human biomarkers and human drug responses. Limitations include species differences in compensatory genes, metabolic pathways and neuroanatomical substrates. In the case of autism, further limitations are inherent in the theoretical face validity of the behavioral assays selected for analogies to the specific types of social communication deficits, stereotyped and repetitive behaviors, insistence on sameness and restricted special interests that best characterize autism. In the current early stage of defining drug targets for neurodevelopmental disorders, proof of principle for reversal of phenotypic traits, including behavioral symptoms in a mouse model with genetic construct validity, contributes a useful first step. Positive findings of a drug rescue in a genetic mouse model serve primarily to increase confidence that a pharmacological target warrants further investigation.

One pressing need for therapeutic development is to select the most useful endpoint for clinical trials. The accepted diagnostic instruments, the Autism Diagnostic Observation Schedule paired with the Autism Diagnostic Interview, require many hours of scoring by highly trained clinicians, and include a large number of scored items. To surmount obstacles inherent in ADOS outcome measures, clinical trials for autism seek to identify symptom improvements with rating scales based on more circumscribed measures, including the Clinical Global Impression Scale, Aberrant Behavior Checklist and Vineland Adaptive Behavioral Scale. Results from these instruments present a double-edged sword by design. Minor benefits can be exaggerated, raising false hopes. Conversely, some trials have been discontinued owing to a lack of impressive, robust findings on the primary outcome measure. Thus, significant improvements on secondary endpoints could receive insufficient attention. Benefits for the subset of positively responding patients remain uncapitalized. Alternative rating scales with brief formats, and single endpoints that might be sufficient for evaluating specific therapeutic responses in stratified subgroups of individuals with autism, are under development for pharmacological clinical trials.

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A second pressing need is for biomarkers that are tightly coupled to the life history and progression of the core behavioral symptoms of ASD. Responses to therapeutics might be most effectively quantitated with biological measures, such as electroencephalogram theta activity, auditory processing time or morphological abnormalities in neurons grown from induced pluripotent stem cells derived from individuals with autism [59,60]. As mentioned above, rodent models can contribute to the early stage identification of meaningful biomarkers. Specific markers that replicate across repeated samples within an individual with autism, and are consistent across a large number of cases of autism, have been difficult to identify. The search for autism biomarkers is in its infancy, but recognized by all stakeholders as a high priority.

A third fundamental issue in clinical trials for autism is age at trial entry. Although parents often administer off-label drugs to their younger children with autism, ethical and medical considerations are likely to require that the first rigorous clinical trials to enroll adults and/or adolescents. Improvements in older adults, and at adolescent stages of development, might be considerably more difficult to detect, compared with longitudinal improvements when therapeutics begin at a younger age.

The promise of treating symptoms by treating mechanisms

Optimism is escalating for the discovery of medical interventions for many neurodevelopmental disorders, including autism. Cooperation among stakeholders is unprecedented. Public-private partnerships among federal, academic, pharmaceutical and family foundation supporters include The Foundation for NIH Biomarkers Consortium, the European Autism Intervention Innovative Medicines Initiative (EU-AIMS) and the Autism Speaks Preclinical Autism Consortium for Therapeutics (PACT). Given the preponderance of genes causing autism that act through known biochemical pathways at synaptic sites, the likelihood of identifying pharmacological interventions that improve core symptoms of autism is inspiring high. Given that synapses form, mature, strengthen and weaken in real time at all ages, neurodevelopmental syndromes caused by synaptic dysfunctions present remarkable new opportunities for efficacious medical interventions across the lifespan.

Acknowledgments

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