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Publication Date

2015

DOI

10.1007/7854_2015_5003

Peer reviewed

HHS Public Access

Author manuscript

Curr Top Behav Neurosci. Author manuscript; available in PMC 2016 November 21.

Published in final edited form as:

Curr Top Behav Neurosci. 2016 ; 28: 1–52. doi:10.1007/7854_2015_5003.

Translational Mouse Models of Autism: Advancing Toward Pharmacological Therapeutics

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Abstract

Animal models provide preclinical tools to investigate the causal role of genetic mutations and environmental factors in the etiology of autism spectrum disorder (ASD). Knockout and humanized knock-in mice, and more recently knockout rats, have been generated for many of the de novo single gene mutations and copy number variants (CNVs) detected in ASD and comorbid neurodevelopmental disorders. Mouse models incorporating genetic and environmental manipulations have been employed for preclinical testing of hypothesis-driven pharmacological targets, to begin to develop treatments for the diagnostic and associated symptoms of autism. In this review, we summarize rodent behavioral assays relevant to the core features of autism, preclinical and clinical evaluations of pharmacological interventions, and strategies to improve the translational value of rodent models of autism.

Keywords

Autism; Mice; Rats; Genes; Mutant models; Social behavior; Sociability; Repetitive behavior; Cognition; Ultrasonic vocalization; Pharmacological treatment; Mouse; Preclinical; Translational; Clinical trials; Face validity; Construct validity; Predictive validity

1 Introduction

Autism spectrum disorder (ASD) includes common, impairing neurodevelopmental disorders that are present from early childhood and occur in approximately 1 % of the population (Kim et al. 2011; Elsabbagh et al. 2012). To receive an ASD diagnosis, one must exhibit symptoms from two core domains: (1) social interaction and social communication; and (2) restricted repetitive patterns of behaviors, interests, and activities. (American Psychiatric Association 2013). Associated symptoms, appearing in varying percentages of individuals, include intellectual disability, executive dysfunction, anxiety, seizures, attention deficits and hyperactivity, hyper- and hyporeactivity to sensory stimuli, and sleep disruption. The current standard of care for children is early intensive behavioral intervention (Rogers et

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al. 2012; Lord and Jones 2013). Early intensive behavioral intervention is highly effective in teaching young children to overcome their social challenges, although it does not work for all, and its benefits wane with the appearance of age-related challenges in middle childhood and adolescence. Further, these behavior therapies are expensive and time-intensive, and not uniformly widely available. There is an unmet need for medical therapeutics that can be given in combination with a behavioral intervention or alone. No approved medical treatments exist for reducing or preventing the diagnostic symptoms of autism. Efficacious medications that effectively treat ASD symptoms, and specifically target social deficits, are currently under investigation.

The decision to use the term ASD in DSM-5 reflects the current thinking about the heterogeneous causes and clinical presentations of autism. A large number of de novo single gene mutations and copy number variants (CNVs) are associated with autism, each in a small number of individuals (Parikshak et al. 2013; Coe et al. 2014; Pinto et al. 2014). Environmental risk factors have been implicated, including parental age (Kong et al. 2012) and atypical maternal autoantibodies (Braunschweig et al. 2013). Analogous to “cancers,” there may be multiple “autisms,” to be defined by clustered genetic mutations with common mechanisms and treated with different classes of therapeutics. No definitive biomarkers have yet been identified across all diagnosed cases. Intensive searches are underway to define abnormalities in neurophysiology, neuroanatomy, brain chemistry, immune markers, and other potential biological abnormalities that may stratify individuals with autism, and offer outcome measures for future clinical trials (Ecker et al. 2013).

Rodent models offer preclinical tools to understand the role of genetic mutations and environmental factors in producing the diagnostic and associated symptoms of autism. Knockout (KO) and humanized knock-in mice have been generated for many of the mutations and CNVs detected in ASD and comorbid neurodevelopmental disorders such as fragile X syndrome and tuberous sclerosis (Silverman et al. 2010b; Ey et al. 2011; Baudouin et al. 2012; Zoghbi and Bear 2012; Gross et al. 2015). Several of these genetic mouse models are in use for the preclinical testing of pharmacological targets to treat the core symptoms of autism (Spooren et al. 2012; Silverman and Crawley 2014; Vorstman et al. 2014; Gross et al. 2015).

One fundamental conundrum is defining mouse behavioral assays with high relevance to the diagnostic symptoms of autism, which is a uniquely human disorder (Crawley 2004). Modeling ASD in rodents is challenging in that the clinical phenotype is heterogeneous and encompasses a wide range of behaviors. Researchers focused on developing animal models based on ASD-related behaviors benefit greatly from participating in clinical observations to obtain a comprehensive understanding of the clinical phenotypes found in individuals with ASD. We have been fortunate to observe diagnostic interviews of children with autism at the University of California Davis MIND Institute. Knowledge gained through these sessions and from lectures and conversations with many generous colleagues working with children, adolescents, and adults with autism guided our thinking in the development of analogous behavioral assays to evaluate mouse models of autism. This chapter presents state-of-the-art assays for mouse social and repetitive behaviors and reviews the preclinical progress in

evaluating hypothesis-driven pharmacological interventions, employing these behavioral assays in selected mouse models of autism.

2 Animal Models to Understand the Causes of Autism

The causes of autism are under intense investigation. Evidence supporting a large number of risk genes and CNVs at chromosomal loci is strong. Twin and family studies suggest that the genetic heritability of ASD is very high, ranging from 50 to 90 % (Ritvo et al. 1985; Smalley et al. 1988; Hallmayer et al. 2011; Miles 2011; Nordenbaek et al. 2014; Sandin et al. 2014). Genetic causes, primarily de novo mutations, have been identified in approximately 20–30 % of ASD cases, with no identified gene mutation in the majority of ASD cases (Miles 2011; Devlin and Scherer 2012; Murdoch and State 2013). Of the known genetic abnormalities associated with ASD, at least 5 % are caused by single gene mutations (Lim et al. 2013; De Rubeis et al. 2014; Iossifov et al. 2014), and at least 10 % are due to CNVs that cause structural variation, including duplications, deletions, inversions, and translocations (Marshall et al. 2008; Rosenfeld et al. 2010; Matsunami et al. 2013; Poultney et al. 2013). A remarkable preponderance of genetic mutations in ASD code for proteins mediating synaptic functions, such as those coding for the synaptic protein families SHANK (Durand et al. 2007), CNTNAP (Alarcon et al. 2008; Arking et al. 2008; Bakkaloglu et al. 2008), NLGN (Jamain et al. 2003; Laumonnier et al. 2004; Yan et al. 2005a; Talebizadeh et al. 2006; Lawson-Yuen et al. 2008), and NRXN (Kim et al. 2008). Examples of CNVs associated with ASD include chromosomal loci 15q11-q13 (Christian et al. 2008), 16p11.2 (Fernandez et al. 2010), and 22q11.21, and the *UBE3A*, *NRXN1*, and *CNTN4* genes (Fernandez et al. 2008; Kim et al. 2008; Glessner et al. 2009; Roohi et al. 2009). A subset of single gene mutations associated with ASD are responsible for other neurodevel-opmental disorders, including *FMR1* in fragile X syndrome, *TSC* in tuberous sclerosis, and *MECP2* in Rett syndrome.

Genetic and environmental risk factors identified in ASD have led to the development of many useful model systems. The best animal models display all three types of validity: construct, face, and predictive (Crawley 2004). The initial development of a new animal model may determine the extent to which construct validity leads to face validity in these models, and offers predictive validity. Construct validity requires that the animal model is generated with the same underlying biological cause, e.g., a genetic mutation, neuroanatomical abnormality, or environmental factor implicated in ASD. Face validity requires that symptoms displayed in the animal model are analogous to the human symptoms, such as social deficits and repetitive behaviors that define ASD. Predictive validity requires that treatments that are efficacious for treating the human syndrome are similarly efficacious in reversing symptoms in the animal models, such as improving social deficits or reducing repetitive behaviors. As no drug treatment has been approved for the effective treatment of the diagnostic symptoms of autism, predictive validity cannot yet be determined in animal models of ASD.

Construct validity in mouse models of autism has most frequently addressed risk genes by generating targeted mutations in the syntenic genes in the mouse genome. The number of different genetic mutations identified in ASD, each in only a few individuals (De Rubeis et al. 2014; Iossifov et al. 2014; O'Roak et al. 2014), suggests that each of these mutations may

be worthwhile to explore in mice with homologous mutations (Abrahams and Geschwind 2008; Silverman et al. 2010b; Ey et al. 2011; Spooren et al. 2012; Silverman and Crawley 2014; Wohr 2014). More recently, technological advances have enabled the development of genetically modified rats. Knockout rats (Engineer et al. 2014; Hamilton et al. 2014), as well as other species with sophisticated social behavioral repertoires, such as voles (Bales and Carter 2003a; Modi and Young 2012) and non-human primates (Bauman et al. 2014), provide additional research tools to determine how specific gene abnormalities, neurotransmission, neuroanatomical correlates, and environmental influences contribute to autism-relevant phenotypes across species.

In addition to the genetically modified rodent models of ASD, several inbred mouse strains incorporate face validity as ASD models, because they display robust and well-replicated social deficits and repetitive behaviors. These inbred strains are considered to be models of idiopathic autism, as their ASD-relevant behaviors are not caused by known genetic mutations. In assays of sociability, discussed below, the inbred strains A/J, BALB/cByJ (BALB), BTBR $T^{+}Itpr3^{tf}/J$ (BTBR), C58/J (C58), and 129S1/SvImJ mice exhibited lack of sociability, as compared to inbred mouse strains with high sociability, such as C57BL/6J (B6) and FVB/NJ mice (Brodkin 2007; Moy et al. 2007; Yang et al. 2007; McFarlane et al. 2008; Moy et al. 2008b). Additionally, several mouse strains, such as BTBR and C58, also display overt motoric stereotypies or repetitive behaviors, including jumping, digging, and high levels of self-grooming and marble burying (Bolivar et al. 2007; Moy et al. 2007; Panksepp et al. 2007; McFarlane et al. 2008; Moy et al. 2008b; Yang et al. 2009; Pobbe et al. 2010; Ryan et al. 2010; Silverman et al. 2010a; Wohr et al. 2011a; Yang et al. 2012a; Burket et al. 2013; Fairless et al. 2013; Silverman et al. 2013; Han et al. 2014). Of these, BTBR has been the most extensively characterized and well-replicated for ASD-related behaviors. In addition to abnormal sociability and repetitive behaviors, BTBR mice deposit fewer scent marks and emit fewer ultrasonic vocalizations (USVs) during social interactions, display an unusual repertoire of call categories during their USVs, exhibit a lower number of complex calls (Scattoni et al. 2008; Roullet et al. 2010; Scattoni et al. 2010), and are impaired on social transmission of food preference (McFarlane et al. 2008). These inbred strains add to the genetic mouse models, along with the rat, vole, and non-human primate models of ASD, which are available to evaluate therapeutics.

3 Mouse Behavioral Assays Relevant to the Diagnostic and Associated Symptoms of Autism

3.1 Social Tests

Several behavioral assays have been developed to assess various aspects of sociability in rodents. Like humans, both mice and rats are social species that display a wide repertoire of social behaviors, engaging in intraspecies reciprocal social interactions, parenting and mating behaviors, and scent marking and aggressive behaviors (Carter et al. 1992; Miczek et al. 2001; Terranova and Laviola 2005; Arakawa et al. 2008; Silverman et al. 2010b; Kaidanovich-Beilin et al. 2011). Behavioral phenotyping can utilize many of these species-specific behaviors to address whether preclinical animal models exhibit social deficits relevant to those seen in ASD.

Reciprocal social interactions—When placed together in a confined arena, juvenile and adult pairs of mice will engage in reciprocal social interactions, participating in various types of social sniffing and physical play (Terranova and Laviola 2005; McFarlane et al. 2008; Silverman et al. 2010b). Depending on the testing parameters, juvenile or adult mice of either the same sex or opposite sex can be evaluated in dyads. Additionally, genetically modified mice can be tested with partners of the same or different genotypes. Types of social partner investigation include nose-to-nose sniffing, nose-to-body sniffing, and nose-to-anogenital sniffing. Interactions include front approach, following, chasing, physical contact such as crawling over and under each other, wrestling, and pushing past each other. Because the complex interactions of these reciprocal social interactions cannot be fully captured by automated software, individual social behaviors are typically scored by investigators using event-recording software. Several ASD-relevant genetic mouse models have been evaluated using this paradigm and were found to exhibit reduced reciprocal social interactions, including *Engrailed2* (*En2*) null mutants (Cheh et al. 2006; Brielmaier et al. 2012), conditional *Pten* mutants (Kwon et al. 2006), *Shank3* heterozygotes (Bozdagi et al. 2010; Yang et al. 2012b), and *Tsc1* heterozygotes (Goorden et al. 2007; Tsai et al. 2012). Reduced reciprocal social interactions are also seen in two inbred strains, BTBR and BALB (Bolivar et al. 2007; Panksepp et al. 2007; Yang et al. 2007; McFarlane et al. 2008).

3-chambered social approach—A well-characterized automated test of sociability is our simplified three-chambered social approach task, which offers a high-throughput approach for assessing sociability (Nadler et al. 2004; McFarlane et al. 2008; Yang et al. 2011; Silverman et al. 2012, 2013). In this task, a subject mouse is assessed for its exploration of a novel mouse (e.g., a novel social stimulus) versus a novel object. The novel mouse is typically confined by an inverted wire pencil cup, which allows for visual, auditory, olfactory, and some tactile stimuli between the novel mouse and the subject mouse. An identical inverted wire pencil cup serves as the novel object, either alone or with an inanimate object inside. Mice that display species-typical sociability will spend more time in the side chamber with the novel mouse than in the side chamber with the novel object. Sociability is further defined more specifically by more time sniffing the novel mouse than sniffing the novel object. Chamber time is calculated automatically in a photocell-equipped apparatus, where beam breaks count chamber entries as a measure of locomotor activity. Videotracking systems can perform the same functions by defining zones around the cup or similar container (Ahern et al. 2009; Silverman et al. 2015). Many lines of mice with targeted mutations in risk genes for autism, as well as inbred strains, have been evaluated in the three-chambered social approach task (Moy et al. 2006; Moy and Nadler 2008; Moy et al. 2009; Silverman et al. 2010b; Patterson 2011; Qiu et al. 2012; Jiang and Ehlers 2013). Many genetic models of ASD were reported to exhibit low sociability in this assay including $GABA_A$ receptor *Gabrb3* KO mice (DeLorey et al. 2008), conditional *Pten* KO mice (Kwon et al. 2006), haploinsufficient *Pten* mutant mice (Page et al. 2009; Clipperton-Allen and Page 2014), *Ube3a* triplication mice (Smith et al. 2011), *Cntnap2* KO mice (Penagarikano et al. 2011), 15q11–13 duplication mice (Nakatani et al. 2009), and 17p11.2 duplication mice (Molina et al. 2008). In addition, BTBR, BALB, and C58 mice display low levels of sociability in the social approach assay (Brodkin et al. 2004; Brodkin 2007; Moy et al. 2007;

Yang et al. 2007; McFarlane et al. 2008; Moy et al. 2008b; Yang et al. 2009; Ryan et al. 2010; Silverman et al. 2010a, 2012a, 2013).

Partition test—The partition task is another straightforward assay for assessing sociability in mice, utilizing a perforated partition to separate a subject mouse from a target mouse. Similar to social approach, the subject mouse is exposed to visual, auditory, and olfactory stimuli from the target mouse, but the two mice do not physically interact. Social interest is represented by the time spent near the partition by the subject mouse. Paylor and coworkers often conduct the partition test first and then remove the partition to evaluate reciprocal social interactions in a habituated environment (Spencer et al. 2005).

Social recognition and social memory can be evaluated through the sequential use of different social partners in the partition task and in the three-chambered social approach apparatus (Moy et al. 2007; Arakawa et al. 2008). Given that mice are novelty-seeking, the subject mouse displays recognition of social novelty if it approaches and spends more time at the partition near the novel mouse as compared to the partition near the familiar mouse (Kudryavtseva 2003; Spencer et al. 2011). Similarly, in the three-chambered social approach task, social recognition is demonstrated if the subject mouse spends more time with a second novel mouse than with the previously novel but now familiar mouse. Adding delay periods of minutes or hours between presentations of the same and novel partners permits evaluation of social memory (Bielsky and Young 2004). Several genetically modified mice that exhibited reduced reciprocal social interactions or low sociability in three-chambered social approach also displayed a lack of preference for social novelty. Others were normal on social approach but failed on preference for social novelty (Moy et al. 2006; Moy and Nadler 2008; Moy et al. 2009; Silverman et al. 2010b; Patterson 2011; Qiu et al. 2012; Jiang and Ehlers 2013), including *Fgf17* KO mice (Scearce-Levie et al. 2008), *Gabrb3* KO mice (DeLorey et al. 2008), and *Nlgn4* KO mice (Jamain et al. 2008). Other genetic mouse models, such as *Nlgn3* KO mice (Radyushkin et al. 2009), demonstrated reduced social novelty, but did not have deficits in other aspects of sociability. Qualitatively divergent findings on social approach versus social recognition and social memory in several models reinforce the interpretation that sociability is distinct from social recognition memory, especially in the 3-chambered assay.

Visible burrow—Mice will typically form colonies that include shared nests composed of underground burrow and tunnel complexes (Lloyd 1975; Bouchard and Lynch 1989). Large visible burrow systems are enclosures that capitalize on the mouse social structure to investigate social interactions in a seminatural habitat using a series of tunnels, burrows, and a large open surface area (Blanchard et al. 1995, 2001). Compared to the social B6 strain, BTBR mice participate in fewer interactive behaviors, such as huddling and following, in the visible burrow system while spending more time alone and engaging in increased self-grooming (Pobbe et al. 2010).

Social transmission of food preference occurs when a subject mouse, after interacting with a cagemate that recently consumed a novel food, eats more of that novel food (Galef 2003; Wrenn et al. 2003; Wrenn 2004; Ryan et al. 2008). In addition to low sociability in several

social tasks, BTBR mice also exhibit reduced social transmission of food preference (McFarlane et al. 2008).

Social dominance is measured in a tube task. Mice of two different genotypes with approximately similar body weights are placed in opposite ends of a long, narrow plastic tube. A socially dominant mouse is characterized as the mouse that advances past the halfway point of the tube or pushes the opposing mouse out of the tube. Tube test deficits in social dominance have been detected in mice with mutations in *Dvl1* (Lijam et al. 1997; Long et al. 2004), the serotonin transporter (Kerr et al. 2013), *Fmr1* (Spencer et al. 2005) and others, while 17p11.2 duplication mice exhibited increased dominant behavior in this assay (Molina et al. 2008).

Assessment of sociability in two or more cohorts of animals using multiple assays increases the strength of findings, by generating a more complete behavioral profile, assessing generalizability, and evaluating robustness and replicability. Robust, easily replicated social deficits in mutant lines of mice can then serve as primary preclinical models for the development of novel therapeutics.

3.2 Social Communication

Communication impairments are a hallmark of autism (Lord et al. 2000; Kim et al. 2014b). Depending on the intellectual ability of the individual, communication deficits can manifest as the absence of speech, language delay, the use of odd prosody and intonation, stereotyped speech, perseverative phrases, and difficulties with language pragmatics such as those involved in initiating and maintaining appropriate and meaningful conversations (Rapin and Dunn 2003).

Rodents communicate primarily through olfactory pheromones. However, mice and rats also emit vocalizations in the ultrasonic range during social interactions, and also in non-social contexts (Chabout et al. 2012). Extensive research has been done to identify components of rodent USVs that might be analogous to human language communication. The utility of USV emissions for modeling aspects of social communication deficits in autism is being extensively investigated by several laboratories. Determining whether mouse USV calls have a communication function during specific types of social interactions is a work in progress.

Mouse and rat pups emit USVs when separated from the mother and the nest (Ehret 2005). Pup USVs reliably elicit maternal retrieval (D'Amato et al. 2005; Fischer and Hammerschmidt 2011; Okabe et al. 2013) and are therefore thought to represent a communicatory signal emitted by pups at an age when they solely depend on the dam for thermoregulation and feeding. Separated pups emit even more USVs after a brief reunion period with the mother, followed by a second separation. This phenomenon, called "maternal potentiation", has been found in both mice and rats and has been used as a measure of attachment (Shair et al. 2014). Mouse pups with a null mutation in the μ-opioid receptor gene (*Orpm*$^{-/-}$) emitted fewer USVs when separated from the mother and did not exhibit maternal potentiation, reflecting deficits in attachment (Moles et al. 2004). In mice, pup call numbers peak between postnatal days (PND) 7 and 9 and diminish around the age of hearing onset (PND12) (Ehret 2005; Adise et al. 2014), suggesting that pup USVs are

produced by innate mechanisms without a requirement for auditory feedback. It may be reasonable to suggest that pup USVs are a useful measure of physical development, reactivity to stress, anxiety, and attachment. However, since pup calls are likely more analogous to infant crying, quantitative and qualitative components of pup USVs are less likely to serve as a useful proxy for human language communication.

Juvenile and adult mice emit USVs during same-sex social interactions (Maggio and Whitney 1985; D'Amato and Moles 2001; Panksepp et al. 2007; Scattoni et al. 2011; Hammerschmidt et al. 2012). Pretest social isolation is usually a prerequisite for eliciting USVs in same-sex pairs. Currently, there is no practical method to differentiate calls from the two interacting animals. In juveniles, emission of USVs was positively correlated with social behaviors during juvenile social interaction (Panksepp et al. 2007), suggesting that USVs may be an affiliative component of the juvenile social repertoire. Adult mice emit large numbers of calls during same-sex interactions, following a short period of isolation. Female mice with null mutations in the *Shank2* gene emitted fewer calls as compared to wild-type females (Poultney et al. 2013). Adult male and female mice with null mutations of *Neuroligin4* emitted similar numbers of calls as compared to the wild-type controls (Ey et al. 2012). Calls emitted by the resident female during the resident–intruder paradigm have been used as a measure of social memory (D'Amato and Moles 2001).

Male–female social interactions have the advantages of not requiring pretest social isolation and a greater certitude that most calls are emitted by the male (Whitney et al. 1973; White et al. 1998; Wang et al. 2008; Sugimoto et al. 2011). The number of USVs emitted by a subject male in the presence of an estrus female has been widely used as an assay for social communication in mouse genetic models of autism (Ey et al. 2012; Yang et al. 2012b; Sowers et al. 2013).

Fresh female urine and other social odors are similarly effective in eliciting USVs from adult male mice (Nyby et al. 1977; Whitney and Nyby 1979; Byatt and Nyby 1986; Holy and Guo 2005; Hoffmann et al. 2009; Malkesman et al. 2010; Roullet et al. 2011; Wohr et al. 2011b). Playback studies indicate that female mice prefer male USVs over pup USVs, artificial control sounds, or silence (Hammerschmidt et al. 2009; Shepard and Liu 2011) and prefer vocalizing males over devocalized males (Pomerantz et al. 1983), suggesting that male USVs may have a role in facilitating courtship. Recent evidence indicates that male mice exhibit abrupt changes in call repertoires when the female stimulus mouse was removed (Hanson and Hurley 2012; Yang et al. 2013), suggesting that vocal flexibility may reflect the ability to detect sudden changes in salient social cues.

Distinct call categories have been cataloged within the highly complex structures of USVs (Holy and Guo 2005; Scattoni et al. 2011). The pioneering study by Holy and Guo (2005) catalyzed recent research on categorical analysis of mouse USVs. Most investigators classify calls by visually inspecting spectrograms of recorded USVs. Currently, there is no consensus on the number of categories or the definition of each category, with the number of categories ranging from three (Hammerschmidt et al. 2012) to fifteen (Mahrt et al. 2013). Recent electrophysiological recording studies have demonstrated that neurons in the mouse auditory

midbrain respond differently to different call types (Mayko et al. 2012), highlighting the importance of categorizing calls in a manner that is biologically meaningful to mice.

Are USVs in adult mice relevant to human language? Recent studies indicate that call patterns are similar between deaf mice and hearing controls (Hammerschmidt et al. 2012; Mahrt et al. 2013) and that cross-fostering failed to change strain-specific call patterns (Kikusui et al. 2011), suggesting that mouse USVs are not acquired through auditory feedback. It may be more reasonable to suggest that USVs are an important indication of responsivity to social stimuli during social interactions, but are not highly analogous to communicatory functions of complex human language.

3.3 Motor Stereotypies, Repetitive Behaviors, and Restricted Interests

The second ASD diagnostic symptom domain includes motor stereotypies, repetitive behaviors, insistence on sameness, and restricted interests (American Psychiatric Association 2013). Motor stereotypies in ASD include hand flapping and toe walking. **Stereotypies** in mice are species-typical behaviors such as circling and jumping, which occur with frequencies considerably higher than typical levels. Behavioral stereotypies can be assessed in the home cage or observed in an empty cage, by a trained investigator using an event recorder (Crawley 2012). Many genetic models of autism exhibit motor stereotypies. For instance, *Nlgn4* KO mice exhibited increased circling behavior (El-Kordi et al. 2013) and C58 mice exhibited high levels of jumping behavior (Moy et al. 2008b; Ryan et al. 2010; Silverman et al. 2012). *Gabrb3* KO mice showed high levels of circling behaviors (Homanics et al. 1997; DeLorey et al. 2008).

Repetitive self-grooming in mice has face validity to repetitive behaviors in ASD, such as assembling the same puzzle or playing one video game repeatedly. Normal patterns but unusually long bouts of self-grooming have been demonstrated in several mutant mouse models of autism, including *Shank3* (Peca et al. 2011), *Cntnap2* (Penagarikano et al. 2011), *Neurexin1α* (Etherton et al. 2009), and *Neuroligin1* (Blundell et al. 2010). High levels of self-grooming have been well-replicated in the BTBR mouse model of idiopathic autism (Yang et al. 2007; McFarlane et al. 2008; Yang et al. 2009; Pobbe et al. 2010; Silverman et al. 2010a; Amodeo et al. 2012, 2014b; Zhang et al. 2015), while the BALB inbred mouse line does not display repetitive self-grooming (Silverman et al. 2010b). Recent work in transgenic rats reported perseverative chewing behavior in *Fmr1* KO rats (Hamilton et al. 2014). Higher levels of **marble burying** are considered to reflect a repetitive behavior (Thomas et al. 2009). Marble burying relies on the species-typical burying of small objects placed into the cage. Higher marble burying was detected in BTBR (Amodeo et al. 2012; Silverman et al. 2012) and several mutant models (Silverman et al. 2010b), including *Tsc2* KO mice (Reith et al. 2013) and monoamine oxidase (MAO) A and A/B KO mice (Bortolato et al. 2013).

Versions of **open field holeboard exploration** are under development to model autism-relevant restricted interest/perseverative behaviors. Unusual hole board exploration was reported in BTBR and NMDA receptor (*Grin1*) mutant mice using olfactory cues (Moy et al. 2008a), and in MAO A and A/B knockout mice without olfactory cues (Bortolato et al. 2013).

Cognitive rigidity in autism has been modeled in several rodent models of autism. Morris water maze reversal learning assesses the ability of a mouse trained to locate a hidden platform in a pool of water to inhibit its previously learned navigation responses and learn a new platform location. Mice first learn the location of a hidden platform in a large pool of opaque water over the course of several days. After mice reach a criterion level of performance (i.e., latency under 15 s), the hidden platform is moved to the opposite side of the pool so that attempts to find the platform in the previous location must be suppressed and a new goal-directed behavior emerges for successful escape from the water. Two other versions of **maze reversal** are available: spontaneous alternation on a Y-maze, where reduced numbers of alternations between the two arms might represent perseverative behavior, and **rewarded T-maze reversal**, where the rewarded response shifts from the initial location of a food reinforcement located at one end of the T to the other end of the T. Other related tasks include extinction of fear conditioning, where a discrete cue previously paired with an aversive footshock is presented continuously without a footshock pairing, until the species-typical freezing response is attenuated. Deficits on some of these reversal tasks have been reported in BTBR (Moy et al. 2007; Yang et al. 2012a), 15q11-13 duplication (Nakatani et al. 2009), MAO A and A/B KO mice (Bortolato et al. 2013), and in eIF4E overexpressing mice (Santini et al. 2013). Similar to results of Morris water maze reversal tasks, MAO A and A/B KO mice also had decreased alternations in a forced-choice alteration T-maze (Bortolato et al. 2013) and BTBR showed deficits in water T-maze reversal (Guariglia and Chadman 2013).

Intellicages offer a home cage approach to test conditioned place preference learning and reversal, which showed a significant reversal-specific effect of valproic acid (VPA) in B6 mice, but not BALB mice (Puscian et al. 2014). Further, a **set-shifting** assay (Birrell and Brown 2000) showed a compound discrimination reversal deficit in Reeler heterozygous mice (Macri et al. 2010). An assay which employed alternation learning, followed by non-alternation learning, followed by reversal learning, used an H-shaped maze to demonstrate that tryptophan hydroxylase 2 mutants showed perseveration when the reinforcement contingencies changed (Del'Guidice et al. 2014).

The **five-choice serial reaction time task** (5-CSRTT) affords a robust measure of perseveration. The subject mouse pokes its nose into one of five holes at the front of an operant chamber, based on a stimulus presentation located in one of the five possible locations. Perseverative behavior is defined as choosing the previously rewarded stimulus location instead of choosing the currently active location. Mice with mutations in genes coding for the muscarinic acetylcholine receptor M1 and the NMDA receptor subunit Grin1 displayed perseverative deficits in 5-CSRTT (Bartko et al. 2011; Finlay et al. 2014). Despite the broad range of autism-relevant phenotypes displayed by BTBR mice, BTBR did not show perseverative behavior as assessed by the 5-CSRTT (McTighe et al. 2013).

3.4 Associated Symptoms

In addition to the core deficits associated with an autism diagnosis, there are several associated symptoms that commonly occur as comorbid conditions. A recent meta-analysis found that around 40 % of individuals with an ASD had elevated and clinically relevant

symptoms of an **anxiety disorder** (van Steensel et al. 2011). Specific phobias were the most common anxiety disorder, occurring in approximately 30 % of autistic individuals, while obsessive–compulsive disorder and social anxiety disorder/agoraphobia occurred in 17 % of autistic individuals (van Steensel et al. 2011). Common rodent behavioral tasks for the assessment of anxiety-like behaviors are the elevated plus-maze and light ↔ dark exploration. These tasks rely on the conflict between the tendency of mice to explore a novel environment versus avoidance of brightly lit open areas. Mice generally enter and spend less time in the two open arms of an elevated plus-maze as compared to the two enclosed maze arms. Mice generally spend less time in the brightly lit compartment of the light ↔ dark apparatus and make fewer transitions between the brightly lit and dark compartments. Anxiolytic drugs selectively increase the number of open arm entries and time in the open arms in the elevated plus-maze, and increase time in the light compartment and number of transitions between compartments in the light ↔ dark apparatus, confirming predictive validity (Crawley 1985; Cryan and Sweeney 2011). Other less widely used tests that detect effects of anxiolytic drugs include the operant-based Geller-Seifter and Vogel conflict assays, vocalizations emitted by pups separated from their dams to model separation anxiety (Insel et al. 1986), and marble burying, which has been described as a model of obsessive–compulsive disorder (Thomas et al. 2009).

Seizure disorders are very common in autism. At least 20 % of individuals who meet the diagnostic criteria for autism experience seizures (Volkmar and Nelson 1990). Several genetic mouse models of autism recapitulate aspects of the increased seizure susceptibility, including mice with mutations in *Synapsin1* (Greco et al. 2013), *En2* (Tripathi et al. 2009), *Cntnap2* (Penagarikano et al. 2011), *Tsc1* (Meikle et al. 2007) and *Tsc2* (Zeng et al. 2011), *Gabrb3* (DeLorey et al. 2011; Homanics et al. 1997), and *Fmr1* (Chen and Toth 2001).

Intellectual disability is present in approximately 30–40 % of ASD subjects (Matson and Shoemaker 2009; Perou et al. 2013). Learning and memory deficits have been demonstrated in several mouse models of autism, often along with electrophysiological abnormalities detected in hippocampal slice assays. Water maze and fear conditioning deficits were reported in mice with mutations in *Pten*, *Tsc1*, *Shank3*, *Cntnap2*, *En2*, and in the BTBR inbred strain, among others (Upchurch and Wehner 1988; The Dutch-Belgian Fragile et al. 1994; D'Hooge et al. 1997; Paradee et al. 1999; Goorden et al. 2007; Moy et al. 2007; MacPherson et al. 2008; Baker et al. 2010; Penagarikano et al. 2011; Brielmaier et al. 2012; Sperow et al. 2012; Yang et al. 2012a, b; Scattoni et al. 2013).

Sleep disorders are common in children with ASD. As many as two-thirds of autistic individuals may have some kind of sleep disorder (Richdale 1999). Sleep patterns and circadian rhythms have not been extensively reported in mouse models of autism. Mutant mice lacking *Cadps2*, located in the 7q autism susceptibility locus, showed an aberration in intrinsic sleep-wake cycle maintenance (Sadakata et al. 2007). *Fmr1* KO mice demonstrated abnormal circadian activity patterns, which may suggest alterations in sleep–wake cycle stability (Baker et al. 2010). *Gbrb3* KO mice exhibited differences in activity-rest neural activity as assessed by EEG (DeLorey et al. 1998).

Attention deficits and hyperactivity are a commonly associated symptom of autism. Several mutant mouse models of autism display higher exploratory locomotion in the open field test, including *Fmr1* (Kramvis et al. 2013), *Cntnap2* (Penagarikano et al. 2011), *ProSAP1/Shank2* (Schmeisser et al. 2012), and a 16p11.2 deletion (Portmann et al. 2014).

Sensory symptoms, including under-and over-responsivity to sensory stimuli, are frequently found in those with ASD (Rogers and Ozonoff 2005). Idiosyncratic overreaction to a sudden loud noise can be tested in mice by assessing response to acoustic stimuli at various decibel levels. An increased response to sensory stimuli was observed in *Fmr1* mice (Chen and Toth 2001). Reduced acoustic startle was reported in several other mutant mouse models of autism including *Gabrb3* (DeLorey et al. 2011), *EphrinA* (Wurzman et al. 2014), and female *Mecp2* heterozygotes (Samaco et al. 2013). Idiosyncratic underreaction to painful stimuli can be assessed in mice with hot plate or tail flick thermal stimuli. Genetic models of autism have revealed increased sensitivity in these nociceptive tasks in *Gabrb3* KO mice (DeLorey et al. 2011).

Mouse behavioral assays described above have proven useful in phenotyping genetic mouse models of autism. Approaches to develop ideal models of ASD may utilize multiple species to ensure that the same outcomes are present across species, to best advance the potential for an integration of systems neuroscience with the human syndrome. Successful multiple species approaches will contribute to fast-forwarding our progress to develop effective mechanism-based therapeutics. Mouse models provide relatively low cost, high-throughput, valid phenotypes in various behavioral assays relevant to the diagnostic symptoms of ASD.

Comparative studies utilizing rodent vole models are another powerful approach for modeling social behavior relevant to ASD. Prairie and pine voles (*Microtus ochrogaster and Microtus pinetorum*, respectively) are a monogamous species living in highly social burrows (Carter and Getz 1993; Carter et al. 1995). In contrast, montane and meadow voles (*Microtus montanus and Microtus pennsylvanicus*, respectively) are non-monogamous and often live in social isolation. Differences in oxytocin peptide and receptor binding have been reported between these species of vole and are functionally related to their differences in social behavior (Winslow et al. 1993; Young et al. 2002). Carter, Bales, and colleagues have reported both facilitation and deleterious effects of oxytocin administration in voles in the partner preference pair bonding assay. These effects were both sexually dimorphic and developmentally specific (Bales and Carter 2003a, b; Carter et al. 2009; Bales et al. 2013). Intranasal oxytocin paradigms developed in the vole have recently been examined in mouse models, with reports of either adverse or minimally beneficial behavioral outcomes, dependent on length of exposure (Bales et al. 2014; Huang et al. 2014). Novel pharmacology using vole models recently illustrated that d-cycloserine, a partial agonist of the *N*-methyl-D-aspartate (NMDA) glutamate receptor that enhances receptor activation in the presence of glutamate, dose dependently enhanced partner preference in female prairie voles (Modi and Young 2011).

Rats have sophisticated behavioral repertoires which make this rodent species excellent for modeling the nuances of complex social behavior. Recent advances in genetic technologies allow for manipulation of rat gene expression. Two genetic models with relevance to ASD

have been generated. One example is a rat knockout of the *Fmr1* gene, which is associated with fragile X syndrome. Behavioral phenotyping revealed that *Fmr1* KO rats have low levels of social play behavior and higher levels of a repetitive block chewing (Hamilton et al. 2014). Other genetic ASD-relevant rat KO models are the neuroligin-3 (*Nlgn3*) null and the neurexin-1α (*Nrxn1-α*) KO rats model. *Nlgn3* KO rats display reduced juvenile social play (Hamilton et al. 2014), while *Nrxn1-α* KO rats exhibit hyperactivity, exaggerated startle responses, and impairments in latent inhibition and spatial-dependent learning (Esclassan et al. 2015). Genetic rat models of autism offer a new set of tools for evaluating pharmacological interventions.

Several studies suggest a role for environmental factors, in combination with genetic susceptibility, in the etiology of ASD. An impressive population-based Danish study in 2013 outlined prenatal exposure to the anticonvulsant VPA, but not to other anti-seizure medications, nearly tripled the risk of ASD (Christensen et al. 2013). The larger study confirmed an earlier smaller report that exposure to VPA during gestation increased relative risk for ASD and maladaptive ASD-related behavioral dysfunction in children born to women who took VPA to treat their epilepsy (Bromley et al. 2008). Mouse models exposed to gestational VPA recapitulate selective behavioral and electrophysiological deficits analogous to those seen in the clinic (Wagner et al. 2006; Gandal et al. 2010; Mehta et al. 2011). Similarly, rats exposed to VPA in utero show increased frequency of motor stereotypies in adolescence, reduced social exploration, and low levels of juvenile rough and tumble play supporting the validity of this model (Schneider and Przewlocki 2005). Although the mechanisms underlying the link between VPA and autism are not fully understood, prenatal exposure to VPA alters GABA and monoamine systems, induces a loss of specific subsets of neurons, and acts through epigenetic mechanisms via histone deacetylase inhibition (Bambini-Junior et al. 2014).

Excitatory–inhibitory imbalance is a prominent hypothesis for the etiology of ASD. Pharmacological interventions that shift the balance closer to normal are under consideration. Acute exposure to the glutamate antagonist, MPEP, reduced marble burying phenotypes in offspring of dams treated with VPA, but did not alleviate anxiety-like behavior (Mehta et al. 2011). GABAergic neurons switch from excitatory to inhibitory during key developmental processes. This sequence was reported to be absent in hippocampal CA3 neurons of offspring of VPA-treated rat dams (Tyzio et al. 2014). Moreover, VPA-treated offspring emitted low numbers of isolation-induced pup USVs. Bumetanide pretreatment to dams rescued the GABA developmental impairments and restored call emissions in VPA rodent offspring (Tyzio et al. 2014).

The first non-human primate model of ASD involved the bilateral removal of the medial temporal lobe of young rhesus macaque monkeys. Normal infant monkeys develop strong affiliative bonds. Lesioned subjects displayed atypical dyadic social interactions at 2 and 6 months and exhibited aberrant stereotypies (Bachevalier 1994; Bachevalier et al. 2001). Other lesion studies produced selective amygdala lesions in 2-week-old macaques. By 6–8 months of age, the lesioned animals demonstrated substantial fear behaviors during dyadic social interactions while maintaining much of the age-appropriate repertoire of social behavior (Prather et al. 2001).

Other reported non-human primate models of ASD have tested the hypothesis that exposure of the fetal brain to maternal autoantibodies during gestation increases ASD risk. Rhesus monkeys exposed to human immunoglobulin collected from mothers of multiple children diagnosed with ASD consistently demonstrated increased whole-body stereotypies and hyperactivity across multiple testing paradigms (Martin et al. 2008). In extended studies, these monkeys consistently deviated from species-typical social norms by more frequently approaching familiar peers in a social approach paradigm (Bauman et al. 2013).

Oxytocin administration in rhesus macaques was reported to significantly increase plasma oxytocin concentrations when administered using the aerosol or intranasal routes (Modi et al. 2014). Social perception in the dot-probe task in monkeys receiving intranasal oxytocin detected selectively reduced attention to negative facial expressions, but not neutral faces or nonsocial images (Parr et al. 2013). This first pharmacological report using non-human primates provides promising evidence for oxytocin-based compound efficacy in clinical populations.

4 Evaluating Pharmacological Therapeutics in Animal Models with High Construct Validity and Strong Face Validity for ASD

Clinical trials for ASD core symptoms are challenged by the heterogeneity of the disorder, which can limit study design parameters and statistical power for outcome measures. Currently, there are no pharmacotherapies approved by the US Food and Drug Administration specifically for social interaction, communication deficits, and repetitive behaviors. The only FDA-approved pharmacological treatments for autism are the antipsychotics risperidone and aripiprazole, which treat the associated irritability symptoms of aggression, self-injury, and temper tantrums. Greater than 50 % of children diagnosed with ASD in the USA are using at least one psychoactive drug (Spencer et al. 2013), as prescribed for irritability (Siegel and Beaulieu 2012), or given off-label. Risperidone, which modulates dopamine and serotonin systems, had a significant effect on stereotyped behavior in children with ASD (McCracken et al. 2002; McDougle et al. 2005; Chavez et al. 2006), although this was not seen in all studies (Ghaeli et al. 2014). Risperidone studies that included behavioral scales measuring aspects of sociability, such as social relationships and language, had large effect sizes, but failed to reach statistical significance (McDougle et al. 2005). Other studies that utilized additional behavioral scales, such as the Aberrant Behavior Checklist Social Withdrawal subscale and the Childhood Autism Rating Scale (CARS), found that risperidone treatment was effective compared to placebo (Scahill et al. 2013; Ghaeli et al. 2014). The lack of consistency for risperidone’s effects on aspects of social behavior may be due to clinical heterogeneity within the studies’ ASD subject population, differences in treatment duration, as well as differences in the tools used for sociability outcome measures. Treatment studies with antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, have yielded mixed results on improvement of repetitive behaviors. For example, SSRI treatment with fluoxetine or citalopram did not produce a clinically significant improvement on repetitive behaviors in children (Hollander et al. 2005; King et al. 2009). However, additional studies with fluoxetine and fluvoxamine demonstrated improvement on repetitive thoughts, repetitive

actions, and scores of an obsessive–compulsive scale in adults (McDougle et al. 1996; Hollander et al. 2012), suggesting that SSRI treatment approach may depend on the age of individuals with ASD.

As described in Table 1, additional classes of compounds have been evaluated for their efficacy in treating ASD core symptoms, although large-scale, randomized, double-blind, placebo-controlled trials are lacking. Administration of oxytocin, a neuropeptide involved in social pair bonding, social memory, and affiliative behaviors (Gimpl and Fahrenholz 2001), increased social awareness and emotional recognition in both neurotypical individuals and those with ASD in pilot studies (Hollander et al. 2007; Bartz and Hollander 2008; Rimmele et al. 2009; Bartz et al. 2010; Guastella et al. 2010). Interestingly, functional neuroimaging results from a randomized, double-blind cross-over study in children with ASD found that brain structures associated with sociability (e.g., striatum, posterior cingulate, and premotor cortex) showed greater recruitment after intranasal oxytocin administration, suggesting that this neuropeptide enhanced the saliency of social stimuli (Gordon et al. 2013).

STX209 (Arbaclofen), a selective $GABA_B$ agonist thought to stimulate inhibitory neurotransmission, was evaluated as a treatment for fragile X syndrome, a neurodevelopmental disorder with a high incidence of ASD comorbidity (Berry-Kravis et al. 2012). Although there were no statistically significant differences in the primary outcome (Aberrant Behavior Checklist-Irritability subscale), male subjects were noted as having positive improvements on several global measures including socialization scores. Additionally, in a study with individuals with ASD, Arbaclofen was well tolerated and improved scores on social responsiveness, social withdrawal, and clinical global impression scales (Erickson et al. 2014a).

D-cycloserine, a partial agonist of the ionotropic glutamatergic NMDA receptor, has been evaluated in one single-blind, placebo-controlled trial, where the majority of children with ASD treated with D-cycloserine improved their scores on the Autistic Behavior Checklist Lethargy and Social Withdrawal subscale (Posey et al. 2004). Memantine, an NMDA receptor antagonist approved for Alzheimer’s disease, has been assessed in several open label studies and retrospective reports. Some studies found that more than half of clinical responders had improvements in Clinical Global Impression scores or language and social behaviors (Chez et al. 2007; Erickson et al. 2007), although not all studies found similar effects (Owley et al. 2006; Niederhofer 2007). Open label studies with children with ASD using cholinesterase inhibitors suggest that there may be some improvement in expressive language, parent reports, and CARS scores (Niederhofer et al. 2002; Chez et al. 2004; Nicolson et al. 2006).

Many of these early clinical trials were based on hypotheses generated from mouse models. Of particular interest is Rubenstein’s proposed excitatory inhibitory imbalance, which arose from electrophysiological assays in mutant mouse models (Rubenstein 2010). Both forward translation, to discover new pharmacological targets using mouse models, and back translation, to test compounds in mutant mouse models of ASD that are used off-label or have moved into clinical trials, are described below and in Table 1.

Drugs that increase GABAergic inhibition have been tested in several mouse models of autism. Using *Fmr1* mice, in which mGluR5 expression and AMPA receptors are elevated and dendritic spines are abnormal, r-baclofen corrected basal protein synthesis, reduced AMPA receptor internalization and increased spine density in *Fmr1* KO mice (Henderson et al. 2012). In the few studies that evaluated classical benzodiazepines, reduction in repetitive behaviors was reported in BTBR mice treated with clonazepam (Han et al. 2014), which also showed efficacy in social and cognitive deficits in *Scn1* heterozygous mice, a mouse model of Dravet's syndrome that exhibits ASD symptoms (Han et al. 2014). Further, acute intraperitoneal administration of r-baclofen reduced repetitive self-grooming and improved sociability in BTBR mice, and reduced stereotyped vertical jumping in C58 mice (Silverman et al. 2015).

Another strategy to reduce excitatory neurotransmission is to inhibit mGluR receptors with negative allosteric modulators. The mGluR antagonist MPEP was evaluated in the BTBR mouse model. Acute MPEP treatment reduced repetitive behaviors, including self-grooming and marble burying (Silverman et al. 2010a), and improved cognition in BTBR (Seese et al. 2014), and demonstrated anti-epileptic effects in *Fmr1* mice (Yan et al. 2005b). The mGluR5 receptor inverse agonist CTEP showed efficacy in ameliorating cognitive deficits, signaling abnormalities, and dendritic spine deficits in the *Fmr1* KO mouse (Michalon et al. 2012). The mGluR5 negative allosteric modulator GRN-529 rescued social deficits and repetitive self-grooming in BTBR mice and reduced stereotyped jumping in C58 mice (Silverman et al. 2012).

A large number of novel pharmacological targets are being tested in mouse models. Table 1 provides a partial summary of compounds tested in various mouse models. Some of these strategies have been evaluated in clinical investigations. Others may be under consideration. Well-replicated results with a compound that reverses autism-relevant phenotypes, both behavioral and biological, in multiple animal models, may contribute to decisions about pursuing a clinical trial for ASD.

5 Conclusions

The summary above and in Table 1 provides descriptions of behavioral assays relevant to the symptoms of autism, representative results of behavioral phenotypes in many rodent models, and drug treatment outcomes in several mouse models of autism. Initial hypotheses for pharmacological targets derived from animal studies that documented (1) elevated excitatory neurotransmission or excess mGluR5 receptors, (2) reduced GABAergic inhibitory physiology, circuitry, or interneurons in genetic mouse models of autism, along with (3) oxytocin modulation of social behaviors and growth factors that mediate brain development. Preclinical findings of improvements by drug treatments in mouse models of fragile X and autism have led to a small number of clinical trials. Unfortunately, the Arbaclofen trial by Seaside Therapeutics did not detect significant improvement in its primary outcome measures, and the mGluR5 antagonist trial by Roche was terminated due to lack of initial efficacy. Central questions at present include (a) whether the animal results did not incorporate sufficient predictive validity and (b) whether the clinical trials were not

optimally designed in terms of dose, age, treatment regimen, patient population, or outcome measures.

Many concerns have been raised about the predictive usefulness of results from animal models in the discovery of treatments for neuropsychiatric disorders (Markou et al. 2009; Belzung 2014). The autism field is similarly facing this dilemma. Our view is that animal studies must incorporate a high level of validity and reproducibility. Assays in rodents can be designed to maximize face validity, for maximal analogy to the behavioral and biological symptoms of autism. However, results from animal studies need to be interpreted cautiously, without exaggeration or hyperbole about relevance to the diagnostic symptoms. Requirements for replication of positive results in two cohorts of mice would greatly increase the strength of findings. Preclinical drug studies may be most predictive when dose–response relationships have been explicated, acute and chronic treatment regimens have been tested, and clinically relevant routes of administration have been used in two or more species. These expectations represent a great deal more effort than is often invested in early preclinical studies with animal models. More complete preclinical data may be needed to provide the confidence needed to move forward into a clinical trial.

In the autism field, where no pharmacological interventions have definitively improved the core diagnostic symptoms of social interaction and communication deficits and repetitive behaviors, early failures are to be expected. Without a gold standard therapeutic, mouse models cannot be tested a priori for predictive validity. The process will be iterative. Pharmacological target discovery is benefitting from mouse models with mutations in synaptic genes and signaling pathways identified in individuals with autism, especially in cases where the gene codes for a protein in a biological pathway which is susceptible to pharmacological intervention with available compounds. Back translation, to test compounds that are being used clinically for phenotypic reversal in animals, will help to establish whether a mutant rodent model is sufficiently predictive. The current trend for autism symposia and consortia to mix clinical and basic researchers working on pharmacological interventions is encouraging, to promote this iterative discovery process.

One major hurdle is the need for simple, real-life outcome measures of appropriate social interaction, social communication, and repetitive behaviors to use as discrete endpoints for human drug trials. Gold standard instruments for the diagnostic assessment of ASD are complex and expensive, limiting their usefulness for large-scale multi-site clinical trials of new medications. Simplified, shortened rating scales are in use and under development.

Another major hurdle is the behavioral heterogeneity which characterizes ASD, which presents a huge challenge for both clinical trials and preclinical animal models. One strategy would be to stratify the ASD population based on behavioral subgroups with specific associated symptoms, e.g. seizures, aggression, anxiety, repetitive behaviors, language skills, or IQ. Another strategy is to employ proposed biomarkers, e.g., EEG gamma activity (Bosl et al. 2011; Rojas and Wilson 2014), or delayed auditory responses (Edgar et al. 2014). Parsing ASD symptoms into more tractable endophenotypes would further allow the use of animal models to illuminate genetic underpinnings and relevant molecular pathways. Both behavioral and biomarker subcategorization of the ASD behavioral spectrum would be

valuable for preclinical drug discovery, to provide sufficiently robust cross-species biological phenotypes to complement behavioral phenotypes and permit rigorous preclinical evaluation of pharmacological interventions.

In conclusion, we return to our initial discussion of construct, face, and predictive validity in animal models. Collaboration of clinical and basic science researchers will be required at each level. Progress in the refinement of construct validity will require both clinical observation and genetics research to hasten the identification of strong risk genes for ASD and endophenotypes with relevance to its symptoms. To improve the face validity of animal models, basic scientists need to discuss the meaning of species-typical behaviors in rodents and non-human primates with clinical scientists working with individuals with ASD. In this way, there will be better assurance that the behaviors selected and assessed in animal models are relevant to humans with ASD. At the level of predictive validity, the first step will be the discovery of hypothesis-driven compounds that improve endophenotypes in both rodents and humans, particularly through the use of simpler, more real-life single outcome measures of appropriate social interaction and repetitive behaviors. While effective medical treatments for autism are greatly needed, the knowledge base about the most relevant pharmacological targets is currently at an early stage. Appropriate choices of animal model constructs, assays with strong face validity, and rigorous analysis of drug effects will contribute to the maturation of therapeutic development.

Acknowledgments

This work was supported by the MIND Institute Autism Research Training Program MH0073124 (TK), Autism Speaks Targeted Award #8703 (JC, JS) NINDS 1R01NS085709 (JC, PL), the MIND Institute Intellectual and Developmental Disabilities Research Center 1U54HD079125, and NIMH 1R01 MH103284 (MS).

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Table 1

Examples of preclinical and clinical evaluations of drug treatments for autism

Mechanistic class	Preclinical model	Compound	Preclinical phenotype rescues	Reference
mGluR5 modulation	BTBR C58/J	MPEP MTEP GRN529	• Improved sociability • Reduced repetitive behavior • Improved cognition	Silverman et al. (2010a), Silverman et al. (2012) and Seese et al. (2014)
	Fmr1	AFQ056 CTEP MTEP MPEP Fenobam JNJ16259685	• Rescued abnormal dendritic spine morphology • Corrected excessive protein synthesis • Normalized altered long-term depression • Reduced seizure susceptibility • Decreased hyperactivity • Rescued cognitive deficits • Rescued sensorimotor gating • Reduced repetitive behavior	Yan et al. (2005b), De Vrij et al. (2008), Busquets-Garcia et al. (2013), Michalon et al. (2012), Gantois et al. (2013), Thomas et al. (2012), Gandhi et al. (2014) and Pop et al. (2014)
	Shank2	CDPPB	• Restored abnormal long-term potentiation and long-term depression • Improved sociability	Won et al. (2012)
	Valproic acid	MPEP	• Reduced repetitive behavior	Mehta et al. (2011)
	Clinical population	**Treatment**	**Phase**	**Reference***
	ASD—5 to 17 years old	Acamprosate	Phases 2 and 3; single-blind placebo lead-in trial	NCT01813318; Erickson et al. (2014b)
	ASD—6 to 13	Acamprosate	Open label	Erickson et al. (2011a)
	Fragile X males with ASD—18 to 23 years old	Acamprosate	Open label	Erickson et al. (2010)
	Fragile X—5 to 17 years old	Acamprosate	Phase 3; open label	NCT01300923; Erickson et al. (2013)
	Fragile X—3 to 11 years old	AFQ056	Phase 1	NCT01482143

Mechanistic class	Preclinical model	Compound	Preclinical phenotype rescues	Reference
	Fragile X—12 to 17 years old	AFQ056	Phases 2 and 3	NCT01357239, NCT01433354
	Fragile X—18 to 45 years old	AFQ056	Phase 2	NCT01253629, NCT01348087, NCT00718341
	Fragile X—5 to 13 years old	RO4917523	Phase 2	NCT01750957
	Fragile X—14 to 50 years old	RO4917523	Phase 2	NCT01517698, NCT01015430
$GABA_B$ modulation	BTBR C58/J	R-Baclofen	• Improved sociability • Reduced repetitive behavior	Silverman et al. (2015)
	Fmr1	STX209 (Arbaclofen)	• Normalized normal dendritic spine morphology • Corrected excessive protein synthesis • Reduced seizure susceptibility	Henderson et al. (2012)
	NMDA NR1 subunit knockout mice	Racemic baclofen	• Improved excitation/inhibition balance • Rescued gamma EEG band deficits • Reduced hyperactivity • Rescued sensorimotor gating deficits	Gandal et al. (2012)
	Clinical population	**Treatment**	**Phase**	**Reference***
	ASD—5 to 21 years old	STX209 (Arbaclofen)	Phases 2 and 3	NCT01706523, NCT01288716; Frye (2014)
	ASD—6 to 17 years old	STX209 (Arbaclofen)	Phase 2; open label	NCT00846547; Erickson et al. (2014a) and Frye (2014)
	Fragile X—6 to 40 years old	STX209 (Arbaclofen)	Phase 2	NCT00788073; Berry-Kravis et al. (2012)
	Fragile X—12 to 50 years old	STX209 (Arbaclofen)	Phase 3	NCT01282268
$GABA_A$ modulation	BTBR	Diazepam Low dose of benzodiazepines L-838,417	• Increased GABAergic inhibitory neurotransmission • Improved social interactions	Pobbe et al. (2011) and Han et al. (2014)

Mechanistic class	Preclinical model	Compound	Preclinical phenotype rescues	Reference
			• Ameliorated cognitive deficits	
	Clinical population	**Treatment**	**Phase**	**Reference***
	ASD—18 to 45 years old	Pregnanolone	Phase 2	NCT01881737
	High functioning ASD —18 to 35 years old	AZ7325	Phase 2	NCT01966679
mTOR inhibitors	BTBR	Rapamycin	• Improved sociability	Burket et al. (2014)
	Pten	Rapamycin RAD001 (Everolimus)	• Improved macrocephaly • Inhibits neuronal hypertrophy • Improved abnormal sociability • Reduced seizures	Zhou et al. (2009)
	Tsc1		• Improved survival rates and weight gain • Prevented seizures • Ameliorated abnormal EEG • Improved neuronal morphology • Prevented cell loss • Restored myelination abnormalities • Improved motor phenotypes • Improved sociability • Ameliorated cognitive deficits	Meikle et al. (2008), Zeng et al. (2008), Sato et al. (2012) and Tsai et al. (2012)
	Tsc2		• Improved cognition • Improved sociability	Ehninger et al. (2008) and Sato et al. (2012)
	Fmr1	Temsirolimus	• Rescued cognitive impairment • Reduced seizure susceptibility	Busquets-Garcia et al. (2013)
	Clinical population	**Treatment**	**Phase**	**Reference***

Mechanistic class	Preclinical model	Compound	Preclinical phenotype rescues	Reference
	Tuberous sclerosis complex—4 to 15 years old	Rapamycin (Sirolimus) RAD001 (Everolimus)	Phases 2 and 3	NCT01730209
	Tuberous sclerosis complex—2 to 61 years old		Phases 1, 2, and 3	NCT01929642, NCT00789828, NCT00790400, NCT00411619; Krueger et al. (2010), Tillema et al. (2012), Bissler et al. (2013) and Franz et al. (2013), Krueger et al. (2013)
Neuropeptides	BTBR	Oxytocin	• No behavioral effects	Bales et al. (2014)
	C57BL6/J		• Reduced several social behaviors	Huang et al. (2014)
	C58/J		• Improved sociability	Teng et al. (2013)
	Oxytocin knockout mice		• Improved sociability	Ferguson et al. (2001)
	Oxytocin receptor mice		• Improved sociability • Restored cognitive inflexibility	Sala et al. (2011)
	Clinical population	**Treatment**	**Phase**	**Reference***
	ASD—3 to 17 years old	Oxytocin	Phases 2 and 3	NCT01944046, NCT01308749, NCT01624194; Tachibana et al. (2013)
	ASD—12 to 17 years old			NCT01417026, NCT02090829, NCT01931033, NCT02007447, ACTRN12609000513213; Guastella et al. (2014)
	ASD—18 to 60 years old			NCT00490802, NCT01337687, NCT01788072; Hollander et al. (2003) and Lin et al. (2014)
	ASD—21 to 38 years old		Randomized cross-over double-blind study	UMIN000002241, UMIN000004393; Aoki et al. (2014a, b) and Watanabe et al. (2014)
	ASD—19 to 56 years old		Randomized, placebo-controlled, double-blind study	Hollander et al. (2007)
	ASD—6 to 12 years old	Vasopressin	Phase 2	NCT01962870
	ASD—18 to 55 years old	RG-7314	Phase 2	NCT01793441
Growth factors	*Fmr1*	BDNF	• Rescued long-term potentiation abnormalities	Lauterborn et al. (2007)

Mechanistic class	Preclinical model	Compound	Preclinical phenotype rescues	Reference
	Shank3	IGF1	• Improved long-term potentiation	Bozdagi et al. (2013)
	Mecp2−/−		• Reversed respiration deficits	Tropea et al. (2009)
	Clinical population	**Treatment**	**Phase**	**Reference***
	ASD—5 to 12 years old	IGF1	Phase 2	NCT01970345
	22q13 deletion (Phelan-McDermid syndrome)			NCT01525901
	Rett syndrome—4 to 11 years old	IGF1	Pilot study; case study	Pini et al. (2012, 2014)
NMDA glutamate receptor modulation	*Fmr1*	Memantine	• Corrected spine morphology	Wei et al. (2012)
	Shank2	D-cycloserine	• Improved sociability	Won et al. (2012)
	Clinical population	**Treatment**	**Phase**	**Reference**
	ASD—3 to 12 years old	D-cycloserine	Phase 3; Prospective, open label study	NCT00198120; Owley et al. (2006)
	ASD—14 to 25 years old		Pilot study; double-blind randomized trial	Posey et al. (2004) and Urbano et al. (2014)
	ASD—2 to 26 years old	Memantine	Open label; retrospective study	Chez et al. (2007) and Erickson et al. (2007)
	ASD—6 to 12 years old		Phase 2	NCT01592786, NCT01592773
	ASD—13 to 17 years old		Phase 3	NCT01972074
	ASD—18 to 85 years old		Phase 4	NCT01078844, NCT01333865
AMPA glutamate receptor modulation	BTBR	AMPAkines CX546 CX1837 CX1739	• Improved facets of sociability	Silverman et al. (2013)
	Mecp2		• Reversed respiration deficits	Ogier et al. (2007)
	Clinical population	**Treatment**	**Phase**	**Reference***
	Fragile X or ASD—18 to 50 years old	CX516	Phase 2	NCT00054730; Berry-Kravis et al. (2006)
Atypical antipsychotics	BTBR	Risperidone M100907	• Improved reversal learning	Amodeo et al. (2014a)
		Risperidone	• Failed to improve sociability	Chadman (2011) and Gould et al. (2011)

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Mechanistic class	Preclinical model	Compound	Preclinical phenotype rescues	Reference
	Cntnap2	Risperidone	• Reduced hyperactivity • Decreased repetitive behavior	Penagarikano et al. (2011)
	Clinical population	**Treatment**	**Phase**	**Reference***
	ASD—30 months to 17 years old	Aripiprazole	Phase 2, 3 and 4	NCT00619190, NCT01617447, NCT00337571, NCT02069977, NCT00198107
	ASD—12 to 18 years old	Aripiprazole	Phase 2	NCT00208533
		Ziprasidone	Phase 2	NCT00208559
	ASD—5 to 18 years old	Aripiprazole	Phases 3 and 4; Pilot study; Open label, Chart review	NCT00332241, NCT00337571, NCT01227668, NCT00365859;, Marcus et al. (2009), Owen et al. (2009), Blankenship et al. (2010), Marcus et al. (2011a, b), Robb et al. (2011), Varni et al. (2012), Ishitobi et al. (2013), Mankoski et al. (2013), Findling et al. (2014), Maloney et al. (2014) and Adler et al. (2015)
		Risperidone	Phases 2, 3, and 4; Open label; Randomized, double-blind trial	NCT01171937, NCT00576732, NCT01624675, NCT00005014; McDougle et al. (2000), McCracken et al. (2002), McDougle et al. (2005), Rausch et al. (2005), Desousa (2010), Handen et al. (2013), Kent et al. (2013a, b), Scahill et al. (2013), Ghaeli et al. (2014) and Ghanizadeh and Ayoobzadehshirazi (2015)
		Lurasidone	Phase 3	NCT01911442
	Fragile X—6 to 25 years old	Aripiprazole	Open label	Erickson et al. (2011b)
Serotonin reuptake inhibitors	BTBR	Busprione	• Enhanced social interactions	Gould et al. (2011)
		Fluoxetine	• Increased sociability	Chadman (2011) and Gould et al. (2011)
	Fmr1		• Reduced anxiety • Reduced locomotor activity	Uutela et al. (2014)
	Clinical population	**Treatment**	**Phase**	**Reference***
	ASD—2 to 6 years old	Buspirone	Phase 2	NCT00873509
	ASD—6 to 17 years old		Open label	NCT01850355, IRCT201307303930N28; Ghanizadeh and Ayoobzadehshirazi (2015)

Mechanistic class	Preclinical model	Compound	Preclinical phenotype rescues	Reference
	ASD—5 to 17 years old	Citalopram	Phase 2; Randomized controlled trial	NCT00086645, NCT00211770; King et al. (2009)
		Fluoxetine	Phase 3; Open label; Placebo-controlled crossover trial	NCT00515320, ACTRN12608000173392; Buchsbaum et al. (2001), Hollander et al. (2005), Desousa (2010), Chantiluke et al. (2014a, b) and Mouti et al. (2014)
	ASD—3 to 10 years old	Fluvoxamine Sertraline	Phase 3	NCT00655174
	ASD—3 to 12 years old	Olanzapine	Phase 2	NCT00057408
	ASD—6 to 16 years old		Open pilot study; double-blind, placebo-controlled trial	Potenza et al. (1999), Malone et al. (2001), Kemner et al. (2002) and Hollander et al. (2006)
	ASD—18 to 39 years old	Sertraline	Open label	McDougle et al. (1998)
	ASD—18 to 53 years old	Fluvoxamine	Double-blind, placebo-controlled trial	McDougle et al. (1996)
	ASD—18 to 65 years old	Fluoxetine	Double-blind, placebo-controlled trial; open trial	NCT00027404; Fatemi et al. (1998) and Hollander et al. (2012)
	Fragile X—12 to 50 months old	Sertraline	Retrospective chart review	Indah Winami et al. (2012)
Acetylcholine modulation	BTBR	Donepezil	• Improved cognitive flexibility • Enhanced sociability	Karvat and Kimchi (2014)
	Valproic acid		• Improved sociability • Reduced repetitive behavior • Reduced hyperactivity	Kim et al. (2014a)
	Clinical population	**Treatment**	**Phase**	**Reference***
	ASD—22 to 44 months	Donepezil	Phase 2	NCT01887132
	ASD—2 to 7 years old		Open label	Buckley et al. (2011)
	ASD—7 to 19 years old		Double-blind, placebo-controlled trial	Hardan and Handen (2002) and Handen et al. (2011)
	ASD—10 to 18 years old		Phase 4	NCT01098383
	ASD—4 to 12 years old	Mecamylamine	Phase 2	NCT00773812; Arnold et al. (2012)
	Fragile X males—6 to 15 years old	Donepezil	Randomized, double-blind, placebo-controlled pilot study	CTRI-2008-000229; Sahu et al. (2013)

[a] Identifier numbers for clinical trials were indexed from clinicaltrials.gov (NCT), anzctr.org.au (ACTRN), umin.ac.jp/ctr (UMIN), irct.ir (IRCT), and ctri.nic.in/Clinicaltrials (CTRI) Web sites