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The utility of rodent models of autism spectrum disorders

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Purpose of review
This review discusses the ways that rodent models of autism spectrum disorders (ASDs) have been used to gain critical information about convergent molecular pathways, the mechanisms underlying altered microcircuit structure and function, and as a screen for potential cutting edge-treatments for ASDs.

Recent findings
There is convergent evidence that impaired developmental pruning of connections may be a common finding among several mouse models of ASDs. Recent studies have uncovered impaired autophagy by pathological mTOR activation as a potential contributor to microcircuit dysfunction and behavior. ASD-related disinhibition and exaggerated synaptic plasticity in multiple distinct circuits in cortex and reward circuits in striatum also contribute to social dysfunction and repetitive behaviors. New exciting molecular therapeutic techniques have reversed cognitive deficits in models of ASD, indicating that mouse models could be used for preclinical translational studies of new treatments.

Summary
Rodent models of ASDs coupled to new emerging technologies for genome editing, cell-specific functional and structural imaging, and neuronal activity manipulation will yield critical insights into ASD pathogenesis and fuel the emergence of new treatments.

Keywords
mouse, social, translation, treatment

INTRODUCTION

Autism spectrum disorders (ASDs) are developmental disorders characterized by deficits in social interactions and language, as well as repetitive and restrictive behaviors. Autism is clinically heterogeneous, and often accompanied by one or more comorbidities, including intellectual disability, hyperactivity, sensory processing abnormalities, motor deficits, and seizures. The cause of ASDs is complex and has been attributed to genetic factors as well as poorly understood non-genetic causes (reviewed in [1]). Large-scale next-generation sequencing studies from large cohorts of ASD patients and controls have found highly validated de-novo and inherited genetic changes implicating dozens of susceptibility genes contributing to the disorders [2–5]. With increasing size of sequencing cohorts, this list of validated causative gene mutations is expected to increase to include several hundred genes [2]. However, identification of causative genetic changes is only the first essential step for understanding how each genetic change alters downstream molecular cascades, perturbs brain development and function, and ultimately leads to autism-related behaviors. Rodent models incorporating this growing list of genetic changes are one of the prime methods used to dissect the effects of gene mutations on neuronal anatomy, connectivity, physiology, and behavior. In this article, we review many of the more recent advances made in the field using mouse models of ASDs and discuss ways these models could be used to study ASD pathogenesis and find new treatments (Table 1).

WHY USE MOUSE MODELS

Mouse model systems have long been used to provide mechanistic insights into the cause of disease and have been instrumental in the discovery of pharmacologic therapies for human illness. Because

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KEY POINTS

- Rodent models of ASDs are useful for unraveling the molecular pathways associated with ASD-related gene mutations.
- Rodent models of ASDs can help us find convergent microcircuit changes associated with the disorder.
- Rodent models of ASDs may be useful for preclinical behavioral studies before testing drugs in humans.

of their close evolutionary relationship, mice and humans share great preservation of genes, biological processes, brain circuitries, and to some extent, behaviors. Although ASDs are uniquely human disorders, many of the core deficits of the disorders can be paralleled in mice through close behavioral investigation [6,7]. This evolutionary conservation, together with our ability to employ experimental manipulations through genetic engineering and other cutting-edge technologies [8,9], may not only help us probe the underlying mechanism of the disorder, but may also lead to the development of targeted and effective therapeutic approaches that can later be translated to humans.

Rodent models of ASDs have been useful in a number of mutually reinforcing ways for ASD research. First, these models present a relevant and tractable intact biological system for understanding the complex interaction of a specific mutated gene product with other proteins, helping to define convergent molecular pathways that that can later be targeted for treatment. Second, these models can be used to define the anatomical and physiological changes in precisely defined microcircuits that may contribute to ASD. Examining these changes across multiple models carrying gene mutations in distinct molecular pathways would help identify fundamental changes in neural circuitry that are the cumulative result of the genetic mutations and the ultimate cause of social behavioral dysfunction. Accordingly, these models would help identify biomarkers that may be translated to use in humans, predicting outcome and gauging response to treatment. Third, these models would be useful for screening therapeutic effects of behavioral and pharmacological treatments. A battery of behavioral tests has been developed that can provide careful assessment of behavioral deficits in rodent models [7,10]. Behavioral measures are indispensable for gauging of effect and drug treatments and therapeutics. Fourth, the advent of models that allow temporally specific genetic deletion and rescue of ASD-related genetic changes would allow us to define the critical developmental windows wherein interventions would be effective [11–14]. Many of these genetic changes may not only alter brain development but also affect the function of fully developed brain circuits [15]. Thus, these conditional genetic perturbation techniques hold the potential for effective treatment of adults with certain forms of ASD. Finally, these models would be useful in the future for assessing the interaction of specific environmental insults with autism susceptibility genes.

SEARCH FOR CONVERGENCE: MOLECULAR CASCADES (THE MTOR PATHWAY)

To better understand the core pathological mechanisms leading to ASD, it is critical to comprehend the biological function of a given gene and its protein product, and to find convergent pathways among the many genes. The best example of a molecular pathway that was identified and dissected using mouse models involves the PI3K-mammalian target of rapamycin (mTOR) signaling cascade wherein mutations in *Tuberous Sclerosis Complex 1 and 2 (TSC2, TSC2)*, and *Neurofibromatosis 1* (*NF1)* and *PTEN* genes all cause syndromes that include ASD-related behaviors. Multiple studies in these mouse models have shown the beneficial effects of the mTOR inhibitor rapamycin in ameliorating anatomical, physiological, and behavioral deficits [16–21]. Parallel studies in mice and humans have also shown that other seemingly unrelated ASD-associated proteins can also be incorporated into the canonical mTOR pathway. One example is the loss of FMR1 that causes Fragile X syndrome; the lack of FMR1 also upregulates mTOR activation, leading to elevated cap-dependent translation and impaired plasticity in Fragile X mice [22]. These findings suggest that effects on mTOR-dependent translation could act as a final common pathway for a number of ASD-related molecular cascades. Moreover, pharmacological downregulation of mTOR using rapamycin could be beneficial not only for the traditional mTOR-related disorders but also for a wide range of other ASD syndromes. Mouse models can help us determine which syndromes would respond to particular treatments to therapies targeting the mTOR system and help us tailor clinical trials to patient populations that are most likely to respond and benefit from certain therapies.

SEARCH FOR CONVERGENCE: MACRO AND MICROCIRCUITS

Mouse models have also been extremely useful in helping us discover autism-related changes in cortical circuit connectivity during brain development

Table 1. Table demonstrating each ASD model, and associated ASD-related behaviors, functional disruptions, and response to treatments

Model	ASD-related behaviors	Functional disruptions	Treatment	Reference
15q11–13dup	Decreased sociability	Spine pruning deficits in Purkinje neurons	None	Piochon *et al.*, 2014 [27]
	Increased vocalizations in pups	Enhanced LTD		
	Reduced vocalizations in adults			
	Behavioral inflexibility			
	Increased grooming			
	Hyperactivity			
	Anxiety			
16p11.2del	Reduced sociability	Alterations in dopaminergic pathways in MSNs	None	Portmann *et al.*, 2014 [29▪▪]
	Repetitive behaviors	Decreased striatal and nucleus accumbens volume	Decreased sensitivity to risperidone	
	Hyperactivity			
BTBR	Reduced sociability	Decreased inhibition		
	Repetitive grooming	Alterations in multisensory integration	Diazepam	Gogolla *et al.*, 2014 [38]
	Increased vocalizations in pups			
	Altered vocalizations in adults			
FMR1	Altered social behavior	Spine pruning deficits	mGluR antagonists	Bear *et al.*, 2004 [42]
	Increased vocalizations	Delayed inhibitory maturation and inhibitory function	BK-Ca channel openers	Patel *et al.*, 2014 [24]
	Stereotypies	Altered developmental synchrony	Prenatal bumetanide	Patel *et al.*, 2013 [36]
	Repetitive behaviors	Delayed inhibitory maturation		Goncalves *et al.*, 2013 [37]
	Anxiety	Enhanced LTD		Tyzio *et al.*, 2014 [39]
	Hyperactivity	Increased dendritic and cortical excitability (BK-Ca channels)		
	Cognitive deficits			
Mecp2	Altered sociability	Excessive spine pruning	Levodopa	Jiang *et al.*, 2013 [26]
	Decreased vocalizations	Altered inhibition	Dopa-decarboxylase inhibitors	
	Increased grooming		IGF1	
Nlgn3	Altered sociability	Alterations in dopaminergic pathways (Nac)	None	Rothwell *et al.*, 2014 [28]
	Repetitive behaviors	Impaired inhibition onto MSNs		
	Inflexibility	Decreased perisomatic inhibition		
PTEN	Decreased sociability	Decreased LTD	None	Takeuchi *et al.*, 2013; Garcia-Junco-Clemente *et al.*, 2013 [42,53]
	Increased grooming	Decreased intrinsic excitability (SK channels)		
TSC1	Decreased sociability	Cerebellum	Rapamycin/mTOR	Bateup *et al.* 2013 [33]
	Inflexibility	Decreased inhibition		
	Increased grooming	Decreased LTD		
	Increased pup calls			
TSC2	Decreased sociability	Deficits in developmental spine pruning and autophagy	Rapamycin/mTOR	Tang *et al.*, 2014 [23▪▪]
	Increased grooming			

Table 1 (*Continued*)

Model	ASD-related behaviors	Functional disruptions	Treatment	Reference
Ube3a	Decreased sociability	Decreased synaptic pruning	ASOs	
	Decreased vocalizations	Decreased excitatory neurotransmission		Meng *et al.*, 2014 [56▪▪]
	Repetitive behaviors			Piochon *et al.*, 2014 [27]

ASOs, antisense oligonucleotides; ASD, autism spectrum disorder; MSNs, medium spiny neurons.

(Table 1). Tang *et al.* [23▪▪] made an important advance in our understanding of cortical connectivity by showing that the developmental pruning of cortical dendritic spines is defective in TSC2 knockout mice. In addition, they were able to further dissect the cause of this pruning impairment by mating their knockout animals to mice with impaired autophagy and showing that the blockade of autophagy mediates the specific spine pruning phenotype as well as the social impairment in these animals. Interestingly, rapamycin could no longer rescue the pruning deficits in the TSC2 knockout mice when they were bred with mice with impaired autophagy. This discovery of an entirely novel molecular mechanism downstream of mTOR, which links changes in cortical connectivity with impaired social behavior, was made possible by the creative use of mouse genetic models [23▪▪]. Similar to findings in the TSC2 model, electrophysiological studies in the FMR1 model of Fragile X syndrome show a developmental deficit in the pruning of connections between L5A cortical neurons, suggesting that deficits in developmental pruning may extend across multiple models of ASD [24]. Similar deficits in pruning induced by loss of chemokine receptor Cx3cr1 in microglia also induce deficits in social interactions and an increase in repetitive behaviors, providing convergent evidence that pruning deficits could directly contribute to abnormal autism-related behaviors [25]. Excessive dendritic spine pruning in cortical neurons later in life, as seen in the MECP2 duplication syndrome mouse, also strongly correlates with onset of behavioral abnormalities, indicating that spine density needs to be precisely controlled for proper motor, cognitive, and social function [26]. Impaired developmental pruning of connections in autism models is not limited to cortical pyramidal neurons, but has also been observed at the climbing fiber-Purkinje cell synapse in the 15q11–13 duplication model, suggesting that impaired developmental pruning of connections may extend to other circuits across the brain, contributing to a global deficit [27].

In addition to identifying new molecular mechanisms contributing to ASD-related changes in connectivity, mouse models of ASD have also been highly effective for localizing the precise circuit abnormalities causing specific ASD-related behaviors. A prime example of this was a recent study by Rothwell *et al.* who showed that cell type-specific deletions of the autism-related *NLGN3* gene in dopamine (D1) receptor-positive nucleus accumbens (NAc) neurons (Drd1+ neurons) [but not in D2 receptor positive neurons (Drd2+ neurons) or cerebellar neurons] was sufficient to induce a motor phenotype [28]. Furthermore, they showed that this deletion impaired inhibition onto Drd1+ medium spiny neurons (MSNs) of the NAc [28]. This suggests that ASD-related genetic changes can result in highly specific changes onto distinct microcircuit elements within specific subcortical structures. Another study in the mouse model of 16p11.2 deletion syndrome used single-cell transcriptomics to discover an increase in number of striatal Drd2+ neurons, and decrease in the number of Drd1+ neurons in the deep cortical layers. In this model, excitatory input onto striatal MSN in the NAc shows decreased NMDA/AMPA ratios and decreased probabilities of release as assayed by paired pulse ratios. Behaviorally, the mice show hyperactivity, circling, deficits in movement control, and a lack of habituation [29▪▪]. Together, both studies highlight the importance of striatal reward circuits for understanding repetitive behaviors and motor control in autism.

These findings are somewhat at odds with findings in the TSC1 model that found that cerebellar dysfunction was key for all ASD-related behaviors in this model. Specifically, deletion of TSC1 in cerebellar Purkinje cell resulted in abnormal social interactions, repetitive behaviors, and abnormal vocalizations [17]. These findings supported earlier histological work implicating the cerebellum in autism [30–32]. They also highlight the importance of unbiased screens in searching for circuits inducing ASD-related behaviors. Further studies in multiple models would be needed to understand the complex interactions of the multiple cortical, cerebellar, and subcortical regions in mediating abnormal motor and nonmotor behaviors [17]. A mouse model for 15q11–13 duplication syndrome, which in humans causes autism, intellectual disability, and seizures, also shows profound changes in cerebellar physiology, as well as both motor and

social behaviors, providing convergent evidence of cerebellar disorder in autism [27].

Loss of inhibition seems to be a convergent theme among many ASD models. There is a specific loss of inhibition in the hippocampus of TSC1 mice [33], and a massive loss of parvalbumin neuron-specific inhibition in the hippocampus of NLGN3 R451C mice [34▪▪]. In contrast, inhibition from cholecystokinin-positive (CCK+) basket cells was strongly increased through loss of tonic endocannabanoid signaling, suggesting highly precise cell-type-specific changes to perisomatic inhibition in the NLGN3 R451C model [34▪▪]. In the FMR1 knockout mouse, there is a delayed developmental switch of excitatory to inhibitory chloride reversal potential [35], and a reduction of excitation onto fast-spiking cortical interneurons, which ultimately reduces inhibitory output [36]. These alterations correlate with delayed developmental desynchronization of network activity in the Fragile X mouse model, suggesting that alterations in synaptic connectivity directly impact network synchrony and potentially activity-dependent circuit development [37]. In the BTBR model of autism, an inbred mouse strain with severe social deficits and repetitive behaviors, loss of inhibition leads to abnormal multisensory integration in the insular cortex [38]. In both the BTBR and Fragile X models, there is diminished oxytocin-dependent decrease of intracellular chloride at birth, leading to excitatory GABAergic responses. Treatment of pregnant females with bumetanide, a blocker of the Na-Cl-K co-transporter NKCC1, prevented these pathological changes and improved autism-related behaviors by normalizing intracellular chloride concentrations and therefore the driving force for GABAergic transmission [39]. This study highlights the long-lasting effects of altered inhibition in early development. In support of these findings, bumetanide administration to a small group of children with autism resulted in some improvements in autism-related behaviors; these findings will need to be replicated in larger studies [40].

These changes in inhibition will likely not only impact basal synaptic transmission but also alter synaptic plasticity. For example, TSC1 [33] and PTEN models [41] show a loss of metabotropic receptor-dependent long-term depression (LTD) in the in CA1 and dentate gyrus regions of the hippocampus, respectively, whereas the FMR1 model of Fragile X and the Ube3a knockout model of Angelman syndrome both show an enhancement of mGluR-dependent LTD [42–44]. In the FMR1 model, mGluR-dependent LTD pathologically persists in the absence of protein synthesis [45]. This suggests that either diminished or excessive plasticity could result in abnormal circuit function. The Fragile X studies led to the mGluR theory of Fragile X syndrome that posited that many of the physiological and behavioral deficits in Fragile X arise from increased mGluR signaling [42]. This led to several studies that showed mGluR5 inhibition rescues cognitive deficits, auditory hypersensitivity, aberrant dendritic spine density, overactive ERK, and mTOR signaling [46,47] or social behavioral deficits [48] in FMR1 knockout mice. Unfortunately, these findings have not translated to successful treatment of individuals with Fragile X in clinical trials. This may require more careful selection of patients and outcome measures [49].

Changes in connectivity are functionally translated into alterations in neuronal output by engaging intrinsic ion channels. In the PTEN mouse model of autism, adult single copy deletion leads to diminished intrinsic excitability of L2/3 visual cortical neurons through increased expression of calcium-activated small conductance (SK-type) potassium channels. This decreased intrinsic excitability in turn leads to decreased visual cortical response magnitudes without altering selectivity [50▪▪]. Conversely, in the FMR1 model of Fragile X, there is decreased expression of dendritic BK-type calcium-activated potassium channels, which increases dendritic excitability and heightens sensitivity to incoming somatosensory inputs [51]. Therefore autism-related changes in intrinsic excitability can dramatically alter sensory responses and may respond to pharmacological interventions [51,52].

New discoveries using optogenetic and DREADD (Designer Receptors Exclusively Activated by Designer Drugs)-based interventions in wild-type mice have greatly improved our understanding of specific circuit elements driving social and nonsocial behaviors. Increasing excitatory activity in the medial amygdala, for example, inhibits social behaviors such as aggression and mating behaviors, whereas increasing inhibitory neuron activation in the same structure promotes social behaviors, and inhibits repetitive self-grooming behavior [53▪▪]. Similar but not identical effects were observed when activating or inhibiting amygdala projections within the ventral hippocampus, highlighting the importance of this projection for regulating social behavior [54]. Future studies in mouse models of autism can focus on dissecting microcircuit changes in the medial amygdala or determine whether pharmacological or cell-specific treatments in the medial amygdala can be used to treat social behavioral dysfunction in these models.

THE UTILITY OF RODENT MODELS: TESTING NEW-GENERATION TREATMENTS

Mouse models can also enable us to test a new generation of rationally designed treatments for

ASDs. A remarkable example is the use of antisense oligonucleotides (ASOs) against the nuclear-localized long noncoding RNA, UBE3A antisense transcript (UBE3A-ATS), which silences the paternal copy of UBE3a in a model of Angelman syndrome. This treatment caused sustained unsilencing of paternal UBE3a, both *in vitro* and *in vivo*, and improved cognitive deficits in the mouse model of the disorder [55▪▪]. Although many details remain to be worked out on timing and mode of delivery of the ASOs, this approach shows the essential role of mouse models for serving as an intermediate preclinical step for the development of novel human therapeutics.

CONCLUSION

The utility of rodent models for autism will increase nonlinearly with improvements in emerging transgenic, genome editing, cellular functional imaging, and activity modulation techniques [8,56,57]. These techniques will allow us to genetically perturb highly specific neuronal subpopulations and follow activity patterns in these cells and their connected neighbors before, during, and after potential treatments, over months, as rodents interact with other animals [58]. Mouse models will complement the results obtained in other in-vitro models such as induced pluripotent stem cell-derived cultured neurons [59]. Most importantly, understanding of basic neuron circuit function at the most fundamental level will likely yield the most impact for understanding ASDs in the long run.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Mehta SQ, Golshani P. Clinical neurogenetics: autism spectrum disorders. Neurol Clin 2013; 31:951–968.
2. De Rubeis S, He X, Goldberg AP, *et al.* Synaptic, transcriptional and chromatin genes disrupted in autism. Nature 2014; 515:209–215.
3. Iossifov I, O'Roak BJ, Sanders SJ, *et al.* The contribution of de novo coding mutations to autism spectrum disorder. Nature 2014; 515:216–221.
4. Krumm N, O'Roak BJ, Shendure J, Eichler EE. A de novo convergence of autism genetics and molecular neuroscience. Trends Neurosci 2014; 37:95–105.
5. O'Roak BJ, Vives L, Fu W, *et al.* Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. Science 2012; 338:1619–1622.
6. Penagarikano O, Abrahams BS, Herman EI, *et al.* Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. Cell 2011; 147:235–246.
7. Kas MJ, Glennon JC, Buitelaar J, *et al.* Assessing behavioural and cognitive domains of autism spectrum disorders in rodents: current status and future perspectives. Psychopharmacology (Berl) 2014; 231:1125–1146.
8. Platt RJ, Chen S, Zhou Y, *et al.* CRISPR-Cas9 knockin mice for genome editing and cancer modeling. Cell 2014; 159:440–455.
9. Boyden ES, Zhang F, Bamberg E, *et al.* Millisecond-timescale, genetically targeted optical control of neural activity. Nat Neurosci 2005; 8:1263–1268.
10. Silverman JL, Yang M, Lord C, Crawley JN. Behavioural phenotyping assays for mouse models of autism. Nat Rev Neurosci 2010; 11:490–502.
11. Robinson L, Guy J, McKay L, *et al.* Morphological and functional reversal of phenotypes in a mouse model of Rett syndrome. Brain 2012; 135:2699–2710.
12. Cobb S, Guy J, Bird A. Reversibility of functional deficits in experimental models of Rett syndrome. Biochem Soc Trans 2010; 38:498–506.
13. Guy J, Gan J, Selfridge J, *et al.* Reversal of neurological defects in a mouse model of Rett syndrome. Science 2007; 315:1143–1147.
14. Rabaneda LG, Robles-Lanuza E, Nieto-Gonzalez JL, Scholl FG. Neurexin dysfunction in adult neurons results in autistic-like behavior in mice. Cell Rep 2014; 8:338–346.
15. Ehninger D, Li W, Fox K, *et al.* Reversing neurodevelopmental disorders in adults. Neuron 2008; 60:950–960.
16. Chow DK, Groszer M, Pribadi M, *et al.* Laminar and compartmental regulation of dendritic growth in mature cortex. Nat Neurosci 2009; 12:116–118.
17. Tsai PT, Hull C, Chu Y, *et al.* Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. Nature 2012; 488:647–651.
18. Ehninger D, Han S, Shilyansky C, *et al.* Reversal of learning deficits in a Tsc2+/- mouse model of tuberous sclerosis. Nat Med 2008; 14:843–848.
19. Zhou J, Blundell J, Ogawa S, *et al.* Pharmacological inhibition of mTORC1 suppresses anatomical, cellular, and behavioral abnormalities in neural-specific Pten knock-out mice. J Neurosci 2009; 29:1773–1783.
20. Sato A, Kasai S, Kobayashi T, *et al.* Rapamycin reverses impaired social interaction in mouse models of tuberous sclerosis complex. Nat Commun 2012; 3:1292.
21. Cambiaghi M, Cursi M, Magri L, *et al.* Behavioural and EEG effects of chronic rapamycin treatment in a mouse model of tuberous sclerosis complex. Neuropharmacology 2013; 67:1–7.
22. Sharma A, Hoeffer CA, Takayasu Y, *et al.* Dysregulation of mTOR signaling in fragile X syndrome. J Neurosci 2010; 30:694–702.
23. ▪▪ Tang G, Gudsnuk K, Kuo SH, *et al.* Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits. Neuron 2014; 83:1131–1143.

This study identifies impaired autophagy by elevated mTOR activation as a potential cause of impaired dendritic spine pruning in the TSC2 model.

24. Patel AB, Loerwald KW, Huber KM, Gibson JR. Postsynaptic FMRP promotes the pruning of cell-to-cell connections among pyramidal neurons in the L5A neocortical network. J Neurosci 2014; 34:3413–3418.
25. Zhan Y, Paolicelli RC, Sforazzini F, *et al.* Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. Nat Neurosci 2014; 17:400–406.
26. Jiang M, Ash RT, Baker SA, *et al.* Dendritic arborization and spine dynamics are abnormal in the mouse model of MECP2 duplication syndrome. J Neurosci 2013; 33:19518–19533.
27. Piochon C, Kloth AD, Grasselli G, *et al.* Cerebellar plasticity and motor learning deficits in a copy-number variation mouse model of autism. Nat Commun 2014; 5:5586.
28. Rothwell PE, Fuccillo MV, Maxeiner S, *et al.* Autism-associated neuroligin-3 mutations commonly impair striatal circuits to boost repetitive behaviors. Cell 2014; 158:198–212.
29. ▪▪ Portmann T, Yang M, Mao R, *et al.* Behavioral abnormalities and circuit defects in the basal ganglia of a mouse model of 16p11.2 deletion syndrome. Cell Rep 2014; 7:1077–1092.

This study uses multiple cutting-edge techniques including single cell transcriptomics to characterize the altered basal ganglia circuitry and repetitive behaviors in the 16p11.2 deletion model.

30. Jones W, Hesselink J, Courchesne E, *et al.* Cerebellar abnormalities in infants and toddlers with Williams syndrome. Dev Med Child Neurol 2002; 44:688–694.
31. Fatemi SH, Halt AR, Realmuto G, *et al.* Purkinje cell size is reduced in cerebellum of patients with autism. Cell Mol Neurobiol 2002; 22:171–175.
32. Courchesne E, Saitoh O, Townsend JP, *et al.* Cerebellar hypoplasia and hyperplasia in infantile autism. Lancet 1994; 343:63–64.

33. Bateup HS, Johnson CA, Denefrio CL, *et al.* Excitatory/inhibitory synaptic imbalance leads to hippocampal hyperexcitability in mouse models of tuberous sclerosis. Neuron 2013; 78:510–522.

34. ■■ Foldy C, Malenka RC, Sudhof TC. Autism-associated neuroligin-3 mutations commonly disrupt tonic endocannabinoid signaling. Neuron 2013; 78:498–509.

This article shows that disrupted tonic endocannabanoid signaling in the NLGN3 model of autism leads to increased inhibition from CCK+ neurons. The article also shows a dramatic reduction in PV+ perisomatic inhibition in this model.

35. He Q, Nomura T, Xu J, Contractor A. The developmental switch in GABA polarity is delayed in fragile X mice. J Neurosci 2014; 34:446–450.

36. Patel AB, Hays SA, Bureau I, *et al.* A target cell-specific role for presynaptic Fmr1 in regulating glutamate release onto neocortical fast-spiking inhibitory neurons. J Neurosci 2013; 33:2593–2604.

37. Goncalves JT, Anstey JE, Golshani P, Portera-Cailliau C. Circuit level defects in the developing neocortex of Fragile X mice. Nat Neurosci 2013; 16:903–909.

38. Gogolla N, Takesian AE, Feng G, *et al.* Sensory integration in mouse insular cortex reflects GABA circuit maturation. Neuron 2014; 83:894–905.

39. Tyzio R, Nardou R, Ferrari DC, *et al.* Oxytocin-mediated GABA inhibition during delivery attenuates autism pathogenesis in rodent offspring. Science 2014; 343:675–679.

40. Lemonnier E, Degrez C, Phelep M, *et al.* A randomised controlled trial of bumetanide in the treatment of autism in children. Transl Psychiatry 2012; 2:e202.

41. Takeuchi K, Gertner MJ, Zhou J, *et al.* Dysregulation of synaptic plasticity precedes appearance of morphological defects in a Pten conditional knockout mouse model of autism. Proc Natl Acad Sci U S A 2013; 110:4738–4743.

42. Bear MF, Huber KM, Warren ST. The mGluR theory of fragile X mental retardation. Trends Neurosci 2004; 27:370–377.

43. Huber KM, Gallagher SM, Warren ST, Bear MF. Altered synaptic plasticity in a mouse model of fragile X mental retardation. Proc Natl Acad Sci U S A 2002; 99:7746–7750.

44. Pignatelli M, Piccinin S, Molinaro G, *et al.* Changes in mGlu5 receptor-dependent synaptic plasticity and coupling to Homer proteins in the hippocampus of Ube3A hemizygous mice modeling Angelman syndrome. J Neurosci 2014; 34:4558–4566.

45. Nosyreva ED, Huber KM. Metabotropic receptor-dependent long-term depression persists in the absence of protein synthesis in the mouse model of fragile X syndrome. J Neurophysiol 2006; 95:3291–3295.

46. Michalon A, Sidorov M, Ballard TM, *et al.* Chronic pharmacological mGlu5 inhibition corrects fragile X in adult mice. Neuron 2012; 74:49–56.

47. Michalon A, Bruns A, Risterucci C, *et al.* Chronic metabotropic glutamate receptor 5 inhibition corrects local alterations of brain activity and improves cognitive performance in fragile X mice. Biol Psychiatry 2014; 75:189–197.

48. Gantois I, Pop AS, de Esch CE, *et al.* Chronic administration of AFQ056/Mavoglurant restores social behaviour in Fmr1 knockout mice. Behav. Brain Res 2013; 239:72–79.

49. Jacquemont S, Berry-Kravis E, Hagerman R, *et al.* The challenges of clinical trials in fragile X syndrome. Psychopharmacology (Berl) 2014; 231:1237–1250.

50. ■■ Garcia-Junco-Clemente P, Golshani P. PTEN: a master regulator of neuronal structure, function, and plasticity. Commun Integr Biol 2014; 7:e28358.

This study identifies overexpression of SK-type calcium-activated potassium channels as a potential mechanism for decreased excitability and visual responsiveness in the PTEN model of autism. The study highlights the importance of intrinsic ion channels for cortical function.

51. Zhang Y, Bonnan A, Bony G, *et al.* Dendritic channelopathies contribute to neocortical and sensory hyperexcitability in Fmr1(-/y) mice. Nat Neurosci 2014; 17:1701–1709.

52. Garcia-Junco-Clemente P, Chow DK, Tring E, *et al.* Overexpression of calcium-activated potassium channels underlies cortical dysfunction in a model of PTEN-associated autism. Proc Natl Acad Sci U S A 2013; 110:18297–18302.

53. ■■ Hong W, Kim DW, Anderson DJ. Antagonistic control of social versus repetitive self-grooming behaviors by separable amygdala neuronal subsets. Cell 2014; 158:1348–1361.

This article demonstrates that activation of excitatory neurons in the medial amygdala inhibits social interaction behaviors and promotes self-grooming, whereas activation of inhibitory medial amygdala neurons inhibit repetitive behaviors and promote social behaviors. The study may lead to experiments in ASD model animals to determine how these distinct neuronal types are pathologically activated or silenced.

54. Felix-Ortiz AC, Tye KM. Amygdala inputs to the ventral hippocampus bidirectionally modulate social behavior. J Neurosci 2014; 34:586–595.

55. ■■ Meng L, Ward AJ, Chun S, *et al.* Towards a therapy for Angelman syndrome by targeting a long noncoding RNA. Nature 2014. [Epub ahead of print]

This study uses a cutting-edge molecular treatment to increase expression of Ube3a in a model of Angelman syndrome. The treatment has potential for translation to human patients.

56. Prakash R, Yizhar O, Grewe B, *et al.* Two-photon optogenetic toolbox for fast inhibition, excitation and bistable modulation. Nat Methods 2012; 9:1171–1179.

57. Rickgauer JP, Deisseroth K, Tank DW. Simultaneous cellular-resolution optical perturbation and imaging of place cell firing fields. Nat Neurosci 2014; 17:1816–1824.

58. Ziv Y, Burns LD, Cocker ED, *et al.* Long-term dynamics of CA1 hippocampal place codes. Nat Neurosci 2013; 16:264–266.

59. Shcheglovitov A, Shcheglovitova O, Yazawa M, *et al.* SHANK3 and IGF1 restore synaptic deficits in neurons from 22q13 deletion syndrome patients. Nature 2013; 503:267–271.