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Disrupted circuits in mouse models of autism spectrum disorder and intellectual disability

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Autism spectrum disorder (ASD) and intellectual disability (ID) are caused by a wide range of genetic mutations, a significant fraction of which reside in genes important for synaptic function. Studies have found that sensory, prefrontal, hippocampal, cerebellar, and striatal regions, as well as the circuits that connect them, are perturbed in mouse models of ASD and ID. Dissecting the disruptions in morphology and activity in these neural circuits might help us to understand the shared risk between the two disorders as well as their clinical heterogeneity. Treatments that target the balance between excitation and inhibition in these regions are able to reverse pathological phenotypes, elucidating this deficit as a commonality across models and opening new avenues for intervention.

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Introduction

Numerous genes that are implicated in synapse development and function are mutated in ASD and ID [1,2]. Because the morphology and activity of synapses are disrupted, it follows that the development and function of the circuits that they form are also impaired. It is therefore critical to examine neural circuits in order to understand the underpinnings of functional phenotypes. Furthermore, discovering neural circuits with similar vulnerability across multiple monogenic syndromes associated with ASD and ID will help to uncover the biological bases of these pathological manifestations and possibly of their heterogeneity. Over the years, animal models of monogenic disorders have been used to address circuit defects across multiple brain regions. Studies have found that sensory, prefrontal, hippocampal, cerebellar, striatal and other midbrain regions, as well as the circuits that connect them, are perturbed in mouse models of ASD and ID.

Here we will discuss recent findings about these deficits in four of the most studied models of ASD and ID monogenic disorders: mice with mutations in *Mecp2*, *Syngap1*, *Shank3*, and *Fmr1* genes. While *Syngap1*, *Shank3*, and *Fmr1* encode synaptic proteins, *Mecp2* encodes a transcriptional regulator affecting synapse physiology. These models, which all have mutations in genes that encode proteins involved in synapse formation, recapitulate highly prevalent monogenic disorders in ASD and ID populations.

Rett Syndrome (RTT), caused by mutations in the X-linked transcriptional regulator *MECP2*, is a neurodevelopmental disorder characterized by 6–18 months of overtly normal development, followed by a regression of acquired skills, loss of speech, gait abnormalities, stereotypic movements, seizures, microcephaly, ID and ASD [3]. MeCP2 regulates the expression of cell type-specific genes in excitatory and inhibitory neurons [4] and thus mutations in the gene affect both glutamatergic [5] and GABAergic synapses [6].

SHANK3 haploinsufficiency, caused by 22q13.3 deletions or point mutations within the gene, leads to Phelan-McDermid syndrome (PMS), a severe neurodevelopmental disorder manifesting in neonatal hypotonia, generalized developmental delay (DD), absent or delayed speech, seizures, motor deficits, mild dysmorphisms, ID, and ASD [7]. SHANK3, the protein encoded by the *SHANK3* gene, is a scaffolding protein of the post-synaptic density of excitatory synapses that is essential for proper synaptogenesis and neuronal physiology [8].

Loss or mutations in the Fragile X Mental Retardation Protein (FMRP), encoded by the *FMR1* gene, cause Fragile X Syndrome (FXS), a leading monogenic cause

of ASD and the most frequent form of inherited ID [9]. FMRP is an RNA-binding protein regulating the dendritic localization, stability and translation of mRNAs encoding key synaptic proteins and affecting synapse development and physiology [9].

Mutations in *SYNGAP1* are associated with an autosomal dominant encephalopathy manifesting in generalized epilepsy in most cases, hypotonia, unstable gait, mild to severe ID, and ASD [10,11]. SYNGAP1 encodes the Synaptic Ras GTPase-activating protein (SynGAP), a RasGAP protein specific to excitatory synapses and associated to the N-methyl-D-aspartate (NMDA) receptors signaling complex [12]. SynGAP regulates the maturation of excitatory synapses [13–18], the synaptic expression of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors [14,17], excitatory synaptic transmission [16,17,19], and long-term potentiation (LTP) [14,18,19].

Excellent reviews discuss the neuropathological bases of these disorders and the neurobiology of the associated proteins [3,8,9,20]. Therefore, we will limit our discussion to the most recent findings on circuit-level alterations in animal models for these four ASD and ID disorders.

Circuits disrupted in ASD and ID mouse models

The imbalance between excitation and inhibition (E/I) has been proposed as a possible cortical network-level mechanism that underlies neural and behavioral dysfunction in ASD [21,22]. As we will detail below, increases and decreases in behavioral activity in conjunction with hypersynchronous neural activity have recently been recorded across circuits in ASD and ID models.

Sensory circuits

Sensory systems in mouse models for ASD and ID display deficits in neuronal morphology and E/I imbalance, which lead to impairments in event-related potentials (ERP) and sensory sensitivity (Figure 1).

One relevant circuit in rodents is the barrel cortex, which is located in the primary somatosensory cortex and receives input from the whiskers. In wild-type (WT) mice, layer 2/3 neurons of the barrel cortex and other neocortical regions undergo a desynchronization of spontaneous network activity at postnatal (P) day 12, which is thought to be critical for efficient neural coding [23]. In contrast, neurons in the barrel cortex have high correlation coefficients at P14-16 in *Fmr1* knockout (KO) mice, due to higher firing rates during Up/Down states during slow-wave sleep [23]. This indicates a sensory hyperexcitability during a critical developmental window for experience-dependent plasticity.

Auditory sensory circuits also show perturbations and have been investigated in both human and mouse studies. FXS patients, for example, show increased auditory hypersensitivity compared to controls [24,25]. The N1 component of their auditory ERP does not decrease over repetition of the same sound, a sign of reduced auditory habituation [26]. This deficit is recapitulated in *Fmr1* KO mice, which also display audiogenic seizures [27].

When event-related power is examined by recording hippocampal local field potential responses to white noise auditory events, WT mice typically exhibit a decrease in event-related power at low auditory frequencies, an increase in event-related power at high auditory frequencies, and a robust increase in phase-locking factor (PLF), a measure of trial-to-trial reliability, across all frequencies [28]. On the contrary, mice with a *Mecp2* ablation in the forebrain GABAergic neurons exhibit a significant reduction in event-related power and PLF responses across all frequencies and manifest seizures [28], an aggravating symptom of RTT. Restoring MeCP2 expression in forebrain GABAergic neurons in *Mecp2* null mice led to a significant preservation of auditory event-related power and PLF. Therefore, MeCP2 function, specifically in forebrain GABAergic neurons, is required for maintaining proper auditory event-related power [28].

Integration of auditory and somatosensory information is also dysfunctional in models for ASD and ID. Because these response fields overlap in the insular cortex, degree of integration can be quantified through a multisensory index (MI), which is computed by dividing the response amplitude upon combined stimulation of both modalities by the sum of the unisensory responses [29]. *Mecp2* and *Shank3* KO mice displayed decreased MI [29]. Additionally, there was an increase in the size of parvalbumin (PV)-positive neurons in *Mecp2* KO mice and a decrease in PV-circuit function in *Shank3* KO mice [29]. A model that could reconcile the discrepancy of the PV-circuit differences despite convergence on MI decrease is that optimal multisensory integration occurs when excitatory and inhibitory activity is equally balanced, which is dependent upon proper PV-circuit function: if PV function is too high or too low, MI is invariably decreased [29].

In another sensory domain, visual processing, *Mecp2* het female mice displayed smaller visual evoked potential (VEP) amplitudes in comparison to WT littermates, resembling patients with RTT [30]. Interestingly, VEP amplitude negatively correlated with age and severity of phenotype in patients with RTT, suggesting that VEP amplitude might reflect overall neurological outcome and progressively decrease during developmental regression [30]. Additionally, the ability to associate two near-simultaneous sensory inputs (e.g. a light flash and an air puff) with an eyeblink, which depends upon plasticity of the cerebellum, was found to be impaired in *Shank3* het mice and het mice harboring a truncating mutation in *Mecp2* [31]. *Shank3* het mice reached a response probability that