HHS Public Access

Author manuscript

Curr Mol Med. Author manuscript; available in PMC 2016 January 21.

Published in final edited form as:

Curr Mol Med. 2015 ; 15(2): 146–167.

Common Mechanisms of Excitatory and Inhibitory Imbalance in Schizophrenia and Autism Spectrum Disorders

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Abstract

Autism Spectrum Disorders (ASD) and Schizophrenia (SCZ) are cognitive disorders with complex genetic architectures but overlapping behavioral phenotypes, which suggests common pathway perturbations. Multiple lines of evidence implicate imbalances in excitatory and inhibitory activity (E/I imbalance) as a shared pathophysiological mechanism. Thus, understanding the molecular underpinnings of E/I imbalance may provide essential insight into the etiology of these disorders and may uncover novel targets for future drug discovery. Here, we review key genetic, physiological, neuropathological, functional, and pathway studies that suggest alterations to excitatory/inhibitory circuits are keys to ASD and SCZ pathogenesis.

Keywords

Autism; dendritic spine; E/I imbalance; GABAergic interneuron; glutamatergic; mTOR; NMDAR; schizophrenia

INTRODUCTION

Autism Spectrum Disorders (ASD) and Schizophrenia (SCZ) are two highly heritable spectrum disorders with complicated genetic etiologies but overlapping behavioral phenotypes [1]. ASDs are a group of neurodevelopmental disorders characterized by repetitive behaviors and problems with social interaction and communication while SCZ is a disease afflicting thought, perceptions of reality, affect, and cognition [2]. Genetic linkage and genome-wide association studies (GWAS) have discovered a plethora of disease-associated genes, but few have been widely reproducible because each individual gene likely holds small influence on the overall disease pathogenesis [3, 4] Moreover, given the conditions' heterogeneous natures, many studies lack the required power to consistently

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CONFLICT OF INTEREST

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reproduce these weak associations [5]. The behavioral symptoms of ASD and SCZ, however, are intriguingly similar; social interaction deficits, cognitive deficits, emotional processing problems, and executive functions dysfunction are all behavioral features commonly observed in both disorders [6, 7]. In addition, subsets of autism patients have auditory and visual hallucinations, similarly to acutely ill patients with SCZ [8]. Indeed, autism was initially believed to be an early manifestation of SCZ and was once referred to as "schizophrenia syndrome of childhood" [9, 10].

These observations suggest that while the genetics are diverse, the two diseases may convergence upon common pathophysiological mechanisms. One emerging hypothesis maintains that alterations in the ratio of excitatory to inhibitory cortical activity (E/I imbalance) could explain the diseases' similar social and cognitive deficits. Such imbalances may arise from problems in initial neural circuit formation or maintenance, as many of the genes derived from linkage and association studies code for proteins involved with these processes [4, 11]. In addition, postmortem studies have discovered structural/functional changes in both glutamatergic excitatory and GABAergic inhibitory circuits in individuals with ASD and SCZ [12–14].

The end goal, however, is to provide biological evidence that risk variants impact the pathogenesis of the diseases through specific shared pathways, such as E/I imbalance, so that future therapies can be developed in a directed manner. For this purpose, we will briefly discuss the cellular physiology of E/I balance, review evidence of its dysregulation in ASD and SCZ, and categorize the implicated molecules into common signaling pathways involved with E/I homeostasis.

THE PHYSIOLOGY OF E/I BALANCE

Excitatory/Inhibitory Synapses and Dendrite Arborization

Excitatory and inhibitory synapses, although found on pyramidal and interneuron cells alike, have different architectures. While glutamatergic synapses are found almost exclusively on dendritic spines [2], GABAergic synapses are localized along the dendritic shaft, somata, and axon initial segments [15]. Excitatory synapses contain an electron-dense postsynaptic density (PSD) that directly opposes a pre-synaptic active zone while inhibitory synapses are missing this feature and are more symmetric. Likewise, the two also harbor different molecular constituents, which are often used as markers for identification purposes in immunofluorescent studies. Excitatory synapses maintain pre-synaptic vesicular glutamate transporters (VGLUTs), which pack the excitatory neurotransmitter glutamate into synaptic vesicles for release. The postsynaptic side harbors the postsynaptic density protein-95 kDa (PSD-95), a multimeric scaffold that anchor N-methyl-D-aspartate receptors (NMDARs) and 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid receptors (AMPARs) to the surface. Inhibitory synapses have pre-synaptic vesicular GABA transporters (VGATs), which pack the inhibitory neurotransmitter y-aminobutyric acid (GABA) into synaptic vesicles for release, while the adaptor protein gephyrin help cluster y-aminobutyric acid receptors (ionotropic $GABA_A$Rs and metabotropic $GABA_B$Rs) and glycine receptors (largely in spinal cord, brainstem, and retina [16]) onto the postsynaptic surface. Both

synapse types are held together by trans-synaptic interactions between pre- and post-synaptic cell adhesion molecules [17] (Fig. 1).

The structure and arborization of dendrites has a profound impact on the processing of neuronal information because it determines the extent of a neuron's synaptic field. The establishment of the dendritic arbor is highly plastic and involves dendrite extension, addition, elongation, retraction. Much of this early process is dependent on robust synapse formation and hence is particularly sensitive to experience and activity [18]. However, by adulthood, the arbor becomes stabilized and is no longer as dependent on synaptic activity. This mechanistic separation allows mature neurons the ability to fine-tune synaptic connections while retaining a stable dendrite field [19].

Pyramidal Neurons

Pyramidal cells comprise the majority of the neuronal population and are primarily responsible for long-range glutamatergic transmission in the mammalian forebrain. The dendrites of pyramidal neurons are usually regarded as input structures and receive excitatory synaptic contacts from other excitatory neurons on small protrusions called dendritic spines. Thousands of spines stud the pyramidal cell's apical and basal dendritic branches, increasing the neuron's receptive surface area and allowing for integration of thousands of excitatory signals to influence the output [20]. Due to this capability to control neuron activity, spines are morphologically regulated to meet the dynamic demands of the growing brain and thus intimately linked to cognitive function [21]. For instance, during development, spines actively participate in synaptogenesis and contribute to the formation of neuronal circuits [21]. Activity-dependent spine maintenance or elimination, on the other hand, is important for the remodeling of established neuronal circuits during post-natal and adolescence periods [22, 23]. These complicated dynamics are regulated by equally complex molecular pathways, involving cytoskeletal remodeling, trans-synaptic adhesion, receptor trafficking, protein translation, ubiquitination, and gene expression [24–26].

GABAergic Neurons

Cortical GABAergic neurons comprise only 10–15% of the entire neuron population but play crucial roles in regulating neuronal excitability due to their synaptic strengths, high firing rates, and abilities to synthesize the inhibitory neurotransmitter y-aminobutyric acid (GABA) by two isoforms of glutamic acid decarboxylase (GAD65 and GAD67) [27]. Unlike pyramidal neurons, which have long-projecting axons and homogenously characteristic spine-studded pyramidal-shaped arbors that can span several cortical layers, cortical interneurons communicate within spatially restricted regions and are relatively aspiny. Moreover, they are categorized into many subpopulations - classified by a combination of morphological, physiological and molecular properties - each of which possesses specialized functions for regulating pyramidal activity [27, 28]. Of these, interneurons possessing the calcium-binding protein parvalbumin greatly influence the generation and timing of a pyramidal cell's action potentials due to the strategic location of their inhibitory synapses and their fast-spiking electrophysiological properties [29, 30]. For example, the chandelier subtypes electrophysiologically exhibit fast-spiking firing patterns [30] and have long linear axon terminals called cartridges that synapse onto the axon initial

segment of pyramidal neurons [31]. Basket subtypes, on the other hand, have identical fast-spiking electrophysiological features [29], but their axons target the cell bodies and proximal dendrites of pyramidal neurons [32]. Thus, both parvalbumin-positive (PV+) subtypes are situated near the axon and have tight control over the excitatory cell's firing rhythms. Moreover, their biophysical abilities to generate fast synchronized inhibition patterns onto and to receive rhythmic feedback inhibition from pyramidal cells provide the temporal synchrony necessary for generation of network oscillations [33] (Fig. 2). For the purposes of this review, we will focus largely on PV+ interneurons because they play an essential role in proper cognitive function and are noticeably afflicted in ASD and SCZ patients. For a more comprehensive review on interneuron classification and function, we would like to direct the reader to pertinent articles [27, 34].

Excitatory/Inhibitory Balance

Information transfer in the brain relies on a functional balance between excitatory and inhibitory networks. At the level of individual neurons, this balance involves the maintenance of appropriate ratios of excitatory versus inhibitory synaptic inputs [35]. Activation of an excitatory synapse by glutamate depolarizes the cell and increases the likelihood that the cell will fire an action potential while activation of an inhibitory synapse by GABA does the opposite. Thus, the E/I synaptic ratio is critical for keeping the cell's overall firing patterns within a narrow range [36]. However, this ratio is highly asymmetric across development and between neuronal subtypes. For example, individual pyramidal cell dendrites in the cultured hippocampal cultures have E/I ratios of 2:1 at 14 days but 4:1 at 19 days [37] while hippocampal parvalbumin and calretinin-positive interneuron subtypes have 14:1 and 3:1 ratios respectively [38]. Surprisingly, the ratios themselves are tightly regulated with minimal variance even between branches on a single neuron. Yet how do neurons establish and maintain this long- term internal consistency despite such external variability? In a landmark paper, Turrigiano *et al.* [39] discovered chronic activity blockade with tetrodotoxin (TTX) and bicuculline increased and decreased the amplitude of miniature excitatory postsynaptic currents (mEPSC) respectively in cultured neurons, while drug washout restored firing rates to control levels. Thus, in response to outside influences forcibly altering activity, compensatory mechanisms are recruited to restore the initial circuit set point. These responses include modulation of excitatory and inhibitory postsynaptic strength, alterations in presynaptic neurotransmitter release probability, and adjustment of intrinsic membrane excitability [40], all of which affect and are influenced by neuronal architecture, including dendritic spines and arbors. Collectively, multiple levels of homeostatic control exist to ensure the neuron's output is appropriately stable.

Since neural circuits are defined by inter-neuronal communications, output precision in individual cells becomes essential to network function. Cortical interneurons use rhythmic inhibition to create narrow windows for effective excitation, entraining excitatory pyramidal cells to fire certain oscillatory patterns [41–45]. Specific classes of interneurons contribute to the frequency of these particular patterns. For example, the synchronization of neuronal network activity in the human cortex and hippocampus at gamma frequencies (30–80 Hz) is essential for integrating information from different brain regions and is thus relevant for cognition, learning, and memory. Gamma oscillations emerge from the synchronized firing

of interconnected excitatory glutamatergic and primarily inhibitory fast-spiking GABAergic PV+ interneurons (Fig. 2), and its power (i.e. amplitude) is modulated by the E/I balance at distinct synaptic sites in the circuit and the intrinsic excitable properties of the neurons [46]. Given the dynamic variability of early postnatal brain development and its activity-dependent shifts, such internal consistency - from single synapses to entire circuits - requires tight control and is essential for proper circuit formation and adaption to the onset and maturation of sensory input. Genetic perturbations to synaptic homeostatic mechanisms, if uncorrected, can serve as pathophysiological initiation points that lead to network destabilization, which in turn can impact behavior. To illustrate this point, Bateup *et al.* [47] showed loss of *TSC1*, a gene encoding a regulator of mTOR signaling (see **mTOR and ASD**) in hippocampal cultures resulted in a primary decrease of inhibitory synaptic transmission, followed closely by a futile secondary homeostatic response, and concluded with an overall increase in network hyperexcitability. Moreover, optogenetic manipulation of specific excitatory and inhibitory circuits directly caused changes in social and cognitive behavior in mice [48]. Thus, circuits tend to be malleable but vulnerable during postnatal development; notably, several neurodevelopmental disorders, such as ASD and SCZ, manifest during this plasticity period [49, 50].

NEUROPATHOLOGICAL FEATURES OF SCHIZOPHRENIA

One of the defining neuropathological features of SCZ is gray matter loss [51–53]. Postmortem studies have examined brain regions showing the highest indices of gray matter loss and have consistently found reductions in spine density in these parts. Intriguingly, these areas have also been associated with functions which are perturbed in SCZ. For example, the dorsolateral prefrontal cortex (DLPFC) is critical for working memory function and schizophrenic individuals show reduced activity of this region during working memory tasks. Spine loss in the DLPFC has been reproducibly reported, particularly in layer 3 neurons [54]. Moreover, there is also a profound reduction in spine density on pyramidal neurons in the primary auditory cortex, which could explain why schizophrenics suffer from auditory hallucinations [55]. Finally, reductions in hippocampal volume and reduced spine density on CA3 dendrites in SCZ [56, 57] could be the physiological reason why patients have problems with memory and spatial learning. Collectively, these studies reveal strong associations between brain region-specific loss of gray matter, reduced spine density and functional hypoactivity in SCZ.

Dysfunction of DLPFC inhibitory PV+ basket cells is also thought to play a major role in SCZ's working memory deficits. Coordinated firing of DLPFC pyramidal cells at the gamma frequency between a stimulus cue and behavioral response is essential for accurate working memory and relies largely on fast spiking PV+ GABAergic interneurons [58]. For example, PV+ neurons in the monkey DLPFC are active during the delay period of working memory tasks [59], and are responsible for spatial tuning of neuronal responses during this period [60]. In addition, injection of GABA antagonists into the DLPFC disrupts working memory [61]. Fittingly, gamma-frequency oscillations are abnormal in the prefrontal cortex of patients with SCZ who are performing working-memory tasks [45, 62, 63]. Interestingly, multiple postmortem studies have reproducibly found lower levels of parvalbumin mRNA and GAD67, the principal synthesizing enzyme for GABA, in DLPFC PV+ neurons, but

found the absolute number of PV+ cells unchanged, suggesting a functional rather than a numerical deficit [64, 65]. Furthermore examination of PV+ chandelier axon terminals [66] revealed selective reduction of GAT1 - a GABA reuptake transporter - and upregulated levels of the $GABA_A$ receptor α_2 subunit in the axon initial segments of pyramidal neurons, possibly as a compensation to the lowered GABA levels [67]. In conclusion, these findings suggest hyper-excitability and gamma wave disruption in particular brain regions can be etiological contributions of SCZ.

SCHIZOPHRENIA AT THE GLUTAMATERGIC CIRCUIT

As spiny synapses are the basic units of excitatory neural circuits and are intimately involved in neurotransmitter signal transduction, dendritic spine dysfunction may play an important etiological role in SCZ. Interestingly, the strongest results from genetic studies have been haplotypes, single nucleotide polymorphisms (SNPs), and *de novo* mutations associated with genes regulating neuronal excitability, synaptic structure, and plasticity [3, 5, 68]. Here, we will summarize recent findings on some of the most prominent ones and explore their roles in spine dynamics.

Neuregulin1/ErbB4

NRG1 and *ERBB4* are two of the most reproducible SCZ candidate genes [69–76]. Neuregulins (NRGs) are trophic factors that can exist in membrane-bound or soluble forms [77]. ErbB4 is a post-synaptic tyrosine kinase receptor that predominantly binds to soluble NRG1 (type III), through NRG1's epidermal growth factor-like domain [77, 78]. This interaction leads to stimulation of ErbB4's tyrosine kinase activity and downstream changes leading to alterations in synaptic structure and function.

NRG1 and ErbB4 are expressed at the excitatory synapses [79–83] and regulate spine structure and function (although ErbB4's role is more questionable, see next paragraph). Long-term NRG1 treatment increases pyramidal neuronal spine density and the preponderance of spines with mature phenotypes [84] and mice deficient in NRG1 (type III) show reductions in spine density in hippocampal neurons [85]. Similarly, ErbB4 over-expression increases spine density, area, and excitatory synaptic transmission while ErbB4 knockdown reduces spine density and size [86]. In addition, mice lacking ErbB4 in the CNS show reduced spine density in both the hippocampus and cortex and exhibit schizophrenia-related behavioral phenotypes [84].

Perplexingly, ErbB4 is found at much higher levels in interneuron excitatory synapses - especially belonging to the PV+ interneuron subtype - and a recent study used *in vivo* techniques to directly demonstrate ErbB4's specificity in controlling cortical GABAergic circuit development [87]. Thus, it is possible that that ErbB4's role in spines is indirect or an artifact of experimental conditions (see **ErbB4** in **Schizophrenia at the GABAergic Circuit** for further discussion of this discrepancy).

Several SCZ SNPs have caused functional alterations in NRG1 processing, providing an additional level of validity to the NRG1/ErbB4-SCZ hypothesis. For instance, a SCZ-associated SNP in the transmembrane domain of NRG1 leads to disruptions in gamma-

secretase dependent cleavage of the protein, which in turn reduces NRG1-mediated intracellular signaling and abolishes NRG1-regulated growth of pyramidal dendrites [88]. In addition, the second SCZ-associated polymorphism within the original HAP_{ICE} 'at risk' Icelandic haplotype [69] has been shown to transcriptionally regulate NRG1 III levels [89], thus providing a novel mechanism through which this haplotype may increase risk for SCZ.

DISC1

DISC1 was originally identified through a disruption in its open reading frame in a large Scottish pedigree [90] and later verified to be a legitimate SCZ risk gene through polymorphisms and frame shift mutations in other SCZ-afflicted lineages [91]. Further genetic studies have also associated *DISC1* with bipolar, depression, and autism, making it an important psychiatric vulnerability gene [92–97].

DISC1 is a scaffold protein intimately involved with hippocampal development [98–100] and is found abundantly at the spines [101], where it facilitates the formation of protein complexes with its coiled-coil rich C-terminal domain. In SCZ patients carrying high risk *DISC1* SNPs, DISC1-interacting protein expression levels, but not DISC1 mRNA levels, are drastically reduced [102], suggesting that DISC1 function might be affected in SCZ. Disruption of DISC1's ability to scaffold proteins in spines would be expected to have deleterious consequences on spine morphogenesis.

Indeed, long-term DISC1 knockdown leads to reduced spine area in cortical neurons [103]. These effects have been hypothesized to be due to DISC1's interaction with various regulators of spine morphogenesis. Recently, the Rac-GEF Kalirin-7 has been identified as a DISC1 interacting partner and has been shown to directly regulate DISC1's effects on spine morphology through Rac1 [103]. Kalirin loss strongly correlates with spine loss in layer 3 prefrontal cortex neurons in postmortem schizophrenia samples [104]. Finally, a *KALRN*-knockout mouse shows severe reductions in spine density in the frontal cortex and schizophrenic-like behaviors during adolescent years [105]. This is interesting given the onset of SCZ symptoms in adolescence in humans, and points to a tight association between the onset of spine loss and the onset of behavioral impairments in these animals. Taken together, these evidence point to DISC1 as a facilitator in spine function and suggests a role of small GTPases in SCZ spine pathology.

22q11 microdeletion

The 22q11 microdeletion syndrome is the most common copy number variant (CNV) associated with SCZ and accounts for up to 1–2% of the cases [106]. Primary hippocampal neurons from mice engineered to carry hemizygous deletion of the 1.3-Mb orthologous chromosomal region *(Df(16)A+/−)* showed reduced spine density and sizes [107]. Interestingly, loss of either of two genes within this region (*ZDHHC8* and *DGCR8*) was sufficient to impair spine and dendrite morphology [106, 107]. ZDHHC8 is a palmitoyl transferase which palmitoylates PSD-95; its loss results in reduced spine density and simpler dendrites, and its replacement into *Df(16)A+/−* neurons rescued spine and dendrite deficiency [107]. DGCR8 is involved in miRNA processing, and its loss results in smaller spines and simpler dendrites [106].

SCHIZOPHRENIA AT THE GABAergic CIRCUIT

Synchronization of cortical and hippocampal neural networks at gamma frequencies (30–80) Hz is important for proper cognition, memory, and learning [108], but are perturbed in schizophrenic patients [58, 109, 110]. Gamma oscillation amplitudes are reduced in patients with SCZ [111, 112], and multiple postmortem studies show schizophrenic adults have lower levels of GAD67 in DLPFC PV+ neurons [65, 113, 114], suggesting physiological impairment of these interneurons may disrupt working memory circuits in SCZ.

ErbB4

Through multiple mRNA studies, it has been established that ErbB4 is expressed predominantly in GABAergic cells in the neocortex and hippocampus [115–119]. Immunofluorescence studies using specific ErbB4 antibodies have pinpointed ErbB4 to be distributed in somatodendritic regions of several interneuronal subtypes in the neocortex [120, 121] and hippocampus [122, 123] of rodents and primates. More specifically, ErbB4 is expressed in nearly all PV+ interneurons in the neocortex [120] and over half in the hippocampus [123]. PV+ interneurons control E/I balance by either targeting the soma (basket cells) or the AIS (chandelier cells), as both locations have tremendous influence on the amplitude of the excitatory action potential.

Recently, it was demonstrated that perfusion of hippocampal slices with small doses of NRG1 led to increases in kainate-induced gamma oscillations. This effect was ErbB4-dependent, as it was blocked with an ErbB4 antagonist and was absent in *ERBB4*-knockout mice [123]. Similarly, mice harboring full or PV+ targeted ablation of ErbB4 exhibit reductions in kainate induced gamma oscillation power and exhibit severe SCZ-like behaviors [123–125].

A pressing question that arises from these results is if ErbB4 acts pre- or post-synaptically to regulate network activity. While ErbB4's presence in the somatodendritic components of PV + cells has been widely replicated, its role at the GABAergic pre-synaptic terminals has been disputed. Several electrophysiological studies show evidence of ErbB4's presynaptic properties. For example, NRG1 treatment led to GABA release in basket cell terminals, purportedly by the activation of ErbB4 by NRG1 [124]. Moreover, PV+ chandelier cells harboring an ErbB4 conditional mutation were found to have decreases in miniature inhibitory postsynaptic potentials onto excitatory cells [124]. Oddly enough, other immunofluorescence studies using specific ErbB4 antibodies were unable to visually localize ErbB4 to the presynaptic terminal (possibly due to antibody or fixation issues) innervating either the soma or axon initial segment of pyramidal neurons in the hippocampus or frontal cortex of rodents and primates [120, 121].

Such discrepancy may be explained by another theory: ErbB4 is found post-synaptically on dendrites of PV+ interneurons and modulates network activity through the control of glutamatergic feedback. Indeed, targeted ablation of GluAs subunits at post-synaptic GABAergic sites produces intriguingly similar reductions in kainate-induced gamma oscillations [126]. Moreover, the C-terminus tail of ErbB4 directly interacts with PSD-95 [82, 83] and accumulates at synaptic puncta on inhibitory neurons [123, 127, 128].

Ultrastructural analysis in CA1 interneurons using immunoelectron microscopy revealed abundant ErbB4 expression at, and adjacent to, glutamatergic post-synaptic sites on interneurons [128].

These disparate observations were reconciled *in vivo*: an elegant set of experiments demonstrated that: 1) ErbB4 is expressed both in the axon terminals and post-synaptic excitatory synapses of PV+ chandelier and basket cells, but not in pyramidal cells. 2) ErbB4 cell-autonomously regulates the formation of excitatory synapses on these inhibitory subtypes and the formation of inhibitory synapses from PV+ subtypes onto neighboring pyramidal cells. 3) ErbB4 is not necessary for excitatory transmission between pyramidal neurons [87].

DISC1/Dysbindin

Although DISC1's role on spine morphogenesis in excitatory neurons is well established, several lines of evidence have also suggested its requirement for proper cortical PV+ interneurons functioning. For instance, mutant mice that overexpress a dominant negative form of DISC1 have reduced PV+ immunoreactivity in the prefrontal cortex, suggesting DISC1 is necessary for proper functioning of GABAergic cortical interneurons [129]. Likewise, PV+ interneurons in transgenic mice expressing truncated or missense mutated DISC1 are reduced and mislocalized [130, 131].

Dysbindin is another SCZ susceptibility gene and is a possible binding partner to DISC1. Dysbindin is involved with intracellular trafficking and is downregulated in the prefrontal cortex and hippocampus of SCZ patients [132, 133]. *DTNBP1*-knockout mice have reductions in the excitability of cortical and striatal PV+ interneurons, which in turn lead to hyperexcitable pyramidal cells [134].

NEUROPATHOLOGICAL FEATURES OF ASD

Early brain overgrowth and neuronal hyperexcitability are two well-established phenotypes in ASD [135, 136]. About 25–30% of autistic children experience excessive increase in brain size between the first and second year of life when compared with healthy controls [137] while 30% struggle with epilepsy [138]. One possible biological mechanism connecting the two phenotypes is increased spine density, as recent evidence examining post-mortem ASD human brain tissue revealed an increase in spine density on apical dendrites of pyramidal neurons from cortical layer 2 in frontal, temporal and parietal lobes and layer 5 in the temporal lobe [14]. Furthermore, these trends are also observed in tissue from individuals with diseases co-morbid with autism. For instance, the fragile X brain is characterized by macrocephaly, elevated spine density and elongated, tortuous spine morphologies [139]. However, other studies have revealed contradicting findings: several case studies have found smaller neurons and simplified dendrite morphology in the limbic system, consistent with a curtailment of developmental maturity [140, 141]. While these discrepant results must be taken with caution due to lack of large samples (only around 120 postmortem ASD brains have been studied since 1980) and closely matched control groups [142], they also suggest a degree of heterogeneity in the autistic brain, which may be due to brain-region dependent changes caused by alterations in region-specific genetic factors

[143]. Indeed, fMRI studies have consistently reported patterns of long-distance “under connectivity” with short-range “over connectivity” in brains of ASD adult patients [144].

Evidence for alterations in GABAergic circuits in ASD also come from postmortem studies showing significantly reduced GAD65/GAD67 levels in the parietal cortex and cerebellum [145, 146] and alterations in $GABA_A$ and $GABA_B$ receptors in postmortem brains of autistic subjects [147–149]. These alterations may be the result of widespread changes in GABA innervation and/or release, which may lower the threshold for developing seizures, given the high co-morbidity of ASD and epilepsy [150]. In support of this hypothesis, another study showed that ASD patient brains had lower numbers of PV+ interneurons in the prefrontal cortex [151]. As PV+ interneurons provide strong perisomatic innervations of pyramidal cells, a reduction in its absolute number could explain the aberrant GABAergic transmission and predisposition for epileptic symptoms in autism [152]. Together, these results suggest heterogenous changes in glutamatergic and GABAergic systems in the ASD brain can converge upon an overall increased ratio of excitation/inhibition, which can manifest in epileptic symptoms, macroscopic changes in brain volume, and behavioral alterations.

ASD AT THE GLUTAMATERGIC CIRCUIT

The high degree of heritability of ASD has inspired a great deal of research over potential mechanisms [153]. Multiple studies have identified rare mutations and CNVs in genes encoding synaptic proteins in autistic individuals, supporting the hypothesis that excitatory synapse dysfunction may be important in the etiology of ASD. Although each individual gene may not account for a large percentage of ASD cases, consistent with a polygenic mode, they do provide valuable insight into the molecular pathways important for the diseases’ pathogenesis [4]. For the same reason, functional investigations of individual genes may produce markedly different results in simplified experimental systems. However, in the context of a pathogenic brain, these molecules may actually work in conjunction to collectively disrupt common pathways (see section on **Convergent Pathways of ASD and SCZ**). Here, for the sake of simplicity, we will discuss the function of individual ASD risk genes in relation to spiny synapses, E/I imbalance, and behavioral phenotypes.

Neurexins/Neuroligins

Neuroligins (NL1-4) are a group of postsynaptic cell adhesion proteins [154] which interact with presynaptic Neurexins (Nrxns 1–3) to form trans-synaptic adhesions [155–158]. Knockout mice lacking all three α-Nrxns or NLs 1–3 show little change in total number of synapses but exhibit severe synaptic transmission phenotypes [159, 160], thereby implicating Nrxn-NLs in synaptic function, but not formation, *in vivo*. On the other hand, *in vitro* co-culture assays showed non-neuronal cells expressing NLs can trigger presynaptic formation on neighboring neurons and vice versa [161, 162]. These two disparate results were reconciled when Kwon *et al.* [163] showed that synapse formation *in vivo* was specifically dependent on transcellular differences in NL1 levels between neighboring neurons, suggesting that nascent neurons compete for limited presynaptic neurexin ligands, with cells expressing more NL1 forming synapses more readily. This theory explains why total genetic ablation of NLs in mice leads to an overall null effect while overexpression in cultured cells results in synapse formation [164]. While it is not yet known if other NL

isoforms follow the same trend, it is likely Nrxn-NLs are important for both synaptic formation and function *in vivo*.

Both groups have been genetically linked with ASD: point mutants in *NLGN3*, *NLGN4*, or *NRXN1* [165–169] truncations of *NLGN4* or *NRXN1* [170–172], chromosomal rearrangements of regions harboring *NRXN1*, *NLGN1*, or *NLGN2* [173, 174], and a promoter mutation in *NLGN4* [175] have been identified. More recently, a genome-wide copy number variation analysis also implicated *NLGN1* among several candidate genes in ASD susceptibility [176].

Multiple functional studies have implicated specific neurexin and neuroligins isoforms as key molecules for excitatory synaptic activity and normal behavior. Each of the three Nrxn genes encodes two principal types of neurexin proteins, α and β, each of which differs in length, domain composition, and number of splice variants. Therefore, the sheer number of isoforms, along with the lack of high-affinity antibodies and difficulty of studying presynaptic function, make Nrxns incredibly difficult to characterize [154]. Despite these challenges, culture studies have shown that particular splice variants influence the formation of specific synapses [158, 177–180]. In addition, knockout mice have been generated only for α-Nrxn isoforms, while no data are yet available for β-Nrxns; *α-NRXN1*-knockout mice have hippocampal E/I imbalance due to decreased spontaneous excitatory post-synaptic currents and decreased prepulse inhibitions, and also exhibited increases in grooming behaviors [181]. *In vitro* and *in vivo* studies show NL1, NL3, and NL4 localize to excitatory synapses [182–184]; here, Nrxn-NL trans-synaptic signaling recruits NMDARs and AMPARs to the synapse surface, possibly *via* intracellular mechanisms centered around the PSD-95 scaffold [185], although this has been disputed (see **NMDAR Hypofunction and ASD** section). Not surprisingly, over-expression of these NL isoforms increased excitatory synapse number and spine density in cultured neurons, while the NL3 Arg451Cys, NL4 D396X, and NL4 R87W variants - missense mutations found in affected in autistic members of several families - prevented this effect due to surface trafficking defects; conversely, knockdowns lead to excitatory synapse loss [163, 167, 186–188]. The mechanisms behind NL's spinogenic effects are unclear, but may involve activity-dependent proteolytic cleavage [189, 190] and CaMKII phosphorylation [191]. Likewise, a *NLGN1*-knockout mouse exhibited deficits in spatial memory and increased repetitive behavior as a result of decreased long-term synaptic plasticity in area CA1 of the hippocampus and dorsal striatum [192]. Conversely, a transgenic mouse overexpressing NL1 also had disruptions in memory acquisition and LTP, but this time as a result of increased numbers of excitatory synapses [193]. *NLGN3*-knockout mice have reduced ultrasound vocalization, deficits in social novelty preference, and brain volume reduction while *NLGN4*-knockouts exhibit highly selective deficits in social interactions and communication [194, 195]. Unfortunately, investigation into the neuronal architecture has been lacking in these two models. However, Arg451Cys NL3 knock-in mice revealed a large increase in NMDAR and AMPAR-dependent excitatory transmission in the hippocampus, which were accompanied by decreases in spine size and increases in dendritic branching in the stratum radiatum of CA1 [196].

In summary, neurexins and neuroligins may contribute to ASD pathogenesis through its control of synaptic function; deregulation may result in neurodevelopmental imbalances of synaptic transmission and may progress to behavioral changes.

SHANK Family

The Shank family (Shank 1–3) is a group of scaffold proteins that organize extensive protein complexes at the postsynaptic density of excitatory synapses. All three members of the Shank family of have been linked with ASD susceptibility: a large number of de novo mutations in *SHANK3* [197–199], in *SHANK2* [200], and in *SHANK1* [201] have been identified in individuals with ASD. This genetic association provides an immediate link between synaptic dysfunction and ASD pathophysiology and thus led to the creation of numerous knockout mice [202].

SHANK1-knockout mice have small dendritic spines, weakened synaptic transmission [203], and defects in social communication [204]. Mice with heterozygous or homozygous disruption of *SHANK3* have self-injurious repetitive grooming, deficits in social interaction, alterations in learning and memory formation, and defects in synaptic transmission [205–207]. Finally, the *SHANK2*-knockout mice, like their *SHANK3*-knockout counterparts, show abnormalities in behavior tests, impairment in social activities, hyperactivity, and defects in synaptic transmission [208, 209].

The behavioral defects of *SHANK3* mutant mice correlate with impaired basal synaptic transmission in CA3-CA1 connections, reduced GluR1 clusters and protein levels in the hippocampus, and major changes in striatal and corticostriatal synapses [205–207]. Interestingly, Shank3 interacts with the NLs through PSD95 and GKAP, suggesting the importance of this entire complex in ASD pathology [154]. Overall, these studies demonstrate that the *SHANK* genes cause alterations in excitatory synaptic morphology and signaling, as well as changes in behavior characteristics, suggesting they are good animal models for the study of synaptic pathology in ASD.

Syndromic Autisms

Studying syndromic autisms - monogenic disorders that are co-morbid with ASD - can shed light on ASD etiology because their phenotypes are entirely attributed to mutations on individual or particular sets of genes [210]. For example, individuals harboring mutations of tuberous sclerosis proteins 1 and 2 (*TSC1*, *TSC2*) or the phosphatase and tensin homolog (*PTEN*) gene are frequently diagnosed with autism [211, 212]. Fascinatingly, each of these proteins regulates synaptic structure [213–215]. *PTEN* deficiency results in hypertrophy of dendritic arbors and increased spine density [213, 216] while *TSC1* or *TSC2* loss causes enlarged spines [214]. Fragile X syndrome results from transcriptional silencing of the *FMR1* gene, which encodes for the transcription regulator FMRP; loss of FMRP causes an upregulation in global dendritic translation rates that may contribute to the elevated spine density observed in the brains of affected individuals [217]. Similarly, MeCP2, a transcriptional regulator that is mutated in Rett syndrome, controls the function of excitatory synapses and spine morphology in an activity-dependent manner [218]. Lastly, maternal duplications of chromosome 15q11-q13, a region that encompasses the Angelman syndrome

gene *UBE3A*, are associated with autism [219]. *UBE3A* encodes an E3 ubiquitin ligase whose loss reduces dendritic spine density and length in cerebellar and hippocampal pyramidal neurons [220, 221], suggesting a potential link between Angelman syndrome, autism and altered synaptic structure. These disorders, which have an autistic phenotype, can be useful in determining relevant molecular mechanisms in ASD pathogenesis. However, this information must be approached with caution; as these disorders are pathologically and genetically distinct from 'pure' autism, the relevance of specific molecular mechanisms and cellular alterations to pure autism may not be entirely accurate.

ASD AT THE GABAergic CIRCUIT

Converging evidence from genetic and neuropathological studies suggest pathological cellular alterations to GABAergic interneurons may play etiological roles in ASD. Below, we summarize animal model studies which mechanistically link ASD-associated genes to GABAergic interneuron function, E/I imbalance, and behavioral deficiencies.

Neurexins/Neuroligins

Autism is thought to arise from functional changes in neural circuitry and to be associated with an imbalance between excitatory and inhibitory synaptic transmission. Functional studies have linked neuroligin 2 (NL2) to proper inhibitory synaptic function [188, 222]. NL2 tightly regulates inhibitory synapse architecture and function by tethering pre-synaptic α-Nrxns or a subset of β-Nrxns with an insert in splice site 4 [158]. This interaction provides a physical link between pre- and post-synaptic membranes [158], regulates pre-synaptic neurotransmitter release, and post-synaptically recruits gephyrin which scaffolds $GABA_A$ receptors in precise locations [223]. Hence, due to its central role in synapse assembly, even slight alterations to NL2 can significantly alter E/I balance and result in particular behavioral deficits. More specifically, *in vitro* NL2 over-expression or knockdown specifically enhanced or decreased inhibitory circuit transmission respectively [188] and a transgenic mouse harboring an extra copy of the *NLGN2* gene resulted in increased size of inhibitory synapses and a subsequent reduction in the E/I ratio. Moreover, these mice had stereotypied behavior and impaired social interactions [224]. Interestingly, a small population of NL2 is also endogenously present in excitatory synapses and *NLGN2*-overexpressing mice also exhibit small but significant changes in excitatory synapse morphology [224], suggesting NL2 may also have some overlapping and redundant functions at the excitatory synapse.

Similarly, while NL3 is predominantly localized to excitatory synapses [184], it is also found to a lesser extent in GABAergic synapses [183]. A knock-in mouse harboring an autism-associated mutation in a conserved amino acid residue (R451C) of *NLGN3* was found have increased inhibitory transmission but no changes in excitatory transmission in the somatosensory cortex [225]. These mice, similar to the *NLGN2*-overexpression mice, also exhibited impaired social interactions. Thus, the R451C mutation may lead to a gain-of-function shift of NL3 activity to the inhibitory synapse, but additional studies unexpectedly revealed a large increase in excitatory transmission in the hippocampus [196]. Therefore, NL3 R451C mutation causes region-specific alterations in either excitatory or inhibitory neural circuits that accompany the ASD-relevant mouse behaviors.

While previous studies pinpoint NL4 to the excitatory synapse, the conclusions were based on over-expression data [167, 184, 186]. More recently, Hoon *et al*. [226] showed NL4 was endogenously localized to inhibitory glycinergic synapses in the retina and other areas of the CNS, associates with gephyrin but not PSD-95 *in vivo*, and is important for glycinergic-dependent inhibitory transmission in the retina. This conflicting data, along with the fact that *NLGN4*-knockout mice are accurate models of certain monogenic heritable ASDs [195], mandates a more extensive investigation of the physiological properties of this protein.

In conclusion, these studies provide evidence that both reduced and enhanced expression of ASD genes such as NLs can intimately affect the balance between excitatory and inhibitory transmission, and hence provides strong evidence that a change in the E/I balance contributes to the pathogenesis of ASDs.

MeCP2

Rett Syndrome is a neurodevelopmental disorder that presents at around 6–18 months with autistic-like deficiencies in speech, social and motor skills - particularly repetitive movements - which results from the functional loss of one copy of the *MECP2* gene [227, 228]. MeCP2 is a transcriptional regulator which is highly expressed in GABAergic neurons in the brain [229]; interestingly, epilepsy is co-morbid in 80% of cases of Rett Syndrome, suggestive of an underlying inhibitory transmission problem [230].

MECP2-null mice exhibit most of the neurological phenotypes of Rett syndrome [231, 232], but region-specific deletion of *MECP2* can also recapitulate many of these behaviors. For example, mice with specific deletion of *MECP2* from forebrain GABAergic-interneurons exhibit repetitive behaviors, increased sociability, cognitive deficits, impaired motor coordination and neuronal hyperexcitability [233]. Moreover, GABAergic abnormalities in the thalamus [234] and medulla [235] occur in *MECP2*-null mice prior symptom onset.

Given the plethora of MeCP2 binding targets throughout the genome [236], it is particularly difficult to tease apart how MeCP2 specifically impairs inhibitory function [227]. However, it is best to begin with MeCP2-targeted genes that are particularly important in GABAergic neurons. For instance, brain-derived neurotrophic factor (BDNF), which regulates development and maturation of inhibitory circuits in the brain, is a MeCP2 target [237]. Moreover MeCP2 controls the expression of GAD65 and GAD67 in GABAergic neurons in a cell-autonomous manner [233]. Loss of MeCP2 leads to inhibitory neurons containing lower than normal levels of GABA, which may explain the abnormal cellular hyperexcitability observed in these mice [233]. Taken together, these results suggest that MeCP2 function may be more crucial in some inhibitory circuits than others and that behavioral symptoms may be the downstream result of region-specific MeCP2-associated defects in GABAergic neurons.

FMRP

Fragile X Syndrome (FXS) is a monogenetic neurodevelopmental disorder caused by an abnormal expansion of a CGG trinucleotide repeat within the promoter region of the gene *FMR1*, which prevents expression of the encoded protein FMRP [238]. Around 20% of

those with FXS meet formal criteria for an ASD [239–242] and 25% exhibit epileptic symptoms [243], thus implicating *FMR1* both as an autism susceptibility gene and a regulator of cortical inhibitory function. Indeed, FMRP is broadly expressed in GABAergic neuron populations [244] indicating that it is involved interneuron function.

This theory is backed up by evidence from the *FMR1*-knockout mice, which exhibit autistic-like behaviors [245]. Furthermore, knockout mice have significant reductions and drastic lamina redistributions of PV+ interneurons in the neocortex, but not hippocampus, suggesting these effects may involve region-specific gamma oscillation deficiencies [246]. Likewise, other studies reported the reduction of several GABA subunits' mRNA in the cortex but not in the cerebellum in *FMR1*-null mice [247, 248] and various other reports discovered region-specific increases or decreases of GAD 65/67 levels [244, 248–251]. Finally, FXS specifically exhibit profound network hyperexcitability in the amygdala - an area of the brain responsible for emotional processing - due to the loss of GAD65 and GAD67 expression and reduced GABAergic synapses [244]. In conclusion, FXS mice are good animal models analyze how FMRP links region-specific GABA dysregulation to autistic symptoms; however, caution must be taken as that FXS is not a "pure" autism and thus cannot entirely be relied upon to understand the latter's complex pathophysiology.

CNTNAP2

Genetic studies over the past decade have reproducibly associated *CNTNAP2* variants with ASD [252–256]. Contactin-associated protein-like 2 (CNTNAP2) is a neurexin cell-adhesion molecule that is highly expressed throughout the central nervous system, with highest expression in the frontal and anterior lobes, striatum and dorsal thalamus [256], which recapitulates the corticostriato-thalamic circuitry known to control higher order functions such as speech and language.

Recent evidence suggests CNTNAP2 regulates neural networks through E/I balance. CNTNAP2 knockdown led to decreases in dendrite arborization and impaired synaptic transmission in mouse cortical neurons [257]. *CNTNAP2*-knockout mice have reduced numbers of PV+ GABAergic interneurons, as well as neuronal synchrony defects, epileptic seizures, and altered social behavior [258]. Thus, CNTNAP2 loss may lead to impairments in connectivity and reductions in the interneuron population, particularly the PV+ subtype, resulting in a hyper-excitable network that promotes downstream epileptic symptoms and behavioral abnormalities. However, it is unclear if the interneuron phenotype is a result of migratory defects, as CNTNAP2 is expressed at the ganglionic eminences during development [258] and interacts to TAG-1 [259], a protein involved in interneuron migration [260]. Thus further work needs to be done to dissect the relationships of these phenotypes to one another as well as to further tease apart the cellular and neurobiological effects of *CNTNAP2* loss on neural networks.

CONVERGENT PATHWAYS OF ASD AND SCZ

SCZ and ASD have been characterized as polygenic disorders, meaning multiple susceptibility genes may work together - possibly along different points of common pathways - to trigger disease onset [3]. Indeed, genetic studies have consistently identified

reoccurring CNVs mutual overlapping both disorders. Many of these candidates - such as *DISC1*, *NRXN1*, *NLGN3-4*, *SHANK3*, and *CNTNAP2* - encode for synaptic proteins (*NRXN1*, *NLGN3-4*, and *SHANK3*, see **ASD at the Glutamatergic Circuit**) or molecules involved with neuronal development (*DISC1* [261], *CNTNAP2* [258, 262]) and thus support the existence of shared biologic pathways between these two neurodevelopmental disorders. In this section of the review, we will describe the role of two major signaling pathways (through their regulations of neuronal architecture and synaptic function) on E/I homeostasis, explore the functional relationship of risk molecules to these pathways, and discuss how disease-associated disruption of such molecules can disrupt these pathways and contribute to E/I imbalance.

mTOR SIGNALING

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that responds to environmental signals by controlling cell growth and proliferation [263, 264], synaptogenesis [213], and dendrite [265, 266] and axon growth [213, 267] in neurons *via* regulation of protein translation and hence plays an important role in brain development. mTOR is controlled by the tuberous sclerosis complex (TSC1/TSC2), a heteromer which binds and constitutively inhibits the GTPase Ras-homolog enriched in brain (Rheb), a direct activator of mTOR. Phosphorylation of TSC1/TSC2 dissociates with and thereby activates Rheb. Upstream kinases - many of which are downstream effectors of extracellular signals - thereby exert control on mTOR through TSC1/TSC2, making the latter a focal point for integration of cellular energy status, nutritional availability, and growth factor signaling. For instance, in the highly conserved PI3K-Akt-mTOR signaling pathway, binding of various extracellular factors (mitogens, trophic factors, and glutamate) to respective receptors lead to the activation of phosphatidylinositol 3-kinase (PI3K) at the plasma membrane. Activated PI3K promotes plasma membrane translocation and subsequent activation of Protein Kinase B (Akt) *via* production of phosphatidylinositol (3,4,5)- triphosphate (PIP_3); meanwhile, PTEN opposes PI3K by depleting PIP_3. Active Akt phosphorylates TSC1/TSC2 to disinhibit Rheb, leading to protein translation through mTOR's (as a member of mTORC1) phosphorylation of S6 kinase (S6K) and eukaryotic initiation factor (eIF-4B) [268]. For a more comprehensive picture of mTOR's function and other pertinent molecular players and pathways, we direct the reader to a more comprehensive review [269].

Throughout its development, a neuron is faced with changing environmental conditions and must appropriately adapt its energy expenditure for optimal function. For instance, the critical period in early postnatal brain development represents a particularly harsh period of metabolic demand, as neurons undergo neurogenesis, migration, synapse formation, and the establishment of synaptic fields. Individual neurons therefore must perform frenzied anabolic processes to keep up with these rapid changes and mTOR activity becomes essential during this time by controlling key components of homeostasis such as synaptogenesis, spinogenesis, and dendrite arborization [270]. However, sustained periods of high demand can also become periods of enhanced vulnerability if lesions occur in these metabolic pathways. Thus if protein production cannot be in tune with critical developmentally driven shifts, neuronal networks may be pathogenically imbalanced.

mTOR and SCZ

Recent investigations have linked SCZ pathology to the PI3K-Akt-mTOR signaling cascade [268, 271]. Moreover, genetic linkage and association studies have identified *AKT* as a candidate susceptibility gene related for SCZ [272, 273] and the level of Akt-1 protein and its kinase activity decreased significantly both in white blood cells and in postmortem brain tissue of schizophrenic patients [274]. Repeated treatments of MK-801, a non-competitive NMDAR antagonist known for its psychotomimetic effects, led to modulation of Akt, mTOR, and its downstream targets and induced schizophrenia-like behavioral changes in neonatal rats [275, 276].

Recent studies show DISC1 knockdown of adult-born neurons in the dentate gyrus led to acceleration of dendrite development, network hyperexcitability, and an increase in phosphorylated Akt. These effects were rescued when either NKCC1 - a neuronal co-transporter responsible for depolarizing GABA signaling *via* chloride influx - or $GABA_AR$ γ2 subunit was simultaneously knocked down with DISC1, but enhanced when DISC1 knockdown neurons were treated with GABA agonists [277]. Moreover, it was discovered DISC1 interacts with and suppressed KIAA1212, an Akt signaling enhancer, and rapamycin treatment of DISC1 knockdown neurons prevented enhanced Akt phosphorylation and hypertrophic dendritic growth [261]. Together, these results suggest a specific requirement of depolarizing GABA signaling in DISC1-dependent regulation of Akt/mTOR signaling and dendritic growth during adult neurogenesis. Finally, mice with dentate gyrus-specific DISC1 knockdown exhibited schizophrenic-like symptoms including cognitive deficits and anxiety, but rapamycin injection was able to rescue these defects in a time-sensitive manner [278]. Pathological GABA signaling, therefore, may be indirectly responsible for the hallmark alterations in inhibitory circuits and behavior in SCZ *via* the DISC1-Akt-mTOR signaling pathway.

NRG-1 induces the phosphorylation of the ErbB4 receptors, which then become docking sites for upstream mTOR molecules such as PI3K [279]. Lymphoblast lines from schizophrenic patients have upregulated expression of the ErbB4 receptor isoform CYT-1, which contains a PI3K-binding site and triggers activation of the PI3K pathway [280, 281]. Further examination of these cell lines show enhanced transcripts for p110δ (a catalytic subunit of PI3K) and dampened PI3K-catalyzed second messenger PIP_3 levels [281], suggesting enhanced signaling from the ErbB4 isoform CYT-1 lowers PI3K activity. As Akt is a prominent target of PI3K [282], this study also found targeted inhibition of p110δ increased Akt Thr308 phosphorylation and reversed PPI deficits in a neurodevelopmental rat model of SCZ [281], adding evidence that enhanced NRG1-ErbB4 signaling may diminish PI3K-Akt signaling in SCZ. In corroboration, elevated NRG1-ErbB4 activity has been observed in SCZ postmortem brain tissue [283] while analysis from peripheral blood leucocytes from SCZ patients confirmed a 1.3 fold decrease in Akt levels [274]. Since NRG1-ErbB4 and PI3K-Akt are involved in neural circuit development and synaptic plasticity [87, 284], this discovery may have joined two previously disparate pathways.

Finally, over-expression of dysbindin-1 in cortical neurons has a neuroprotective effect against apoptosis *via* PI3K/Akt pathway activation while knockdown has the opposite effect

[285]. Likewise, dysbindin expression in the brain of schizophrenic patients is reduced [132, 133]. These findings suggest that dysbindin-1 deficits may contribute to the pathophysiology of SCZ by affecting neuronal viability of E/I circuits *via* regulation the PI3K/Akt signaling cascade.

mTOR and ASD

As mTOR regulates a variety of neuronal functions, including cell proliferation, growth, and synaptogenesis, disrupted network homeostasis *via* mTOR perturbation has been proposed as a pathophysiology mechanism contributing to autism spectrum disorders due to the disease's synaptopathology, E/I imbalance, and the observations of macrocephaly and epilepsy in 10–30% of the patients with ASD [286].

Individuals with dominant mutations in *TSC1/TSC2* or *PTEN* - genes encoding repressors of mTOR - are often diagnosed with syndromic forms of ASD and are also co-morbid for epilepsy, suggesting a relationship between mTOR hyperactivity and alterations of network circuits [270]. As such, conditional knockout (as germline deletions lead to early mortality) mouse models consistently produced seizure phenotypes. For example, mice with *PTEN* ablation from mature CA3 neurons, dentate granule cells, and layer III-V cortical neurons exhibit spontaneous seizures [213]. Similarly, removal of *TSC1* throughout the cortex, subcortical gray matter, and hippocampal CA3 and hilar neurons produced mice with spontaneous seizures by day 5 and death within 3–5 weeks [287]. Investigations into the pathophysiological mechanisms of these phenotypes revealed mTOR-dependent alterations in synaptic transmission. Hippocampal *TSC1*-knockout neurons exhibited mTOR hyperactivity, decreased inhibitory transmission (yet no changes in excitatory transmission), and network hyperexcitability [47] but normal spine density and size [288]. Loss of *PTEN* hyperactivated mTOR, but surprisingly also enhanced both excitatory and inhibitory neurotransmission in the hippocampus [289] and increased spine density [213]. Thus, despite being functionally similar in some aspects, PTEN and TSC1 may have distinct mechanisms for E/I regulation [289].

It was recently reported loss of FMRP resulted in enhanced mTOR signaling and subsequent increased formation of the eukaryotic initiation factor complex 4F (eIF4F) in a mouse model of FXS [290]. These findings suggest that in addition to its RNA-binding activity, FMRP also plays a role in the regulation of translation initiation and subsequent protein synthesis. Similarly, a *MECP2*-overexpression mouse also has elevated mTOR signaling [291] while a *MECP2*-knockout model displays the opposite effects [292]. Indeed, eIF4E - a cap-binding protein that is a member of the eIF4F complex - was confirmed to be hyperactivated *via* mTOR phosphorylation in fragile-X syndrome (FXS) patients diagnosed with autism [293]. Moreover, transgenic mice harboring knockouts of eukaryotic translation initiation factor 4E-binding protein 2 (4E-BP2) - an eIF4E repressor - or eIF4E overexpression exhibit autistic-like behaviors, E/I imbalance, and increased translation of neuroligins [294, 295]. Thus, while neuroligins mutations have been associated with ASD, these studies provide a framework for this process - namely, the disruption of a synaptic homeostasis process. Taken together, several lines of evidence suggest prominent ASD risk genes converge upon

the mTOR signaling cascade to disrupt E/I balance *via* abnormal synaptic function owing to aberrations in synaptic protein translation.

NMDAR SIGNALING

N-methyl-D-aspartate receptors (NMDARs) are ionotropic glutamate receptors essential for mediating ion flux and hence are clearly positioned to control E/I balance at the synaptic level. Structurally tetrameric, they contain two NR1 obligatory subunits and either two NR2 (A, B, C or D) or two NR3 (A or B) subunits, with the latter two being interchangeable. As a result, NMDARs exist as multiple subtypes - with each having uniquely physiological and pharmacological properties - and are spatially and developmentally regulated and differentially distributed across neuronal subtypes [296]. This complex diversity, coupled with a subtype-dependent permeability to calcium influx, make NMDARs the predominant molecular devices for controlling complex experience-dependent synaptic remodeling and long-lasting synaptic changes, which are crucial for associative learning, working memory, behavioral flexibility or attention [297]. Moreover, NMDAR-associated proteins have key roles in the receptor's trafficking, stability, subunit composition and function through post-translational modifications such as phosphorylation, ubiquitination, and palmitoylation. Dysregulation of these processes can impact channel function and expression and alter synaptic transmission [298, 299]. Thus, NMDAR dysfunction could be a convergence point in ASD and SCZ pathophysiology and may be responsible for disease progression in both disorders.

NMDAR Hypofunction and SCZ

A prominent hypothesis for SCZ pathophysiology posits that NMDARs on PV+ neurons are hypofunctional, thus resulting in lowered GABAergic signaling, overstimulation of excitatory neurons, and a consequent loss of gamma wave oscillations [58]. This theory is based on observations that NMDAR antagonist (e.g. PCP, MK-801, ketamine) administration in normal subjects produce metabolic, neurochemical, and cognitive deficits almost identical to SCZ patients [300], on functional studies showing NMDAR antagonist treatment specifically decreases GAD67 and parvalbumin in PV+ interneurons [301–303], on post-mortem studies reporting abnormalities in NMDAR density and subunit composition in SCZ patients [304, 305], and on a PV-specific *GRIN1*-knockout mouse model displaying pyramidal cell hyperexcitability, neural synchrony reductions, and schizophrenic-like behaviors [306]. Supporting this assertion, several SCZ-specific polymorphisms in *GRIN1* have been discovered [307, 308] and a recent large study from the Consortium on the Genetics of Schizophrenia verified this connection and also discovered several genes encoding for NR1 interacting proteins associated with the disease [309]. Moreover, other studies have found NMDAR subunits tend to be hotspots for *de novo* SCZ-associated mutation: one identified two *de novo* mutations in patients with sporadic SCZ in NR2A (*GRIN2A*) [310] while others show an over-representation of *de novo* mutations in glutamatergic postsynaptic proteins associated with NMDAR complexes in SCZ patients [68, 311], leading to the notion that NMDAR signaling could be a point of convergence for various SCZ-associated pathways.

NRG1 and ErbB4 accumulate at synapses in the adult brain, suggesting its signaling is involved with synaptic maintenance or function (see **Schizophrenia at the Glutamatergic Circuit** and **Schizophrenia at the GABAergic Circuit**). Indeed, NRG1-ErbB4 activity has been shown to down-regulate LTP *via* modifications in NMDAR surface trafficking: bath perfusion of mouse prefrontal cortex (PFC) brain slices with NRG1 decreased NMDAR-mediated EPSCs *via* internalization of the NR1 subunit, with this effect being blocked by ErbB4 inhibitors [312]. ErbB4 is enriched in the PSD and its association with PSD-95 results in enhancement of NRG1-dependent signaling [83]. Similarly, chronic MK-801 treatment in rats enhanced ErbB4's association with PSD-95 and increased ErbB4's phosphorylation levels [313]. NRG1's regulation of NMDAR activity, therefore, may involve ErbB4-controlled postsynaptic mechanisms. Interestingly, the NR2 subunit has a large C-terminus with many putative phosphorylation sites, which affect synaptic targeting and channel physiology [298]. Recent data showed that NRG1-ErbB4 signaling blocks Src kinase-specific phosphorylation of this subunit, leading to suppression of Src-mediated enhancement of NMDAR activity in the mouse prefrontal cortex and hippocampus [314]. Thus, aberrant increases in NRG1-ErbB4 signaling could contribute to E/I imbalance by attenuating NMDAR function *via* different postsynaptic pathways (e.g. NR1 internalization or hypophosphorylation of NR2 subunits). Supporting this assertion, another study showed schizophrenic patients have up-regulated NRG1-ErbB4 signaling and more pronounced NMDAR attenuation in the PFC as compared with control subjects [283].

DISC1 may regulate NMDAR function through various pathways. It interacts directly with PDE4B, a regulator of cAMP and thus can indirectly influence PKA activity [315]. NMDAR phosphorylation by PKA, in turn, can affect the receptor's release from the endoplasmic reticulum onto the surface [316]. DISC1 also stabilizes serine racemase (SR), the enzyme that generates D-serine, an endogenous NMDAR co-agonist. Mutant DISC1 cannot bind to SR, leading to the latter's degradation and resulting in D-serine deficiency and hypofunctional NMDAR neurotransmission [317]. NR1 knockdown mice also exhibit decreased DISC1 levels within synapses [318].

Maintenance of appropriate levels of synaptic NMDARs *via* a balance between receptor insertion and endocytosis is also necessary for the receptor's proper function. Specialized endocytic zones involving clathrin-coated pits have been described for glutamatergic synapses and serve to internalize NMDARs [319, 320]; altered dysbindin expression can modify NMDAR surface expression through this mechanism [321]. Moreover, palmitoylation can either promote NMDAR synaptic stabilization or Golgi apparatus sequestration [322]. Interestingly, altered protein palmitoylation was found in a mouse model of 22q11.2 deletion, a high risk factor of developing SCZ [107], but the connection between NMDAR palmitoylation and SCZ has thus far been relatively underexplored.

NMDAR Hypofunction and ASD

A similar NMDAR hypofunction theory has been proposed for ASD [323]. Likewise, genes encoding NR2A, NR2B, and NR2C [255, 324, 325] have also been associated with ASD and differential splicing of NR1 has been reported in an ASD post-mortem study [326]. Pathway analysis of autism associated genes have also revealed reduced NMDAR-mediated

neurotransmission [324] and several studies found SCZ and autism patients share common *de novo* genetic mutations, some of which are involved with NMDAR trafficking [68]. Knockout mice and molecular studies of several ASD risk genes discussed in this review - *SHANK3*, *NLGN1*, *FMR1*, and *MECP2* - revealed disrupted NMDAR activity, altered synaptic transmission and autistic-like symptoms.

RNAi knockdown of Shank3 in culture leads to reduction of NMDAR-mediated synaptic current as well as loss of NR1 surface expression. This effect was blocked by an actin stabilizer but mimicked with an actin destabilizer and a Rac1 or PAK inhibitor [327], thereby defining Shank3's role for NMDAR surface trafficking *via* the actin cytoskeleton mechanisms. In a similar study, neurons derived from IPS cells generated from Phelan-McDermid syndrome (PMDS) - a syndrome with autistic-like features caused by heterozygous deletions of chromosome 22q13.3, which includes *SHANK3* - patients had reduced Shank3 expression and major defects in excitatory transmission due partially to decreased NMDA receptors and reduced excitatory synapses, both of which were rescued with exogenous Shank3 expression [328]. Recapitulating the *in vitro* data, *SHANK3*-knockdown mouse exhibited a decrease in NMDA/AMPA ratio in area CA1 of the hippocampus, leading to reduced CA1 LTP, and deficits in hippocampus-dependent spatial learning and memory [329]. Similarly, *SHANK2* mutant mice have autistic-like behaviors and decreased functional NMDARs, but both deficits are rescued with NMDAR partial agonist D-cycloserine or through enhancement of NMDAR activity *via* a positive allosteric modulator of mGluR5 [209].

NLGN1-knockout mice have deficits in spatial learning and memory as well as repetitive behavior, which corresponded with impaired hippocampal LTP and decreased NMDA/AMPA ratio [192]. Moreover, the repetitive behavior was ameliorated with NMDA co-partial agonist D-cycloserine, suggesting NL1 is required for NMDAR-mediated currents, normal LTP function, and specific behavioral tasks. Mechanistic studies show NL1 is selectively localized to excitatory synapses [182] and over-expression leads to clustering of synaptic NMDARs in excitatory synapses, suggesting NL1 recruits and retains NMDAR to postsynaptic sites [330]. This was verified using immunoelectron microscopy images and with a MK-801 wash-out paradigm [330]. NL1 may interact with NMDARs through PSD-95 *via* its C-terminal PDZ domain [331], and the association between NL1, PSD-95, and other PSD-95-associated proteins such as Shank3 - a scaffold protein which acts to traffic NMDAR to synapses - may be necessary for the precise incorporation of NMDAR into synapses. This theory, however, has recently been in contention - how can NL1-PSD95 specifically recruit NMDARs to excitatory synapses [188] when all NL isoforms have C-terminal PSD-95 binding sites? A recent study showed NL1-PSD95 interactions to be neither necessary nor sufficient for NMDARs recruitment to postsynaptic sites; rather, the extracellular NL1 cholinesterase domain, which differs between isoforms [154], interacts specifically with the NR1 subunit [330].

MECP2-knockout (RTT) mice have abnormal NMDAR incorporation at the synapse. Using whole-brain fractionation techniques, one study found *MECP2*-null mice to have decreases in overall NR2A/NR2B ratio and NR1 levels at the synapses compared to wildtype [332], which is consistent with attenuated synaptic maturation [333, 334] and fewer overall

functional NMDA receptors respectively, supporting the possible involvement of a malfunctioning NMDAR system in Rett syndrome pathophysiology. However, because the technique involved a whole-brain analysis, this does not provide detailed information to which specific brain region these alterations are taking place. Other studies of RTT mice confirm there are regional differences within neural circuits in regards to connectivity [335], which is also consistent with previous postmortem binding studies showing significant alterations in total NMDA receptor complexes only in particular regions of the Rett syndrome brain [336, 337].

Like many developmental disorders, FXS is associated with alterations in synaptic plasticity that may impair learning and memory processes in the brain. FMRP normally binds to NMDAR subunits NR1, NR2A, and NR2B and components of the postsynaptic density, such as PSD-95 and CaMKIIα [338, 339]. Expectedly, *FMR1*-knockout mice had diminished LTP and lowered NMDA/AMPA ratio in the dentate gyrus (DG) and exhibited defunct context discrimination, a behavior reliant on intact NMDAR function in the DG [340]. DG-specific deficits are also accompanied by a significant reduction in NR1, NR2A, and NR2B subunit levels while treatment with NMDAR co-agonists (glycine or D-serine) independently rescued synaptic impairments in this region [341]. Thus, FMRP differentially affects separate regions of the hippocampus, as the CA1 region of was not impaired in these mice [341].

CONCLUSION

Disorders such as ASD and SCZ have complex genetic etiologies and behavioral phenotypes. However, despite their heterogeneous nature, a significant overlap in symptoms exists, raising the idea that these historically distinct disorders might share overlapping pathogenic mechanisms. The pathways that control E/I balance provide a framework for understanding how different genetic perturbations from two distinct disorders can interact in a convergent way to disrupt excitatory and inhibitory neuron function, neuronal circuit organization, and behavior. Yet how do disruptions of shared mechanisms result in such heterogeneous outcomes? Rather than global impairments, disease-related changes might be subtly specific - affecting only a subset of synapses in a selective group of neurons, for instance. As a result, differential manifestations of alterations in shared cellular substrates might underlie the phenotypic variability, which are then classified as distinct cognitive diseases. Such findings highlight the importance of looking beyond individual genes and into comprehensive mechanisms of molecular convergence. Elucidating the shared functions of newly identified disease-associated genes is a key step to translating genetic findings into clinical applications.

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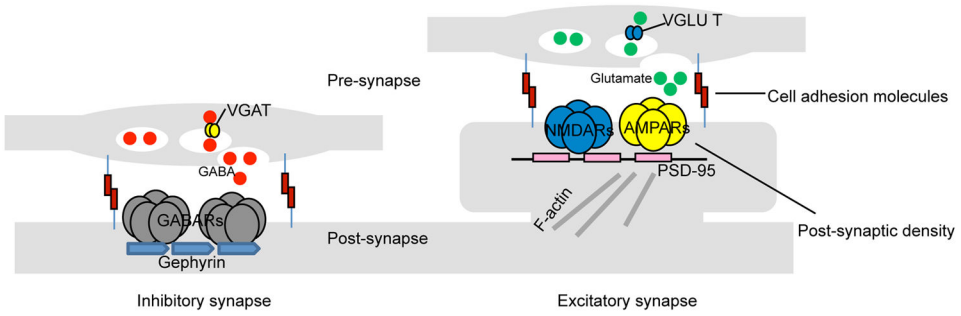

Fig. 1.

Simplified architecture of excitatory and inhibitory synapses on pyramidal cells. Pre-synaptic terminals of excitatory synapses release glutamate neurotransmitters that are post-synaptically received by glutamate receptors (NMDARs and AMPARs) on dendritic spines - small membranous protrusion stemming from the dendrite. The tip of each spine contains an electrodense region called the PSD, which is comprised of cytoskeleton anchoring proteins, such as PSD-95, designed to scaffold glutamate receptors (NMDARs and AMPARs) to the spine's surface and to dock hundreds of signaling molecules (not shown) to the underside. Inhibitory synapses are localized to the dendritic shaft. Pre-synaptic terminals release GABA to be received post-synaptically by GABARs anchored onto the post-synaptic surface by gephyrins (gephyrins also scaffold glycine receptors, which are activated by glycine neurotransmitters - not shown). Noticeably missing is the PSD. Both synapse types are structurally maintained by trans-synaptic adhesions through cell adhesion molecules.

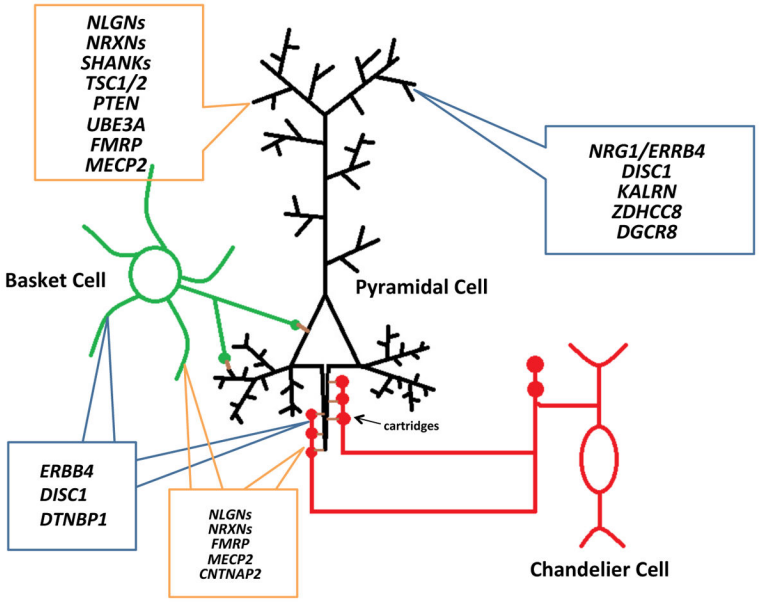

Fig. 2.

Parvalbumin-containing interneurons regulate pyramidal cell firing. Both basket (green) and chandelier cells neurons (red) contain parvalbumin and have fast-spiking electrophysiological properties. Chandelier cells have long linear axon terminals called cartridges that synapse onto the axon initial segment of pyramidal neurons (black) while basket cell axons target the cell bodies and proximal dendrites of pyramidal neurons. Due to the strategic location of their synapses, both subtypes greatly influence the generation and timing of a pyramidal cell's action potentials. The contents inside the blue and orange boxes respectively denote key SCZ and ASD-associated genes involved with dendritic spine or parvalbumin interneuron pathology, as discussed in this review.