

From synapses to circuits: What mouse models have taught us about how autism spectrum disorder impacts hippocampal function

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Abstract

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder that impacts a variety of cognitive and behavioral domains. While a genetic component of ASD has been well-established, none of the numerous syndromic genes identified in humans accounts for more than 1% of the clinical patients. Due to this large number of target genes, numerous mouse models of the disorder have been generated. However, the focus on distinct brain circuits, behavioral phenotypes and diverse experimental approaches has made it difficult to synthesize the overwhelming number of model animal studies into concrete throughlines that connect the data across levels of investigation. Here we chose to focus on one circuit, the hippocampus, and one hypothesis, a shift in excitatory/inhibitory balance, to examine, from the level of the tripartite synapse up to the level of in vivo circuit activity, the key commonalities across disparate models that can illustrate a path towards a better mechanistic understanding of ASD's impact on hippocampal circuit function.

1. Introduction

In patients, a clinical diagnosis of ASD is often based on highly penetrant phenotypes related to impairments in social communication and repetitive behaviors (APA, 2013; Genovese and Butler, 2020; Vyas et al., 2021; WHO, 1992). However, there are often comorbid deficits present in the realm of cognition and memory, including impairments related to the core functions of the hippocampus: episodic memory, social interactions and networks, and cognitive mapping (Banker et al., 2021). As a result, there has been extensive work on the impact of mutations in ASD risk genes on hippocampal structure and function in rodents, spanning many distinct models and conducted on many different levels of analysis, from synapses up through circuits and behavior (for previous reviews see (Ergaz et al., 2016; Lee et al., 2017; Li et al., 2019; Varghese et al., 2017)). Here we attempt to comprehensively examine these current data through the lens of animal models of ASD shown to lead to changes in neuronal excitability and synaptic function and their relationship to shifts in excitatory/inhibitory (E/I) balance on the circuit level, mediated through both neuronal and glia phenotypes. We believe that the commonalities in these findings can be a key reference point in guiding future work, both for the understanding and the treatment of the cognitive and social phenotypes present in ASD.

The hippocampus (Figure 1A), sitting in the temporal lobe, is required for the formation, storage and recall of the episodic memories of our daily lives (Tulving and Markowitsch, 1998). However, it also plays a larger role in mapping cognitive relationships across many domains, including spatial (O'Keefe and Nadel, 1978;

Wilson and McNaughton, 1993), value based (Bakkour et al., 2019; Knudsen and Wallis, 2021; Palombo et al., 2015) and social networks (Rubin et al., 2014; Schafer and Schiller, 2018). While many disorders, both neurodevelopmental and neurodegenerative, compromise hippocampal function, it has increasingly been one focus of research into autism spectrum disorder (ASD) in humans (Boucher and Mayes, 2012; Cooper et al., 2017; Shalom, 2003; Li et al., 2019) While there is broad consensus among both clinical and animal models of ASD that a shift in E/I balance in the hippocampus contributes to aspects of the disorder, the heterogenous changes which fall within the broad scope of this balance make it a challenge to understand (Sohal and Rubenstein, 2019). Further, the dynamic nature of E/I changes across both short and long timescales, as well as the dynamic physiology of the hippocampus itself, have made a mechanistic understanding of how these imbalances are manifest elusive. However, over 50 years of research on the physiology and function of the rodent hippocampus (Zemla and Basu, 2017), both in vitro and in vivo, position it as an ideal model system to probe how changes in E/I balance result in dynamic changes in information representation and circuit dynamics during behavior.

In this review we will highlight a subset of model mice that have been characterized on the level of both the neuronal and glial contributions to synaptic function (Figure 1B), as well as on the circuit level, to connect the finding across these analyses. Specifically, we will focus on four broad families of models, those targeting neurexins/neuroligins, mutations in shank family proteins, loss of function of voltage-gated sodium channels and finally, monogenetic neurodevelopmental disorders, briefly introduced below, for which sufficient data exist for a comprehensive picture to emerge.

1.1. *Neurexins and neuroligins*

Due to their critical role in synapse formation and maintenance, mutations impacting presynaptic neurexins and postsynaptic neuroligins have the potential to cause numerous structural and functional changes in the hippocampal circuit. In the scope of ASD models, one member of neuroligin family, neuroigin 3 (NGL3), expressed postsynaptically at both inhibitory and excitatory synapses, has been implicated both as a non-syndromic gene in ASD patients (Jamain et al., 2003; Uchigashima et al., 2021) and a key regulator of E/I balance in the hippocampus of mice (Tabuchi et al., 2007; Uchigashima et al., 2020). Neuroigin-4 (Nlgn4) loss-of-function mutations are associated with monogenic heritable ASD and although there is debate about the validity of the mouse homolog (Marro et al., 2019; Zhang et al., 2018), Nlgn4-KO mice demonstrate alterations in both synaptic and behavior. A third gene in this family that has become an increasing focus of ASD studies in model animals is Contactin Associated Protein 2 (Cntnap2), a member of the neurexin family in which multiple mutations linked to ASD or ASD-like disorders have been identified (Penagarikano and Geschwind, 2012).

1.2. *Shank family*

The Shank family consists of postsynaptic scaffolding proteins central to the formation and function of protein complexes at the postsynaptic density (PSD) (Guang et al., 2018; Vyas et al., 2021). There are three SHANK isoforms (SHANK1, SHANK2, SHANK3), all of which have been linked to ASD (Guang et al., 2018; Vyas et al., 2021), with a deficiency in SHANK3, a gene that maps to the chromosomal region critical to 22q13.3 deletion syndrome, found in close to 1% of ASD cases (Boccutto et al., 2013; Moessner et al., 2007). However, all three genes are subject to alternative splicing and express a number of protein isoforms with unique interaction domains, complicating a simple mechanistic model of their role in the disorder. Mouse models of specific mutations or loss-of-function of specific protein isoforms have been useful in untangling their roles at the synaptic and circuit level (Yoo et al., 2014).

1.3. *Voltage-gated sodium channels*

A consistent finding, both in the clinic and in the various mouse models discussed here, is a profound comorbidity between ASD and epilepsy (Lee et al., 2015). Thus, it is of no surprise that mutations in a third class of genes, voltage-gated sodium channel subunits, have been linked to both conditions. Mutations in the SCNA1 gene, encoding the Nav1.1 channel, result in Dravet syndrome, a neurodevelopmental disorder defined by treatment-resistant epilepsy, as well as ASD-like phenotypes (Li et al., 2011). A second channel

subunit implicated in both epilepsy and ASD is Nav1.2, encoded by the SCN2A gene. This gene has been highlighted as one of the most common monogenic sources of autism-causing mutations across multiple studies (Kruth et al., 2020).

1.4. Monogenetic Neurodevelopmental Disorders

Fragile X syndrome (FXS), a result of the loss-of-function of the *Fmr1* gene, and Rett’s syndrome, linked to a loss of function in the *Mecp2* gene, are complex neurodevelopmental disorders with some overlapping features (Bach et al., 2021), that both show a high co-morbidity with a diagnosis of ASD (Zoghbi and Bear, 2012; Bey and Jiang, 2014; Lombardi et al., 2015; Bagni and Zukin, 2019). Multiple animal models have been generated of these disorders (Bey and Jiang, 2014; Calfa et al., 2011; Vashi and Justice, 2019; Katz et al., 2012) and although these syndromes do result from single gene mutations, their endophenotypic manifestation can be complex and difficult to unravel. Nonetheless, the numerous studies which have detailed the impact of each mutation at levels ranging from synapses to behavior make them an important asset to understanding how ASD alters hippocampal function.

2. Hippocampal synapses in ASD mouse models

The emergence of symptoms in individuals with ASD is not only linked to a period of intense synaptic reshaping, but also coincides with critical events in hippocampal development (Banker et al., 2021). Recent years have witnessed the unveiling of ASD’s impact on hippocampal synapses, with studies describing synaptic changes in both human samples and mouse models (Zoghbi and Bear, 2012). These modifications in synaptic ultrastructure have been observed across various models and different layers of the hippocampus. For instance, in the Fragile-X model *Fmr1* KO mice, hippocampal CA1 pyramidal cells exhibit an increase in the density of dendritic spines with immature features, including thin spines and macular PSDs (Jawaid et al., 2018). Previous work has established perforated PSDs are enriched in glutamate receptors (mGluRs), in contrast, macular PSDs are thought to be mGluR-poor, suggesting a direct link between PSDs morphology and size, and the observed circuit connectivity in *Fmr1* KO mice (Jawaid et al., 2018).

In the *Mecp2*^{+/−} Rett’s syndrome model mice there are decreases in dendritic spine density and dendritic swelling (Belichenko et al., 2009). On the level of hippocampal synaptic transmission, the lack of functional MeCP2 resulted in reduced long-term potentiation (LTP) and excitatory post-synaptic currents (EPSCs) (Moretti et al., 2006), whereas duplication of MeCP2 causes enhanced LTP and EPSCs (Collins et al., 2004; Zoghbi and Bear, 2012), an effect likely a consequence of an increase or decrease in the number of glutamatergic synapses respectively. A deficiency in MeCP2 also impacts inhibitory synaptic transmission, leading to hyperexcitability of CA1 pyramidal neurons thought to originate from enhanced input from CA3 region, as evidenced through voltage-sensitive dye imaging (Zoghbi and Bear, 2012). These findings suggest a disruption in the E/I balance within the hippocampal circuit, originating from changes in synaptic connectivity (Hao et al., 2015; Lu et al., 2016; Zoghbi and Bear, 2012) (Hao et al., 2015; Lu et al., 2016; Zoghbi and Bear, 2012).

Similar features have also been observed in CA1 pyramidal neurons in Shank models of ASD. In *Shank3*-deficient mouse models, there is a decreased density of GluR1 puncta, associated with a decrease in AMPA receptor levels at the synapses, indicating a deficit in synapse maturation and a reduction in glutamatergic synaptic transmission affecting CA1 connectivity (Bozdagi et al., 2010). *Shank1* KO mice showed reduced PSD thickness and spine length in CA1 pyramidal neurons leading to weakened synaptic transmission and suggesting a reduction of the number of functional glutamatergic synapses (Hung et al., 2008). *Shank2*^{e7} − / − mice also display reduced basal synaptic transmission in the hippocampus, along with decreased EPSC frequency, increased NMDA/AMPA

Mutations in neuroligins (NGL), primarily associated with non-syndromic ASD and related behaviors, have undergone extensive examination within the hippocampus (Uchigashima et al., 2021). In the CA1 region, NGL3 mutation results in alterations in synaptic transmission at excitatory synapses, particularly affecting AMPAR-mediated EPSCs (Uchigashima et al., 2021). NGL3^{R451C} model mice, bearing a missense mutation in the coding region, leads to the retention of NGL3 in the endoplasmic reticulum, reducing its synaptic ex-

pression in CA1 and resulting in increased AMPAR-mediated excitatory synaptic transmission and enhanced NMDAR-dependent LTP (Etherton et al., 2011b; Uchigashima et al., 2021). Morphologically, the R451C mutation increases the dendritic branching of CA1 pyramidal neurons in the stratum radiatum, however synapse density remains unchanged. Changes are also observed at the protein level, with higher concentrations of PSD-95 and SAP-102, two excitatory post-synaptic scaffolding proteins, as well as an increase in the NR2B subunit of the NMDA receptor (Etherton et al., 2011b). Interestingly, during early post-natal development, NGL3^{R451C} mice exhibit an increased frequency of Giant Depolarizing Potentials (GDPs), representing enhanced GABAergic transmission, but no alterations in glutamatergic synaptic transmission (Pizzarelli and Cherubini, 2013). In contrast, NGL3^{R704C} knock-in mice, bearing another neuroligin-3 mutation associated with ASD patients, demonstrate a reduced frequency of mEPSCs linked to decreased AMPAR-mediated synaptic transmission, with no changes in NMDA-mediated synaptic transmission. The R704C mutation also affects glutamatergic receptor levels, evidenced by increased levels of GluR1 and GluR3, although it does not impact synapse density or size (Etherton et al., 2011a). The NGL3^{R704C} mutation truncates NGL3, increasing its interaction with AMPARs, leading to enhanced endocytosis and reduced surface expression levels of the receptor (Chanda et al., 2016). Conversely, the same mutation introduced into the related NGL4 isoform in cultured hippocampal neurons yields opposite effects, increasing AMPAR and NMDAR-mediated synaptic transmission. NGL4^{R704C} neurons also exhibit increased AMPAR levels at the surface, attributed to receptor stabilization rather than internalization, as seen in the NGL3 mutation (Chanda et al., 2016), emphasizing the mutation’s effect specificity and the differential roles of the neuroligin isoforms. In NGL4 KO mice, a decrease in GPH and GABA_AR γ 2, markers of inhibitory synapses, is observed in the pyramidal layer of CA3, although there are no changes in the number of inhibitory synapses or in excitatory synaptic marker PSD95. These changes correlate with a reduction in the amplitude and frequency of spontaneous IPSCs, leading to perturbation of the γ -oscillations during behavioral tasks (Hammer et al., 2015). Furthermore, CNTNAP2-null mutant mice, lacking Caspr2, a neuroligin-related cell-adhesion molecule, also show altered synaptic function in the CA1 region. Notably, the amplitude of IPSCs, especially from perisomatic inputs, is reduced, while the frequency of spontaneous IPSCs is increased (Paterno et al., 2021; Jurgensen and Castillo, 2015). This model also demonstrates a reduced density of PV+ interneurons specifically in the CA1 region (Paterno et al., 2021).

Mutation in the *Scn1a* and *Scn2a* genes, coding for the voltage-gated sodium channel subunits Nav1.1 and Nav1.2, respectively, have been linked to alteration in the neurotransmission (Han et al., 2012; Shin et al., 2019). Specifically, the deletion of Nav1.1 channels in GABAergic interneurons within the hippocampal CA1 region results in reduced sodium currents and lowered firing frequency of GABAergic interneurons, decreasing inhibitory synaptic inputs. Simultaneously, this deletion leads to an increase in excitatory synaptic inputs due to a higher frequency of spontaneous EPSCs (Han et al., 2012). On the contrary, the deletion of Nav1.2 channels in the CA1 region leads to a decrease in the frequency of spontaneous EPSCs and suppress LTP (Shin et al., 2019).

3. Altered hippocampal glia-neuron interactions in ASD model animals

Multiple lines of evidence have demonstrated the essential roles of glial cells, particularly astrocytes and microglia, in maintaining the physiological function of the hippocampus (Kofuji and Araque, 2021; Verkhratsky and Nedergaard, 2018; Tremblay et al., 2011; Kettenmann et al., 2013). Astrocytes, the most abundant cell type in the human brain, coordinate synapse formation and elimination, neuronal survival, and axon guidance in the developing brain (Allen and Eroglu, 2017; Eroglu and Barres, 2010; Chung et al., 2015; Verkhratsky et al., 2019). Moreover, astrocytes form tripartite synapse, actively regulating synaptic transmission by interacting with presynaptic axon terminal and postsynaptic dendritic spines of neurons (Perea et al., 2009; Verkhratsky et al., 2019). On the other hand, microglia, as the dominant immune cells in the brain, possess phagocytic capacity, enabling them to engulf dead cells and detrimental substances in the brain (Kettenmann et al., 2011). They also participate in synaptic pruning by engulfing excessive synapses through interactions with neuron (Kettenmann et al., 2013; Paolicelli et al., 2011; Neniskyte and Gross, 2017). These glial cells work in concert to maintain brain homeostasis (Matejuk and Ransohoff, 2020; Verkhratsky et al., 2019).

Consequently, morphological and functional alterations of glia have been widely observed in many brain disorders, including neurodevelopmental disorders such as ASD (Petrelli et al., 2016) and dysfunction in glial cells has been recognized as an etiological factor in their pathogenesis (Petrelli et al., 2016).

Due to the highly heterogeneous nature of ASD, many different transgenic mice modelling the disorder have been developed, and how hippocampal glia are altered substantially varies depending on the specific model. Nonetheless, most previous studies have commonly reported that, regardless of the model, astrocytes and microglia exhibit morphological, molecular, and/or functional alterations in the hippocampus.

In the Fmr1-KO mouse model multiple studies have reported astrocytic changes (Jawaid et al., 2018; Yuskaitis et al., 2010; Wallingford et al., 2017). During early postnatal development, dynamic alterations in the expression of Hevin, a protein secreted at excitatory synapses, are observed, suggesting the involvement of astrocytic alterations in abnormal synaptic development in FXS (Wallingford et al., 2017). In 2-month-old Fmr1-KO mice, astrocytes and microglia were reported to show reduced function at tripartite synapse and synaptic pruning respectively (Jawaid et al., 2018), while astrocytes showed increased GFAP expression in 3-month-old mice (Yuskaitis et al., 2010). Another notable study has developed astrocyte-specific Fmr1 conditional KO mice and observed that astrocytic GABA synthesis increased alongside a modest elevation in GFAP expression (Rais et al., 2022), demonstrating a positive correlation between astrocytic GABA synthesis and reactivity (Heo et al., 2020; Jo et al., 2014; Nam et al., 2020).

In the Mecp2-KO mouse model astrocytes undergo cytoskeletal atrophy during severe symptomatic time point, but not at earlier time points (Albizzati et al., 2022). The reduced ramification of astrocytes was also observed in postnatal Mecp2-conditional KO mice (Nguyen et al., 2012). Microglia in these mice also exhibit reduced branch complexity in the late-phenotypic stage, whereas no such changes occur during the pre-phenotypic period (Cronk et al., 2015). Furthermore, CA1 astrocytes in the same mouse model have been implicated in the reduction of tonic inhibition due to decreased expression of the GABA transporter 3 (GAT3) within astrocytes (Dong et al., 2020), a phenotype linked to the hyperexcitability and increased seizure susceptibility in these mice. A similar finding was also observed in the astrocyte-specific Mecp2-KO mice (Dong et al., 2020). Collectively, these studies suggest that hippocampal glia are significantly impacted by, as well as contribute to, the pathology of Rett syndrome.

At the level of synaptic proteins, mice with C-terminal deleted Shank3 (deletion of exon 21, which includes the Homer- and Cortactin-binding domains; Shank3^{+/ Δ}) exhibit morphological changes in astrocytes and microglia within the hippocampus, with no observable alterations in the number or size of astrocytes (GFAP+ and S100+) in most hippocampal subregions. However, there was a noteworthy reduction in the GFAP+ area specifically within the CA1 stratum radiatum. In contrast, microglia exhibited no discernible changes in their morphological characteristics (Cope et al., 2016). On the other hand, a separate transcriptomics study conducted with Shank3-KO mice revealed an increase in the expression of gene sets related to astrocytes, microglia, and oligodendrocytes (Yoo et al., 2022). However, Shank2-KO (lacking exon 6 and 7) mice showed that astrocytic and microglial genes are negatively enriched (Yoo et al., 2022). These findings implicate the Shank2 and Shank3 deletions lead to differential transcriptomic changes of glial cells in the hippocampus.

A recent study, utilizing NLG4-KO mice, revealed sex-dependent morphological and functional alterations in microglia (Gunevkaya et al., 2023). These microglial changes were more pronounced in males than in females. Specifically, male Nlgn4-KO mice, aged 13 weeks and 20 weeks, exhibited reduced microglial density and branching, diminished phagocytic activity, decreased expression of MHC1 and CD54, impaired response to injury, and disrupted energy metabolism in the CA3 region of the hippocampus. In contrast, in the NGL3^{R451C} point-mutant knock-in mouse model, DG microglia showed no discernible morphological alterations, while DG astrocytes showed a shrunken morphology (Matta et al., 2020).

In Cntnap2-KO mice there were only subtle morphological changes observed in astrocytes in the DG molecular layer and CA1 stratum radiatum, with no alterations in the numbers or area of GFAP+ cells. Notably, in the ventral hippocampus, there was a significant reduction in the number of S100+ astrocytes, although the area of S100+ pixels remained unaltered. Similarly, microglia exhibited minimal alterations with no

change in the numbers or area of Iba1+ cells. There was a slight, non-significant increase in the CD68+ area observed in the dorsal molecular layer and ventral stratum radiatum, but this was not observed in other hippocampal subregions (Cope et al., 2016). Intriguingly, there was a report with a mouse model that underwent a plasma exchange operation using plasma from two male patients with CASPR2 (contactin associated protein 2, encoded by Cntnap2 gene)-positive encephalitis. In this mouse model, regardless of their age, hippocampal microglia showed no morphological alterations, while there was a significant increase in microglial numbers in the cortex (Coutinho et al., 2017). The modest change or the absence of the alterations in hippocampal glial morphology in the Cntnap2-KO model may distinguish it from many other ASD-like mouse models.

In SCN1A haplodeficient (-/+) mice, a Dravet syndrome model, one recent study reported increased GFAP expression and an increased number of Iba1-positive microglia in DG, implying increased reactivity of astrocytes and microglia (Goisis et al., 2022). Additionally, this study reported a reduction in tonic GABA current in CA1 pyramidal neurons, which needs further investigation due to its inconsistency with existing evidence showing the positive correlation between astrocytic reactivity and tonic GABA current (Goisis et al., 2022). In SCN2A-deficient mice, another study reported partially activated microglia, evidenced by increased cell bodies and reduced branches (Yang et al., 2023). These activated microglia showed excessive phagocytic pruning of synapses, which occurs during development and continues into adulthood. These changes in microglia led to a reduction in spine density and glutamatergic synaptic transmission in CA1 pyramidal neurons (Yang et al., 2023). Collectively, these studies suggest that glial alterations in both SCN1A and SCN2A deficiency-induced ASD-like mouse models could impact E/I balance in the hippocampus.

4. Hippocampal neural circuit activity in ASD model mice

One of the benefits of modeling genetic disorders in the mouse is the ability to understand at a circuit and systems level how changes in behavior are related to changes in the well-understood physiology of the hippocampal formation (Buzsáki et al., 2003; Zemla and Basu, 2017). The last fifty years of research has given us a rich template of physiological signatures or correlates of mnemonic processing in the hippocampus, including the formation and spatial coding of place cells (Moser et al., 2017; O’Keefe and Nadel, 1978), the temporally organized activity of ensembles of place cells, both during movement and sleep, as well as the oscillatory patterns which dominate the hippocampal local field potential, theta (4-12Hz) gamma (30-100Hz) and sharp wave ripples (SWR; 120-180Hz) (Bragin et al., 1995; Nunez and Buno, 2021; Csicsvari et al., 2003; Buzsaki, 2015), which can shed light on how information flow and processing are altered in a dynamic manner (Figure 2). Although these physiological measures are complex, they can serve as indicators of how changes in the balance between excitation and inhibition are manifest on the population level during specific behavioral or memory states.

Theta is most prominent oscillation in the hippocampus during locomotion and attention and has been tightly linked to memory function, with manipulations that decrease theta power linked to encoding deficits (Hines et al., 2022; O’Keefe and Nadel, 1978; Winson, 1978; Vinogradova, 1995; Rudoler et al., 2023). Gamma oscillations are modulated by movement velocity, sensory processing, attention, and cognition and memory and in CA1, have been used as a proxy for the influence of CA3 (low gamma 30-60 Hz) and entorhinal cortical (high gamma, 60-100 Hz) inputs on circuit function (Colgin et al., 2009). Moreover, the timing and amplitude of these distinct gamma bands can be modulated by the slower theta oscillation, a phenomenon termed cross-frequency coupling, thought to be important for the temporal organization of circuit activity (Bragin et al., 1995; Buzsáki et al., 2003; Tort et al., 2008; Chrobak et al., 2000). Finally, SWRs, triggered by input from CA3 and/or CA2 (Buzsaki, 2015; Oliva et al., 2016; Middleton and McHugh, 2016) create short periods (~100-200 msec) of precise temporally organized neuronal spiking during slow-wave sleep and quiet wakefulness and have been implicated in memory consolidation, storage and recall (Buzsaki, 2015). All these oscillations require not just external inputs to the CA1 region, but also precise interaction in local microcircuits containing both excitatory and inhibitory neurons (Buzsaki, 2015). Thus, understanding how genetic models of ASD impact these rhythms and the temporal and sequential coordination of spiking in the

structure they support is an important bridge between behavioral phenotypes and shifts in E/I balance on the level of circuits and synapses.

Both mouse (Bey and Jiang, 2014; Willemsen and Kooy, 2023) and rat (Engineer et al., 2014; Hamilton et al., 2014) models of FXS have been generated and subject to in vivo electrophysiological analysis. Two studies recorded from the CA1 region of $Fmr1^{-/-}$ mice performing an active place avoidance task (Dvorak et al., 2018; Radwan et al., 2016) and observed changes in the temporal and spatial coordination of hippocampal oscillations in a cognitive state dependent manner, with alterations in the patterns of coupling between the theta and slow gamma rhythms, as well as an inflexibility of the spatial representations in the $Fmr1^{-/+}$ mice. A third study from the same lab (Talbot et al., 2018) recorded CA1 neuronal activity and local field potential in $Fmr1$ -KO mice in a fixed context and found that while place fields were relatively intact, on the network level pyramidal cells were less modulated by ongoing theta and gamma oscillations and place cells with overlapping fields showed a decrease in positively correlate firing, forming weaker cell assemblies. Another 2018 study from Arabab et al using the same model (Arbab et al., 2018) reported increases in theta power and local gamma coherence on the LFP level. On the network level they observed the pairs of interneurons in CA1, as well as interneuron-pyramidal cell pairs, showed significant decreases in spike count correlation, indicating a reduction in the correlated variance of these cell assemblies, and hypersynchrony between inhibitory neuron firing and the theta and gamma oscillations. A third group published a 2018 study recording in the CA1 region of $Fmr1$ -KO mice (Boone et al., 2018) finding a significant decrease in the frequency of REM sleep, increased firing of pyramidal cells during both wakefulness and rest, an increase in low gamma power and alterations in SWRs, with longer and slower oscillations coupled with a decrease in pyramidal cell firing across the events. While there are some disparities between these results, which could be related to the tasks and contexts employed for recording, there is consistent findings of dysregulation of oscillatory coupling of neurons with the local field potential and changes in network coordination.

More recently (Asiminas et al., 2022) Asiminas et al reported the first in vivo recordings from the hippocampus of a rat model of FXS. They observed while place fields in a novel environment were similar between control and $Fmr1$ -KO rats, the FXS-model animals failed to show experience-dependent improvements in spatial coding when returned to the context the following day. Further, consistent with results from mice, they observed a decrease in the modulation of pyramidal cell firing by the slow gamma oscillation and significant shifts in the preferred firing phase of pyramidal cells to both theta and slow gamma.

Hippocampal activity in the $Mecp2^{-/+}$ mice has also been carefully studied at the single neuron and network levels. Lu et al (Lu et al., 2016) used both 2-photon calcium imaging and in vivo electrophysiology to establish that while CA1 pyramidal cells in the KO mice are overall less active, they showed a significant increase in synchronous activity, which interestingly could be rescued by deep brain stimulation of the fornix. A second study employing high-density tetrode recording in the CA1 region (Kee et al., 2018) found that, like what was reported in the $Fmr1$ -KO rats (Asiminas et al., 2022), place fields in the KO mice failed to show experience-dependent improvements in the spatial coding. Interestingly, the authors also observed the hypersynchronous activity in these mice extended to the SWR events, perhaps occluding learning-dependent consolidation mechanisms necessary for place field refinement. Finally, a recent study (He et al., 2022) employed 1-photon calcium imaging in the CA1 of $Mecp2^{-/+}$ mice subject to contextual fear conditioning and observed that during memory recall the active CA1 neuronal ensembles were larger and more correlated, changes the authors attributed to a specific deficit in the function of the OLM class of CA1 interneurons.

A recent study examined the impact of the deletion of NGL3 on hippocampal physiology (Modi et al., 2019), focusing on the dorsal CA2 and CA3 regions of the circuit, as they have been implicated in social memory (Chiang et al., 2018; Hitti and Siegelbaum, 2014). These mice, which have an impairment in social behavior, demonstrated CA2 specific alterations in the entrainment of pyramidal cell spiking by slow oscillations, as well as decrease in gamma power in both the CA2 and CA3 regions. Ex vivo recordings found a shift in the E/I balance towards excitation, with CA2 pyramidal cells in the KO mice showing an increase in spontaneous excitatory input with a concomitant decrease in spontaneous inhibitory input, suggesting this shift of the local network excitation could connect the impairments in oscillatory activity and temporal coordination of

spiking to deficits in social behavior.

Cntnap2 KO mice capture ASD-like behavioral phenotypes, including social impairments, reduced vocalization repetitive behaviors and impaired cognition (Penagarikano et al., 2011), and in the CA1 region have an E/I balance shifted towards excitation, with reduced perisomatic inhibition of pyramidal cells (Jurgensen and Castillo, 2015; Paterno et al., 2021). In vivo hippocampal recordings in behaving mice revealed that during movement there was an overall decrease in theta power, as well as impaired phase-amplitude coupling between fast gamma, thought to reflect inputs from the entorhinal cortex (EC), and theta oscillations in the KO mice. During rest, the occurrence of ripples decreased, as did the amplitude of the oscillations themselves, with no change in the size of the sharp wave, suggesting CA3 input was unchanged. This is consistent with the observation of a decrease in PV density and a decrease in inhibitory input to pyramidal cells, suggesting this is a result of the shift in the local E/I balance that dampens the ability of the circuit to generate oscillations capable of entraining pyramidal cell activity (Paterno et al., 2021).

Three studies have examined the impact of the loss of function of Shank3 on hippocampal in vivo physiology, making it one of the best characterized models in terms of circuit function. Dhamne et al. (Dhamne et al., 2017) conducted long-term EEG recordings in control and Shank3B^{-/-} mice, both under baseline conditions and following chemical induction of seizure. Interestingly, these mutants were resistant to PTZ induced seizure, suggesting an E/I balance shifted to increased inhibition and/or reduced excitation, consistent with ex vivo recording data (Dhamne et al., 2017). Further, under baseline conditions Shank3B^{-/-} mice demonstrated increased power in the gamma band. Cope et al. (Cope et al., 2023) recorded from the ventral CA1 region of the same Shank3B^{-/-} mice during social behavior and observed no change in theta or gamma power in the mutants but did observe that chemogenetic activation of the CA2 region increased CA1 theta power specifically in the KO mice and led to a concomitant rescue of social behavioral deficits. Interestingly, a recent study from Tao et al. (Tao et al., 2022) conducted a similar study, recording in vCA1 of control and Shank3^{-/-} mice during a social discrimination task and found a decrease in the fraction of cells encoding social information during the task, as well as a decrease in the power of SWRs and a decrease in the correlation between cell sequences observed during behavior and SWRs. These results suggested an impairment in the reactivation of social sequences in these animals. Mechanistically, the phase locking of interneurons to the SWR oscillation was impaired in the mutants relative to controls, although there were no differences in the entrainment of PC firing, suggesting the shift in the activity of the inhibitory neurons may underlie the impairments in the re-expression of sequential activity.

In vivo hippocampal activity has also been examined in SHANK2 deficient mice. Sato et al. (Sato et al., 2017) employed longitudinal 2-photon calcium imaging of CA1 pyramidal cell activity in head-fixed mice performing a virtual reality-based goal localization task. While the pyramidal cells in control mice stably overrepresented both the locations of landmarks and rewards following learning, Shank2 mutant mice, engineered to mimic a human ASD-linked microdeletion, demonstrated overrepresentation of the reward sites, but not at the location of salient landmarks.

Turning to genes that impact neuronal excitability, mice that are haploinsufficient for Scn1a (SCN1a^{+/-}) exhibit impaired social and spatial cognition and stereotypic behaviors and in vitro recordings in CA1 revealed a profound shift in the E/I balance, with reduced spontaneous inhibitory currents and enhanced spontaneous excitatory currents (Han et al., 2012). Recently, in vivo recording was performed in the hippocampus of rats with injected with a short-hairpin virus to knockdown expression of the Nav1.1 channel (Sakkaki et al., 2020). They observed a specific decrease in the firing rate of inhibitory neurons, consistent with the ex-vivo data, and a shift in the E/I balance towards increased excitation. On the level of oscillations this resulted in weaker phase-amplitude coupling between theta and gamma and impairments in the theta-modulated spiking of PCs. There was a shift of the preferred phase to the descending phase of theta and significantly weaker theta phase precession. Further, on the sequence level, the relationship between the spiking of pairs of place cells with nearby place fields, typically observed in normal rats, was impaired, with a breakdown of the expected relationship between distance of the fields and phase offset.

Finally, recordings in the CA1 region of freely behaving SCN2a^{+/-} mice found no changes in theta or gamma

oscillations during exploration, nor in the firing or spatial coding of the pyramidal cells. However, during SWRs there was a significant reduction in the reactivation of cell assemblies, and on the level of sequences, the replay of behavioral place-cell sequences was significantly shorter, attributed to shift in the E/I balance towards increased inhibition (Middleton et al., 2018). Although the loss of a single copy of Nav1.1 and Nav1.2 led to distinct physiological phenotypes, they both resulted in a decrease in the ability of the hippocampus to accurately represent longer trajectories through space, consistent with dysfunction in the local CA1 circuits.

5. DISCUSSION

The importance of shifts in E/I balance across multiple brain regions in the development of ASD pathology has been recognized for many years (Lee et al., 2017; Sohal and Rubenstein, 2019; Rubenstein and Merzenich, 2003). In the hippocampus, accumulating data now links synaptic changes to the abnormal connectivity and E/I imbalances observed in vivo in ASD model animals. Nevertheless, it is important to note that synaptic alterations in ASD can vary across the different models, brain regions, and age groups under study. Regardless, it remains essential to uncover the key mechanisms necessary for initiation and maintenance of E/I shifts throughout the lifespan, as well as comprehend how those shifts impact brain connectivity and function. As the models discussed here illustrate, these E/I changes can relate to the availability of receptors at the synapses (Bonsi et al., 2022; Guang et al., 2018; Lee et al., 2017), to changes in inhibitory circuits (Jurgensen and Castillo, 2015; Paterno et al., 2021), or alterations in morphology (Eltokhi et al., 2020); many routes to achieve a similar functional outcome.

In understanding the development of ASD, it is crucial to consider, not only neurons, but also the role glia play in these disorders. Accumulating evidence of morphological, transcriptomic, and functional changes in hippocampal astrocytes across rodent models of ASD has begun to clarify the role they play in the shaping synaptic and cognitive phenotypes related to the disorder. Astrocytes play an essential role in sculpting neural circuits by coordinating synapse formation and function, promoting neuronal survival, and guiding axonal growth in the developing brain (Allen and Eroglu, 2017; Eroglu and Barres, 2010; Chung et al., 2015). Recent studies have also demonstrated that astrocytes actively participate in pruning dysfunctional synapses (Chung et al., 2013; Neniskyte and Gross, 2017) and regulate synaptic transmission through gliotransmitter release and removal, forming tripartite synapses in the hippocampus (Nam et al., 2019; Verkhratsky et al., 2019), thus abnormal astrocytic function also often leads to a disruption of E/I balance. A recent study reported the critical importance of astrocytes in ASD pathology by transplanting astrocytes derived from ASD individuals into the hippocampus of newborn mouse pups (P1 to P3) (Allen et al., 2022). The transplanted mice exhibited distinct repetitive behaviors and memory impairment resembling ASD, along with exaggerated astrocytic Ca²⁺ fluctuations in vivo, as well as reduced long-term potentiation, neuronal network firing, and spine density in vitro. In addition, microglia have been well documented to be primarily responsible for synapse pruning, a crucial process for maintaining E/I balance in the developing brain (Neniskyte and Gross, 2017; Paolicelli et al., 2011). However, once again, the nature of these glial alterations varies depending on factors such as the specific model, sex, and age under consideration. Nonetheless, current data make clear that glial cells are not merely passive victims of neurocentric pathology, but rather play an active role in the orchestration of ASD pathology.

While shifts in E/I balance can have a plethora of consequences during development and in the adult brain, as well as on single cell and network activity, several in vivo measures of circuit function, including coupling between slow and fast oscillations, modulation of spiking by the local field potential, and the coordinated activity of ensembles of neurons, both by theta during movement and by ripples during rest, provide temporally sensitive and precise readouts of the consequences of disruptions in the E/I network. While it is well accepted, both experimentally and theoretically, that shifts in E/I balance in either direction— a more inhibited or a more excited network— can have disruptive effects on circuit function and cognition, this is also true on the level of in vivo activity patterns. The most common alterations across the models reviewed were shifts in the fine patterns of temporal coordination of hippocampal activity. This perhaps is unsurprising given the need for a well-tuned E/I balance to achieve precision of spiking at the millisecond,

or even tens of milliseconds, timescale. Interestingly, in models in which single cell properties, like place field size and average pyramidal cell firing rate, were assessed, very few changes were noted. However, when population activity was examined, more significant changes were observed, be the ensemble level, with discoordination observed in the *Fmr1* mice (Talbot et al., 2018), the truncation of replay sequences in the *scn2a*^{-/+} mice (Middleton et al., 2018) or the ensemble level hypersynchrony observed in the *Mecp2* mice (He et al., 2022).

E/I shifts in network activity may also appear in a state-dependent fashion- both in terms of the animal’s cognitive state, i.e. memory encoding or recall, and in terms of the physiological state of the circuits, such as an active theta-dominated state or the large-irregular activity and SWRs that accompany quiet wakefulness and slow wave sleep. While a well-balanced E/I network is important for all, mechanistic differences in the cell-types involved, the dominant excitatory inputs, and the timescales involved may reveal specific dysfunctions in select models. While there is clearly no singular physiological endophenotype of ASD across the mice assessed, there are recurrent themes in the data. A loss of oscillatory coordination and disorganization and inflexibility of population activity, both during rest and after learning, stand out as hallmarks of hippocampal dysfunction in ASD model mice. Moving forward the field would benefit from the application of more standard protocols to facilitate comparisons between the various models, as well as the application of high-density recording and/or imaging approaches to assess the impact of ASD risk mutations on the levels of coordination across the population.

Conflict of interest

The author states no conflict of interest.

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Figures and figure legends

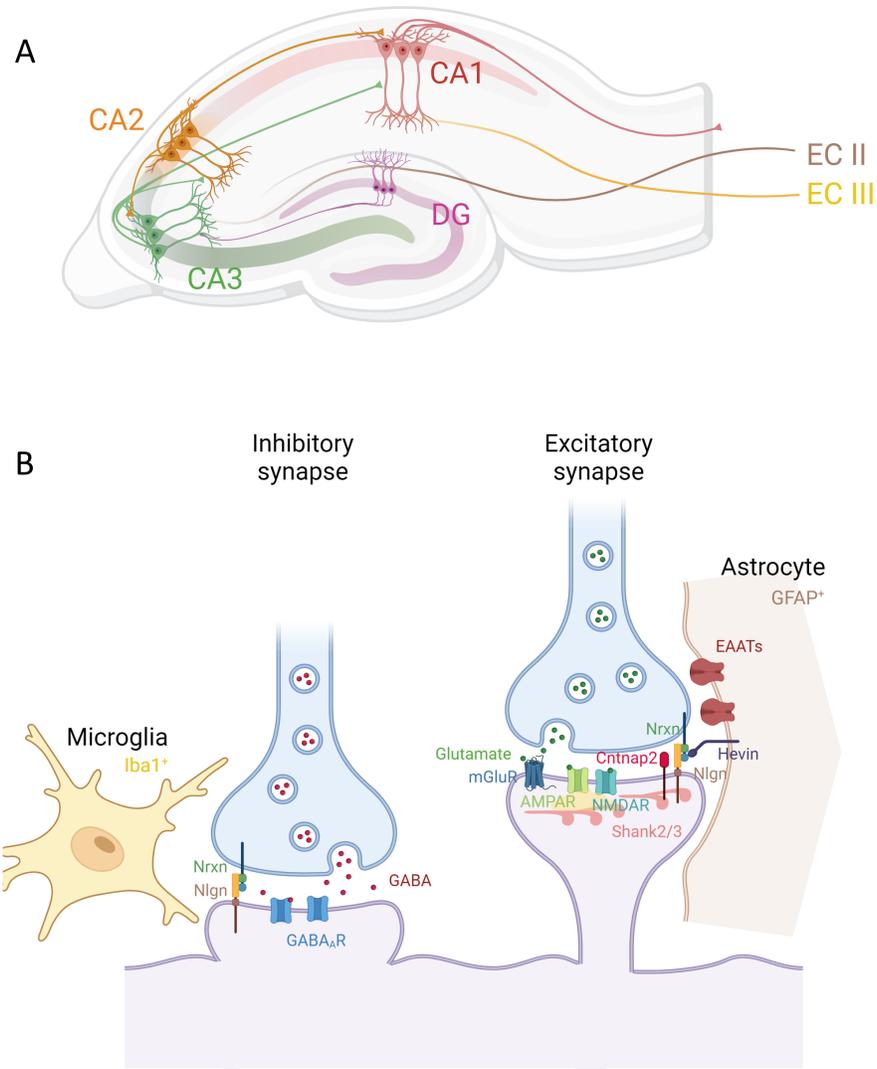


Figure 1: Schematic diagrams of hippocampal circuits (A) and neuron-glia interaction in inhibitory and excitatory synapses (B)

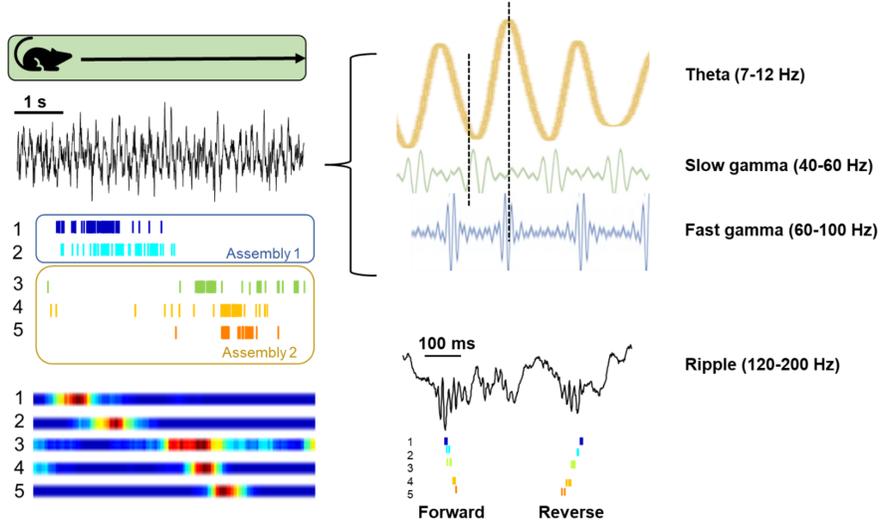


Figure 2: Schematic diagram of local field potential (LFP) analysis in the mouse hippocampus

Gene	Model	Synapses		Astrocytes		E/I shift	In vivo physiology		
		Structural changes	Activity changes	Microglia	Single cells		Assemblies	Oscillations	
Neurodevelopmental disorders	Fmr1 Fmr1-KO	Increased thin/immature spines (Jawaid et al., 2018) Decreased GluR1 (Jawaid et al., 2018)	N/A	Reduced astrocytes at synapse (Jawaid et al., 2018)	Reduced microglia pruning (Jawaid et al., 2018)	E < I	Impaired experience-dependent changes (Asiminas et al., 2022) Decreased theta & gamma modulation (Tabot et al., 2018)	Weaker assemblies (Tabot et al., 2018)	Longer and slower ripples Decreased low gamma power (Boone et al., 2018)
	Mecp2 Mecp2 ^{fl}	Decreased dendritic density Dendritic swelling (Belichenko et al., 2009)	Reduced EPSCs and LTP (Moretti et al., 2008)	Decreased astrocytic Kir4.1 (Kahanovitch et al., 2018) Delayed cytoskeletal atrophy (Albizzati et al., 2022)	Reduced branch complexity (Cronk et al., 2015)	E < I	Impaired experience-dependent changes Decreased pyramidal cell activity (Lu et al., 2016)	Hyper-synchrony larger assemblies (He et al., 2022; Kee et al., 2018)	No changes observed (Kee et al., 2018)
NGL family mutations	NGL3 ^{SH1C}	Increased dendritic branching (Eherton et al., 2011a) Increased synaptic levels of PSD95, SAP-102 and NR2B subunit (Eherton et al., 2011a) Decreased synaptic levels of NGL3 (Eherton et al., 2011a)	N/A	Reduced branch length and area (Matta et al., 2020)	Increased density (Matta et al., 2020)	E > I	N/A	N/A	N/A
	NGL3	N/A	N/A	N/A	N/A	E > I	Impaired slow oscillation modulation in CA2 (Modi et al., 2019)	N/A	N/A
	NGL3 ^{SH2C}	Increased levels of GluR1 and GluR3 (Eherton et al., 2011b)	Reduced frequency of mEPSCs (Eherton et al., 2011b) Decreased AMPAR-mediated synaptic transmission (Eherton et al., 2011b)	N/A	N/A	E < I	N/A	N/A	N/A
	NGL4 ^{SH2C}	Increased AMPAR surface levels (Chanda et al., 2016)	Increased AMPAR and NMDAR-mediated currents (Chanda et al., 2016)	N/A	N/A	E > I	N/A	N/A	N/A
NGL4	NGL4 ^{fl}	Decreased density of GPH and GABA _A R2 (Hammer et al., 2015) No changes in total number of inhibitory synapses (Hammer et al., 2015)	Reduced frequency of sIPSCs (Hammer et al., 2015) Reduced power of γ oscillations (Hammer et al., 2015)	N/A	Male-specific changes in morphology (Guneykaya et al., 2023) Reduced phagocytosis (Guneykaya et al., 2023)	E > I	N/A	N/A	N/A
Cntnap2	Cntnap2 ^{fl}	N/A	Decreased perisomatic average IPSCs amplitude (Jørgensen and Castillo, 2015; Paterno et al., 2021) Increased frequency of sIPSCs (Jørgensen and Castillo, 2015; Paterno et al., 2021)	No changes observed (Cope et al., 2016)	No changes observed (Cope et al., 2016)	E > I	N/A	N/A	Decreased theta power impaired theta/fast gamma coupling (Paterno et al., 2021) Fewer and smaller ripples (Paterno et al., 2021)
Shank family mutations	Shank1	Shank1 ^{fl}	Reduced PSD thickness Reduced spine length (Hung et al., 2008)	N/A	N/A	N/A	E = I	N/A	N/A
	Shank2	Shank2 ^{SH-7}	Reduced spine number (Hung et al., 2008)	Decreased EPSCs frequency (Guang et al., 2018) Increased NMDA/AMPA ratio (Guang et al., 2018) Enhanced LTP (Guang et al., 2018)	Negatively enriched gene sets (Yoo et al., 2022)	Negatively enriched gene sets (Yoo et al., 2022)	E < I	Overrepresentation of rewards, but not landmarks (Sato et al., 2020)	N/A
	Shank3	Shank3 ^{SH-1}	Decreased density of GluR1 (Bozdagi et al., 2010) Decreased levels of synaptic AMPAR (Bozdagi et al., 2010)	Decrease glutamatergic transmission (Bozdagi et al., 2010)	N/A	N/A	E < I	Decreased social coding (Tao et al., 2022)	Less correlated activity (Tao et al., 2022) Increased gamma power (Chahme et al., 2017) Decreased ripple power (Tao et al., 2022)
	Shank3	Shank3 ^{SH-2C}	N/A	N/A	Reduced GFAP+ area (Cope et al., 2016)	No changes observed (Cope et al., 2016)	N/A	N/A	N/A
Sodium channelopathy	Scn1a	Scn1a ^{fl}	N/A	Decreased frequency of sIPSCs (Han et al., 2012) Increased frequency of sEPSCs (Han et al., 2012)	Increased GFAP expression (Gooss et al., 2022)	Increased Iba1+ microglia (Gooss et al., 2022)	E > I	Decreased theta modulation (Sakkaki et al., 2020)	Impaired pairwise correlation (Sakkaki et al., 2020) Impaired theta/gamma coupling (Sakkaki et al., 2020)
	Scn2a	Scn2a ^{fl}	N/A	Reduced frequency and amplitude of sEPSCs (Shin et al., 2019) Decreased LTP induction (Shin et al., 2019)	N/A	Reduced branching excessive phagocytosis (Yang et al., 2023)	E < I	N/A	Reduced assembly reactivation (Middleton et al., 2018) Truncated replays (Middleton et al., 2018)
	Scn2a	Scn2a ^{fl}	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Figure 3: Summary of alterations in synapses, glia, and *in vivo* physiology of hippocampus in various ASD-like mouse models

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