2

Experience-dependent Structural Plasticity in Dendrite Development: Emerging Common Themes Across Model Systems

Justin Rosenthal and Quan Yuan

Dendrite Morphogenesis and Plasticity Unit, National Institute of Neurological Disorders and Stroke, National Institutes of Health, USA
Corresponding Email: quan.yuan@nih.gov

Abstract

From flies to humans, the nervous system of animals is remarkably adept at modifying itself in response to altered neuronal activity. One crucial component underlying this robust plasticity is a complex array of cellular and molecular changes occurring on the dendritic arbor of postsynaptic neurons. Both local events at the synapse, as well as broader effects, such as cell surface receptor-to-nuclear signaling, work together to adjust various features of neuronal dendrites, including branching patterns, arbor size, spine density and maturity. How dendrites respond to experience and activity are also influenced by their cellular environment and neighboring cells, such as astrocytes and microglia. With updated research methods and new technologies, these phenomena remain subjects of intense investigations. Studying dendrite plasticity not only helps us understand fundamental principles guiding the construction and modifications of circuit connectivity, but also begin to uncover root causes for a wide spectrum of neurodevelopmental disorders and neuropsychiatric diseases.

Introduction

One of the essential features of our nervous system is its ability to adapt to changes in both internal and external environments. How this flexibility

is regulated during development and in adulthood, and how it is altered in disease or injury, are fundamental questions that have long captivated neurobiologists' attention. Classic works performed a half century ago in the mammalian visual and somatosensory cortex demonstrated the profound influence of sensory experience on cortical development, and established activity-dependent modifications of neuronal structure and connectivity as critical components of circuit development and remodeling (LeVay, Wiesel et al. 1980, Katz and Shatz 1996) . During the past few decades, through extensive studies using a variety of experimental paradigms and model systems, we have learned that the way a neuron or a circuit responds to sensory experience or neural activity is largely determined by its genetic and cellular contexts, and directly linked to its functional properties. With recent technical innovations and the addition of invertebrate models, the repertoire of phenotypes and underlying molecular pathways associated with experience-dependent plasticity have been further enriched. At the same time, these advances also offer opportunities for comparative studies and help us extract common themes shared across systems.

In this chapter, we will focus on experience-dependent plasticity in dendrite and spine development. Amongst many dynamic cellular events occurring throughout circuit construction and remodeling, dendritic growth and patterning are particularly prone to the influences of experience (Wong and Ghosh 2002). In addition, altered spine dynamics and morphology are considered the cellular substrates for memory storage and are linked to cognitive decline observed in human neurological disorders (Nithianantharajah and Hannan 2006, Forrest, Parnell et al. 2018). There is a large body of literature accumulated on this topic, which we won't be able to cover adequately within the scope of this chapter. Instead, we will first briefly introduce some of the classic studies while referring the readers to broader and more detailed descriptions in excellent review articles (Whitford, Dijkhuizen et al. 2002, Smith, Heynen et al. 2009). We will then discuss the expression and regulation of structural plasticity in developing dendrites and compare studies performed in vertebrate and invertebrate model systems. Next, we will summarize the key molecular events induced by neuronal activity and sensory experience. Lastly, we will review exciting new discoveries exploring the role of non-autonomous contributions, such as neuron-glia interactions, in regulating dendritic plasticity, as well as shared molecular underpinnings between altered dendrite and spine morphology and human neurodevelopmental disorders. Despite the overwhelming degree of complexity and diversity associated with dendritic plasticity, and the many remaining questions, the molecular insights we have gained and the ever-growing new discoveries

enabled by updated technologies have begun to reveal general principles and common pathways governing the dendrite morphogenesis and plasticity in central nervous systems across the animal kingdom.

2.1 Diverse Outcomes Associated with Experience-dependent Dendritic Plasticity

To study experience-dependent dendrite plasticity, numerous model systems have been adopted and each has its unique advantages. Collaboratively, they built the foundation of our knowledge on how developing nervous systems adapt to changes. Early studies have shown that monocular deprivation alters dendrite distribution in the lateral geniculate nucleus and visual cortex (Wiesel and Hubel 1963, Lendvai, Stern et al. 2000, Alvarez and Sabatini 2007), while the enriched environment for motor learning increases dendritic growth and branching in cortical neurons (Volkmar and Greenough 1972, Withers and Greenough 1989). More recently, *in vivo* time lapse imaging of *Xenopus* retinotectal neurons have provided compelling demonstrations of the close relationship between sensory input and dendritic development, where visual stimuli promote dendrite growth (Sin, Haas et al. 2002). Besides regulating growth, experience and synaptic activity also regulate dendritic branching patterns through dendritic remodeling, during which diffusely distributed dendrites retract and only correctly projected dendrites remain, ensuring the proper establishment of specified connectivity patterns during circuit maturation. Both mitral cells in the olfactory system and retinal ganglion cells are classic examples of activity-dependent dendrite remodeling (Malun and Brunjes 1996, Wang, Liets et al. 2001). With the development of two photon imaging techniques and genetically encoded synapse markers, the broad influence of sensory deprivation on both developing and established cortical circuits has been directly demonstrated *in vivo*, including reduced spine elimination in somatosensory cortex (Zuo, Yang et al. 2005), elevated rate of spine formation in visual cortex (Hofer, Mrsic-Flogel et al. 2009) and the abnormal pruning of dendrites in retinal ganglion cells (Tian and Copenhagen 2003). Thus, sensory influences on dendritic structure appear to be ubiquitous and exhibit a great deal of complexity and diversity.

Apart from making the obvious distinctions based on cell types and animal species, two additional factors must be taken into consideration to evaluate dendrite plasticity induced by sensory experience or activity: the cellular substrates being studied and quantified, such as dendrite length, volume, or branch dynamics; and the time window when the experiments are

performed and the data are collected. The importance of these two factors is clearly demonstrated by studies summarized below.

2.1.1 Sensory experience impacts mammalian cortical development

Mammalian cortical development is broadly influenced by sensory experience. Cortical regions corresponding to visual and somatosensory systems are the two most heavily investigated areas and offer unique insights into how sensory deprivation affects circuit development and function in general. Descriptions of findings in other systems, such as auditory, motor, and navigation circuits, can be found in additional reviews (Fu and Zuo 2011).

Somatosensory cortex: In rodent primary somatosensory cortex (S1), the barrel cortex processes whisker-related information. The topographic pattern, or the distinct "barrels", can be disrupted by the ablation of vibrissae follicles. Almost 50 years ago, Van Der Loos and Woolsey first discovered that ablating a whisker follicle at birth disrupts the development of corresponding cortical representation of that whisker, while ablating the vibrissae follicles on the contralateral mystacial pad leads to a reorganization of the barrel patterning (Van der Loos and Woolsey 1973). These large-scale effects on barrel organization are most prominent during a developmental critical period and diminish in mature animals (Weller and Johnson 1975, Woolsey, Dierker et al. 1975).

In the following decades, researchers developed many techniques to produce sensory deprivation in the whisker-to-barrel system, including electrocauterization of whisker follicles, infraorbital nerve (ION) lesions, and whisker trimming in different patterns. Whisker follicle ablation at birth produces long lasting behavioral consequences, leading to reduced sensitivity even after whisker regrowth (Carvell and Simons 1996). In contrast, whisker trimming, a mild form of manipulation, leads to expansion of receptive fields and increased excitability of the barrel cells corresponding to the spared whiskers (Keller and Carlson 1999, Knott, Quairiaux et al. 2002). These manipulations also impose diverse impacts on the dendrite morphology in neurons occupying multiple cortical layers. Among many cell types in the neocortex, pyramidal and spiny stellate cells are the main excitatory glutamatergic types, while the basket, chandelier, double bouquet, and Martinotti cells are inhibitory GABAergic neurons. Consistent with their different functional roles, excitatory and inhibitory neurons show distinct responses to alterations in sensory experience. For instance, bilateral whisker trimming through the first postnatal month leads to dendrite expansion in layer 6 non-pyramidal

neurons. The nearby pyramidal cells, however, showed increases in soma size and basilar dendritic arborization but a reduction in the apical dendrites (Chen, Steger et al. 2009, Chen, Tam et al. 2012). A similar redistribution of dendritic arbors was observed in layer 5 pyramidal neurons following one week of whisker trimming. On the other hand, GABAergic neurons in layer 5 only exhibit subtle changes in their dendritic processes (Zhang, Gao et al. 2013).

Given the variety of experimental techniques and the heterogeneity of cortical neurons, it is not surprising to observe a large range of sensory deprivation-induced phenotypes in the developing barrel cortex (Reviewed by (Chen and Brumberg 2021)). Importantly, the extent of the impact is significantly influenced by the timing and duration of experimental manipulation. In general, early onset of sensory deprivation, before postnatal day 4 (PND4), when the barrel pattern emerges, can cause changes in dendrite growth and patterning. By contrast, sensory deprivation applied in late juvenile developmental stages or adulthood does not lead to measurable changes in dendrite morphology. Instead, the main phenotypes are changes in the number, density, and dynamics of spines (Tian and Copenhagen 2003).

Although structural plasticity in dendritic spines has long been observed, fluorescent labeling techniques and multi-photon microscopy developed in recent years allow researchers to perform *in vivo* time-lapse imaging in living animals. These longitudinal studies helped reveal the dynamic features of spines and demonstrate how sensory experience and various learning paradigms impact circuit connectivity through changes in spine morphology and density. Similar to the case in dendrites, structural plasticity in spines also varies a great deal depending on the cell type, the timing and technique of the experimental manipulations and the specific parameters being evaluated. In general, sensory manipulation by whisker trimming affects spine motility and turnover during the early postnatal developmental period. In rats, trimming all whiskers unilaterally decreases both spine and filopodium motility in the contralateral barrel cortex during P11–13, without affecting spine size or density (Lendvai, Stern et al. 2000). In adolescent mice (1–3 months), sensory deprivation induced by plucking all whiskers on one side reduces spine elimination and delays spine pruning in the contralateral barrel cortex (Zuo, Yang et al. 2005). This diminishes as animals mature but persists into adulthood. Restoring sensory experience after the adolescent period accelerates spine elimination (Zuo, Yang et al. 2005). Interestingly, sensory stimulation induced by either an enriched environment or unilateral chessboard plucking increases spine turnover in this same brain region. In adult mice (>4 months), sensory manipulation continues to modify spine dynamics, but to a milder

degree (Zuo, Yang et al. 2005). Together, studies of spine dynamics in the somatosensory cortex suggest that experience plays an important role in the net loss of synapses over an animal's lifetime, particularly during adolescence (Trachtenberg, Chen et al. 2002, Holtmaat, Wilbrecht et al. 2006, Yang, Pan et al. 2009).

Visual cortex: The mammalian visual cortex is another system highly amenable for investigating the role of sensory experience in regulating circuit development and plasticity. The visual activity can be manipulated relatively easily by raising animals in the dark, or by depriving visual input from one (monocular deprivation, MD) or both (binocular deprivation, BD) eyes. In addition, neurons in primary visual cortex (V1) and somatosensory cortex (S1) share common features in their dendritic organization (Staiger, Flagmeyer et al. 2004). Many of the principles regulating dendrite and spine plasticity in the somatosensory cortex also apply to the visual cortex (Fox and Wong 2005).

Because most mammals are born with their eyes closed, the initial activity-dependent wiring events are driven by spontaneous retinal activity (Del Rio and Feller 2006). Previous studies have shown that eye-specific segregation in the lateral geniculate nucleus (LGN) is regulated by spontaneous retinal waves, which are bursts of action potentials that spread across the retinal ganglion cell (RGC) layer before eye opening (Penn, Riquelme et al. 1998, Huberman, Stellwagen et al. 2002, Stellwagen and Shatz 2002, Feller 2009). After eye opening, however, patterned visual input is thought to be the main driver of maturation of the visual cortical circuit (Smith and Trachtenberg 2007). One example is the experience-dependent dendrite remodeling observed in the RGCs. RGCs reorganize their structure during development to restrict dendritic branching to either light-ON or light-OFF only lamina. This pruning event does not occur in dark-reared animals (Tian and Copenhagen 2003). In addition, dark rearing in mice or rats leads to a reduced number of spines in pyramidal cells of the V1 and a shifted distribution of dendritic branching of layer 4 stellate cells, potentially due to the loss of input within specific layers (Borges and Berry 1978, Majewska and Sur 2003, Tropea, Majewska et al. 2010).

In the 1960s, Hubel and Wiesel performed a series of experiments to demonstrate the strong impact of monocular deprivation on the establishment of ocular dominance columns (Hubel and Wiesel 1963, Wiesel and Hubel 1963). Monocular lid suture in visually inexperienced binocular mammals led to redistribution of afferents from the LGN in layer 4 and changed dendritic branching in spiny stellate cells (Kossel, Lowel et al. 1995). Physiologically, unbalanced input from the two eyes leads to bi-directional changes in visual

cortex circuity (Smith, Heynen et al. 2009), rapid weakening of responses evoked through the deprived eye, followed by delayed strengthening of responses through the open eye. These seminal studies established ocular dominance plasticity (ODP) as a classic model for understanding how experience shapes circuit architecture and function during development (Wong and Ghosh 2002, Tropea, Van Wart et al. 2009, Sun, Espinosa et al. 2019).

Importantly, a series of experiments studying ODP have contributed to a molecular understanding of the mechanism controlling the opening and closing of the critical period. While cortical circuits have a distinct window of sensitivity towards activity manipulations, the sensitivity to MD is restricted to a critical period, which begins about 1 week after the eye opens (PND13) and peaks 1 month after birth in mice (Gordon and Stryker 1996). Studies by Tako Hensch and colleagues have shown that the onset of ODP can be delayed by preventing the maturation of GABA-mediated transmission through genetic deletion of Gad65, a gene encoding a GABA-synthetic enzyme, or by dark-rearing from birth (Hensch, Fagiolini et al. 1998, Morales, Choi et al. 2002, Maffei, Nelson et al. 2004). Conversely, the critical period can be advanced by enhancing GABA transmission using Benzodiazepines right after eye-opening, or by promoting interneuron maturation through Brain-Derived Neurotrophic Factor (BDNF) overexpression (Hanover, Huang et al. 1999, Huang, Kirkwood et al. 1999, Iwai, Fagiolini et al. 2003, Fagiolini, Fritschy et al. 2004).

Although V1 of rodents does not contain ocular dominance columns, a discrete binocular segment has been used extensively to characterize structural and functional rearrangement of cortical circuity in response to alteration in experience. One notable study was designed to capture synaptic restructuring following MD and tested whether the structural impact of the MD experience would outlast the functional changes. Using long-term live imaging studies, the dynamics of dendritic filopodia and spines were systematically evaluated in the binocular region (Hofer, Mrsic-Flogel et al. 2009). These results revealed that sensory experience leaves a long-lasting structural trace that facilitates the functional adaptations at a later time, suggesting a mechanism for storing prior experiences in cortical circuits.

2.1.2 Xenopus retinotectal system

Another classic system that offered many insights into the mechanisms of experience-dependent plasticity is the optic tectum of *Xenopus laevis* tadpoles, established by Hollis Cline and colleagues in the 1990s (Sin, Haas et al. 2002, Ruthazer, Akerman et al. 2003, Dong, Lee et al. 2009, Xu,

Khakhalin et al. 2011, Hiramoto and Cline 2014). This system allows genetically encoded morphology and synapse markers to be introduced into the specific region of developing tadpoles by electroporation, generating single-labeled tectal neurons that can be monitored throughout development by *in vivo* time-lapse imaging and electrophysiology. In a particularly informative study, Sin et al observed enhanced visual activity promotes dendritic arbor growth, which requires NMDA-mediated glutamatergic transmission (Sin, Haas et al. 2002).

A series of studies using this powerful system have further demonstrated how visual experience regulates dendritic arbor development through effects on both excitatory glutamatergic and inhibitory GABAergic synaptic transmission. Visual stimulation promotes maturation of the excitatory synapse by increasing the ratio of AMPA/NMDA type of glutamate receptors, which leads to the elaboration of dendritic arbors. Expressing the C-terminal peptides of GluA (GluA CTP) impairs AMPA Receptor (AMPAR) trafficking, reduces the number of excitatory synapses and decreases complexity of dendritic arbors (Haas, Li et al. 2006). Conversely, expressing the intracellular fragment of the GABA-Ag2 subunit reduces $GABA_AR$ presence at synapses, decreases inhibitory synaptic inputs, while also causing reduced complexity of dendritic arbors (Shen, Da Silva et al. 2009). These genetic manipulations prevent visual activity-dependent enhancement of dendrite arbor growth, supporting the critical function of synapse maturation in driving dendrite arbor development. Importantly, these observations are consistent with predications of the 'synaptotrophic hypothesis', originally proposed by Vaughn based on insight from electron microscopy studies, suggesting that synapse formation promotes the further elaboration of neuronal structures and ultimately circuit formation (Vaughn, Barber et al. 1988, Vaughn 1989).

Studies in *Xenopus* optic tectal neurons have placed synaptic integration of postsynaptic receptors, namely glutamatergic AMPA and NMDA receptors, as the major event regulating synapse maturation and dendrite elaboration. Several other factors involved in this process have since been identified through studies in the optic tectum, including neurexin-neuroligin cell adhesion complexes, glycosylphosphatidylinositol (GPI)-linked protein CPG15 and transcription factor MEF2 (Chen, Tari et al. 2010). Furthermore, experiments have shown that activity-dependent mechanisms can also restrict dendritic arbor growth. For example, elevated calcium and calmodulin-dependent kinase II (CaMKII) activity increases glutamatergic synaptic strength while stabilizing dendritic arbor structure by reducing rates of branch additions and retractions (Wu, Malinow et al. 1996, Wu and Cline 1998) . CaMKII is known to act downstream of synaptic

activity-dependent increases in calcium to regulate synaptic strength and cytoskeletal dynamics, consistent with this observation (Lisman, Schulman et al. 2002, McVicker, Millette et al. 2015). More recently, Protein kinase Mζ (PKMz), an endogenous constitutively active kinase, was identified as a stabilizing factor for dendritic filopodia and restricts dendritic arbor growth (Liu, Tari et al. 2009).

While most of studies in *Xenopus* optic tectum have been performed on excitatory neurons, a recent study also evaluated experience-dependent morphological and physiological changes in inhibitory neurons. These results indicated that developing inhibitory neurons in the tectum, without applying distinguishable molecular markers, can be clustered into two groups that respond to visual stimulations in opposite ways (He, Shen et al. 2016). Half of them showed similar responses as excitatory neurons; upon visual stimulation, their dendritic arbor size and calcium response are both increased. The other half had reduced a dendrite size and calcium response. This study raised the interesting possibility that the inhibitory interneurons act as stabilizers in experience-induced circuit changes and contribute to maintaining Excitation/Inhibition balance during circuit development.

2.1.3 Developing motor and visual circuit in *Drosophila* exhibit homeostatic dendritic plasticity

Many of the initial molecular insights on neural plasticity have come from studies using simple invertebrate systems, such as *Aplysia* and *Drosophila*, which were excellent models for analyzing fundamental aspects of behavior and learning. The work by Eric Kandel and others have illustrated critical functions of members of the cAMP signaling pathway in activity-dependent synaptic potentiation, which were later demonstrated to be a conserved mechanism in many other animal models and were further linked to behavioral modifications such as learning and memory storage (Silva, Kogan et al. 1998). In recent years, powerful genetic systems have allowed *Drosophila* and *C. elegans* models to reveal important principles governing neural development and circuit organization (Dong, Shen et al. 2015). Notably, high-resolution *in vivo* imaging techniques, combined with large-scale forward genetic screens, have facilitated the identification of genetic mutants with defects in various aspects of dendrite development (Grueber and Jan 2004, Jan and Jan 2010, Hong, Park et al. 2014). Although coming on the scene relatively late, fly models have also been informative for questions related to dendrite plasticity and highlighted activity-dependent modifications as a common theme in neural development.

In the motor circuit of the *Drosophila* larval ventral nerve cord (VNC), dendrite morphology in the aCC and RP2 motoneurons are highly sensitive to synaptic activity. Here, homeostatic adjustments in dendrite fields are observed upon changes in presynaptic activity. The embryonic aCC motoneuron dendrite expands or shrinks following inhibited or enhanced neurotransmitter activity, respectively (Tripodi, Evers et al. 2008). Reducing intrinsic excitability during development, either through a temperature-sensitive mutant allele that reduces presynaptic acetylcholine release, or by overexpressing a transgene encoding the potassium channel Kir2.1 in the postsynaptic neurons, both led to an enlarged dendrite arbor size (Hartwig, Worrell et al. 2008). These studies were among the first to describe the activity-dependent homeostatic regulation of dendritic structures, which were later found in other *Drosophila* and mammalian systems (Yuan, Xiang et al. 2011, Kaneko and Stryker 2017), suggesting that structural homeostasis is a shared component in neural plasticity across animal species.

Taking advantage of the genetic tools available to the *Drosophila* system, a series of studies explored the cellular and molecular mechanisms governing homeostatic plasticity in the larval motor circuit. Specifically, genetic studies have identified reactive oxygen species (ROS) signaling pathway as a major regulator of activity-dependent plasticity. The Parkinson's disease-linked protein DJ-1β acts as a redox sensor in neurons, modulates the PTEN-PI3Kinase pathway and regulates structural development of dendrites (Oswald, Brooks et al. 2018). Furthermore, by evaluating the activity-induced changes in motor neuron dendrites, a recent study identified a critical period for the larval motor circuit, which is within 8 hours of larval hatching and strongly modulated by astrocyte-derived cell adhesion signaling and microtubule dynamics (Ackerman, Perez-Catalan et al. 2021) (also see discussion in Section 3).

The larval visual system of *Drosophila* has also been developed into a successful model for understanding the molecular underpinnings of experience-dependent dendrite plasticity. *Drosophila* larvae sense light through Bolwig's Organ (BO), a cluster of photoreceptors that send axonal projections into the brain and make cholinergic synaptic contacts with dendritic arbors of ventral lateral neurons (LNvs) (Malpel, Klarsfeld et al. 2002, Sprecher, Cardona et al. 2011). Importantly, synaptic activity induced by visual experience produces striking changes in the length of LNv dendrites: the amount of light exposure received by the animal is inversely correlated with the total dendritic length of LNvs (Yuan, Xiang et al. 2011). Through neuron specific manipulations, Yuan et al. demonstrated that compensatory structural changes in dendritic arbors could be driven by sensory experience, alterations

in presynaptic neurotransmission or activity, or changes in the intrinsic excitability of postsynaptic neurons (Yuan, Xiang et al. 2011). This unique model allowed systematic *in vivo* analyses to identify molecules and pathways that regulate dendritic plasticity. The follow-up live imaging and genetic studies revealed dynamic dendritic filopodia as the cellular substrate targeted by activity in regulating synaptogenesis and subsequent dendrite expansion. Additionally, RNA sequencing (RNA-seq) guided genetic screens further identified neuron-glia lipid trafficking and nicotinic acetylcholine receptor (nAchR) signaling as two key pathways regulating activity-induced dendritic plasticity in the larval visual circuit (Yin, Gibbs et al. 2018, Rosenthal, Yin et al. 2021).

Beyond the motor and visual systems, which clearly show an experience-dependent structural plasticity during larval development, there are massive neural remodeling events associated with metamorphosis that affect many other cell types in the fly nervous system. In particular, the dendrite remodeling of *Drosophila* multi-dendritic peripheral nervous system (PNS) neurons have been used as a model to understand the molecular cascade responsible for controlling the dendrite degeneration and regrowth during the pupal stage (Singh, VijayRaghavan et al. 2010, Kanamori, Kanai et al. 2013).

In addition to *Drosophila*, neurons of the invertebrate model *C. elegans* also display experience-dependent structural plasticity. For example, calcium-dependent activity in dendrites of the chemosensory URX neurons, which respond to environmental oxygen levels, drives the expansion of dendrite tips during development (Cohn, Cebul et al. 2020). In the motor circuit, Tetrodotoxin-induced dampening of cholinergic synaptic activity in larval animals leads to a reduction of GABAergic neurotransmission at the NMJ and an increase in Postsynaptic Density (PSD) size on the muscle (Barbagallo, Philbrook et al. 2017). Another instance occurs during the peculiar dendrite-axon polarity reversal of the DD motoneuron, known as DD remodeling. Here, ACR-12-positive nAchR clusters emerge on what is originally the axonal neurite around the L1-to-L2 developmental transition. Although manipulation of synaptic activity does not physically impact the resulting dendrite, heightened or reduced circuit activity accelerates and delays, respectively, the timing of this remodeling (Jin and Qi 2018).

Outlook: Despite the complex phenotypes observed in these diverse model systems at different developmental stages, several common components integral for dendrite plasticity are shared across the systems, such as the determinant role of critical period, the intimate relationship with synaptogenesis, and the vital functions of neurotransmitter receptor signaling. Comparative studies combining the power of connectomics and

transcriptomics, as well as bioinformatics analysis, will help us better understand this critical process and how it evolves within different animal species to better serve their physiological functions.

2.2 Molecular Regulation of Dendritic Structural Plasticity

In the past few decades, a large amount of research has been dedicated to searching for cellular and molecular substrates underlying experience-dependent changes in the brain, with the goal of finding the neural basis of human cognition. As a result, several well-conserved molecular pathways associated with activity-dependent structural plasticity in the postsynaptic compartment and dendrites have been identified (Koleske 2013, Nakahata and Yasuda 2018). Moreover, recent advances in two powerful technical approaches, transcriptome analysis and genetic lineage studies, have provided many candidate genes related to neurodevelopmental disorders and neuropsychiatric diseases. Intriguingly, a large proportion of the risk factors revealed by these studies are also key components of the pathways known to be involved in synapse development and plasticity (Forrest, Parnell et al. 2018). Detailed molecular studies using animal models will greatly facilitate our understanding of the network controlling the timing and extent of neurons or circuits responses to experience or activity. They will also be indispensable for identifying target molecules to be tested in therapeutic interventions.

While there are stereotypical transcriptional programs and signaling pathways associated with dendrite development and morphogenesis (Whitford, Dijkhuizen et al. 2002, Lefebvre, Sanes et al. 2015), sensory experience and activity often elicit cell- and context-specific responses, which are molecularly more complex and less understood. One exception is the established role of calcium-dependent signaling. Most of the activity-induced signaling cascades are triggered by changes in intracellular calcium concentration, either through calcium influx generated by calcium-permeable neurotransmitter receptors and voltage-gated calcium channels (VGCCs) at the postsynaptic cell surface, or the Ryanodine and IP_3 receptors on the endoplasmic reticulum membrane (Lohmann and Bonhoeffer 2008, Kanamori, Kanai et al. 2013, Lee, Soares et al. 2016).

Regardless of the source, $Ca2^{+}$ ions entering the cytoplasm can bind to the protein Calmodulin (CaM). The Ca^{2+}/CaM complex then activates the serine/threonine kinase CaMKII, a hub for multiple signaling events induced by neural activity (Lucic, Greif et al. 2008, Lee, Escobedo-Lozoya et al. 2009). Following the initial CaMKII activation, there is a second phase of inter-subunit autophosphorylation on T286/287 of a or b subunits that leads

to persistent activation of CaMKII, which continues even after the dissociation of the Ca2+/CaM complex. This extended response is thought to prolong CaMKII's activity in order to exert its long-lasting effects on synaptic modifications, both functionally and structurally (Chang, Nakahata et al. 2019). This notion is supported by the observation that continuous NMDAR-dependent increases in intracellular calcium enhance CaMKII activity without leading to additional CaM binding to CaMKII. Moreover, despite peak CaMKIIa activation at 0.5 seconds, an extended decay period renders CaMKII partially active for up to 1 minute (Chang, Parra-Bueno et al. 2017). Besides the conformational change, activated CaMKII is translocated from the dendrite shaft to stimulated spines, a process that requires microtubules and actin networks, and is anchored to PSD components such as NMDAR subunits (Lemieux, Labrecque et al. 2012, Lu, MacGillavry et al. 2014, Rangamani, Levy et al. 2016). The terminal step in the CaMKII cycle is its eventual silencing by proteins phosphatases like PP1 (Rangamani, Levy et al. 2016). Additionally, another autophosphorylation event at an alternative site, T305/T306, reduces the enzyme's kinase activity (Lucic, Greif et al. 2008). Together, these distinct mechanisms collaboratively support the versatile and critical role of CaMKII in Ca^{2+} mediated synaptic plasticity.

2.2.1 Rho GTPases and their regulators

One of the most important regulatory mechanisms for dendrite and spine development involves a group of proteins called the Rho GTPases, which are members of the Ras GTPase superfamily of GTP-binding proteins (Govek, Newey et al. 2005, Stankiewicz and Linseman 2014). Through GTP binding and subsequent hydrolysis, Rho GTPases undergo transitions between an active and inactive form, and are key components involved in experience-dependent structural plasticity. They impose their influence through actin cytoskeleton modulation, which results in changes in dynamics and morphology of dendritic arbors and spines. Early investigations were performed in *Xenopus* optic tectal neurons, where increased activity of Rac and Cdc42, two well-studied Rho GTPases, is required for visual stimulation-induced dendrite branch dynamics and arbor growth (Sin, Haas et al. 2002). Conversely, RhoA activation was found to inhibit dendrite branch extension (Li, Van Aelst et al. 2000, Li, Aizenman et al. 2002, Sin, Haas et al. 2002)

Because RhoA and Cdc42 are activated by CaMKII, these small GTPases are capable of relaying transient CaMKII activation to synapse-specific, long-lasting signaling required for structural plasticity. This critical

role is demonstrated by a set of sophisticated imaging experiments. The spatial activation pattern of RhoA and Cdc42 were probed in single dendritic spines using 2-photon fluorescence lifetime imaging microscopy (2pFLIM) and glutamate uncaging in cultured pyramidal neurons (Murakoshi, Wang et al. 2011). Both RhoA and Cdc42 were rapidly activated in the stimulated spine, followed by a dynamic and persistent phase of activity that lasted more than 30 min. Activated RhoA, which was necessary for initiating dendrite spine growth, diffuses and leaves the spine, whereas activated Cdc42 remains in the spine and maintains its morphology. In addition to these examples, there are many additional reports on Rho GTPases' contributions to dendrite plasticity, as well as those of the Rab protein family, which was found to facilitate activity-dependent AMPA receptor trafficking to the spine (Gerges, Backos et al. 2004, Hayashi-Takagi, Yagishita et al. 2015).

Rho GTPase activity itself is controlled by Rho Guanine nucleotide exchange factor (RhoGEFs) and Rho GTPase activating protein (RhoGAPs), molecules that toggle the GTPase between active and inactive states, respectively. One representative example is Kalirin, a RhoGEF involved in dendrite morphogenesis in early development. The *Kalirin* knockout mice display reduced hippocampal and cortical spine density and simplified dendritic arbors (Ma, Kiraly et al. 2008, Xie, Cahill et al. 2010). Similar to the Rho GTPases, Kalirin activation is induced by CaMKII-dependent phosphorylation following NMDA receptor activation. Activated Kalirin promotes enlargement of pre-existing dendrite spines and synaptic recruitment of AMPA receptors (Xie, Srivastava et al. 2007, Herring and Nicoll 2016). Counteracting the RhoGEFs are the RhoGAPs, such as OPHN1, which has been linked to metabotropic glutamate receptor (mGluR)-induced synaptic AMPA receptor removal observed during hippocampal Long-term Depression (LTD) (Nadif Kasri, Nakano-Kobayashi et al. 2011). However, OPHN1 is also implicated in synaptic strengthening through increased AMPA receptor density at NMDA receptor-stimulated dendrite spines (Nadif Kasri, Nakano-Kobayashi et al. 2009). These findings strongly suggest a context-dependent basis for RhoGAP and RhoGEF functionality.

Ultimately, the various Rho GTPases act on their own downstream targets, such as WASP and WAVE complex (Costa, Dines et al. 2020, Duman, Blanco et al. 2021). Rac1 and Cdc42 converge on these proteins, which in turn regulate the actin-branching protein complex Arp2/3 (Soderling, Guire et al. 2007, Watson, Owen et al. 2017). Additionally, Rac1 activation also induces a parallel kinase cascade that results in suppression of the depolymerizing factor Cofilin and thus stabilization of spines (Duman, Blanco et al. 2021).

2.2.2 Local translation

In contrast to general protein synthesis machinery localized in the cell body, a plethora of transcripts coding for synapse-related molecules are deliberately trafficked to synaptic sites so that their translation may be coupled to synaptic transmission (Ju, Morishita et al. 2004, Smith, Starck et al. 2005, Cajigas, Tushev et al. 2012). Other translational components, such as ribosomes and mRNA-binding proteins, have also been found in both dendritic and axonal compartments (Cajigas, Tushev et al. 2012, Younts, Monday et al. 2016, Scarnati, Kataria et al. 2018, Hafner, Donlin-Asp et al. 2019, Biever, Glock et al. 2020). These mRNAs and ribosomes support local translation near synapses and are required for long-lasting forms of synaptic plasticity that are elicited by glutamate binding to NMDA receptors or group I mGluRs. For instance, in the Ventral Tegmental Area (VTA) of juvenile mice, mGluR-induced LTD depends on rapid production of nascent NR2A subunit polypeptides, which shifts the iGluR composition on dopaminergic neuron dendrites in favor of lower ion conductance (Mameli, Balland et al. 2007). A similar finding was made in cultured hippocampal neurons, where locally transcribed mRNAs for CaMKII, β-actin and PSD-95 were examined. The study showed not only did both Long-term Potentiation (LTP) and mGluR-dependent LTD require local translation, but synaptic activity also induces the accumulation of mRNA for these transcripts near spines, indicating that activity-dependent RNA translocation is an additional contributing factor for regulating local translation (Miller, Yasuda et al. 2002, Donlin-Asp, Polisseni et al. 2021). Further investigations have also revealed how the translation instigated by synaptic activity is coordinated. In dentate gyrus cells of the hippocampus, for example, generation of LTP relies on the local translation of the NR2A subunit, which requires the function of poly(A) polymerase Gld2, the phosphorylation of RNA-binding protein CPEB, as well as the removal and downregulation of the deadenylase PARN and translation inhibitor Ngd (Udagawa, Swanger et al. 2012). Additionally, the RNA Induced Silencing Complex (RISC) has a significant contribution in regulating local translation. For example, in cultured hippocampal neurons, NMDA receptor stimulation induces the cooperative activity of phosphorylated Ago2 and miR-134, which represses translation of the cytoskeletal regulator LIMK1 and leads to a reduction in the size of dendritic spines (Rajgor, Sanderson et al. 2018).

Recent live imaging studies further demonstrate how activity-dependent local translation occurs in a stepwise fashion over an extended period. In cultured hippocampal neurons, postsynaptic stimulation through glutamate

uncaging causes the recruitment, and long-lasting localization up to several hours, of β-actin mRNA from surrounding regions of the dendrite shaft to the base of acutely expanding dendrite spines (Yoon, Wu et al. 2016), followed by the translation of these mRNA molecules and the deposition of nascent β-actin polypeptides along the periphery of spine heads. Another advancement made possible by live imaging is single-molecule tracking of individual mRNA transcripts and newly translated peptides. Several studies have used fluorescently labeled RNA and proteins to investigate the differences between cytoplasmic vs. ER-localized translation, burst vs. sporadic translation, and monosome- vs. polysome-based translation (Tatavarty, Ifrim et al. 2012, Ifrim, Williams et al. 2015, Wu, Eliscovich et al. 2016). Notably, a recent study revealed that, basal levels of burst-type translation, for transcripts including PSD-95, ARC and FMRP, is enhanced in *Fmr1* knockout animals, a clinically important finding relevant to Fragile X Syndrome discussed in Section 4 (Richter and Klann 2009).

2.2.3 Activity-dependent transcriptional activation

Activity-dependent structural plasticity requires activation of transcriptional programs that translate synaptic activity to long-lasting morphological and physiological changes. Although this process can be studied in the context of individual cell types and isolated activity regulated genes (ARGs), in more recent years the blossoming of transcriptomic approaches have provided a route for a global understanding of how hundreds or thousands of genes are coordinately altered by neuronal activity in a cell-type specific fashion (West and Greenberg 2011, Yap and Greenberg 2018). From technologies like microarrays, tissue-specific RNAseq and single-cell RNAseq, we have learned that excitatory and inhibitory synapses share common upstream immediate early gene(s), such as a Fos and Egr1, but differ in the downstream factors, including members of the MAPK signaling pathway (Spiegel, Mardinly et al. 2014, Lacar, Linker et al. 2016). These type of analyses have also been applied to the classical visual deprivation model and revealed that ocular dominance relies on the regulation of temporally distinct transcriptional programs, which are perturbed in a dark-rearing condition (Majdan and Shatz 2006).

One of the most studied transcription factors is cAMP Response Element Binding protein (CREB), which is involved in various intracellular signaling events, coordinating changes in neurons and other cell types. Studies have identified a wide variety of extracellular stimuli that induce CREB phosphorylation and activation. In neurons, the part is often played by several CaMK

members, which are potentiated upon cytoplasmic calcium influx generated by neuronal activity (Richter and Klann 2009). Besides CaMKII, which we discussed earlier, the expression of a constitutively-active form of CaMKIV in the developing rat brain elevates hippocampal dendrite spine density, accompanied by enhanced LTP and NMDA receptor-dependent synaptic current, as well as enhanced dendrite growth in cortical neurons (Redmond, Kashani et al. 2002, Marie, Morishita et al. 2005).

While CREB is a transcription factor, its function is partially controlled by its interactions with additional factors such as CREST, CBP and the neuronal-specific chromatin remodeling complex nBAF. Collectively, they modulate calcium-dependent dendrite growth (Aizawa, Hu et al. 2004, Wu, Lessard et al. 2007). Apart from this protein complex, CREB activity can also synergize with that of MKK1 to regulate neuronal morphology in rat Layer 3 visual cortex (Suzuki, Zhou et al. 2007). In addition to integrating diverse inputs, CREB-mediated transcription induces expression of a varied group of genes, including the secreted TrkB ligand BDNF and miRNAs, such as miRNA132 (Abdolahi, Zare-Chahoki et al. 2022). By negatively regulating its target p250GAP, miRNA132 promotes the formation of GluR1-containing spines (Shieh, Hu et al. 1998, Impey, Davare et al. 2010) Finally, although the CaMK-CREB signaling axis represents a major conduit for enacting activity-dependent transcription, many other pathways contribute to the process. For instance, MEF2, a transcription factor, has been shown to play a critical role in activity-dependent structural and functional plasticity in both rat and mouse models (Shalizi, Gaudilliere et al. 2006, Tu, Akhtar et al. 2017). Notably, genetic mutations in *mef2* gene have been linked to human neurological disorders in recent studies (Shalizi, Gaudilliere et al. 2006, Pfeiffer, Zang et al. 2010, Tsai, Wilkerson et al. 2017, Tu, Akhtar et al. 2017).

The second phase of long-term, activity-dependent modifications involves the transcriptional upregulation of immediate early genes (IEG). IEGs are rapidly transcribed upon neuronal stimulation, then act as transcription factors to control the expression of a group of effector molecules responsible for morphological adjustments on dendrites and postsynaptic sites (Lefebvre, Sanes et al. 2015). One example of a well-characterized IEG is Arc, or Arg3.1. Several studies suggest a homeostatic function for Arc in the rodent forebrain. Overexpression of Arc, simulating activity-induced Arc upregulation, leads to reduced AMPAR-dependent currents and decreases postsynaptic presence of the GluR2 and GluR3 subunits (Rial Verde, Lee-Osbourne et al. 2006). Reducing Arc level through RNA interference or a mutant form of Arc has the opposite effect (Rial Verde, Lee-Osbourne et al. 2006). The function of Arc is further supported by other mutant studies. In

Arc mutant mice, although vision is seemingly normal and baseline synaptic activity is intact, the visual system no longer exhibits experience-dependent synaptic depression (Gao, Sossa et al. 2010, McCurry, Shepherd et al. 2010). Other classical IEGs include c-Fos, whose potentiated expression has often been used as an indicator for neuronal activation, as well as Nr4a1, a critical transcriptional regulator for actin cytoskeletal rearrangements and spine formation (Murphy, Worley et al. 1991, Qiu and Ghosh 2008).

IEGs are also an important transducer of activity-dependent changes at inhibitory synapses. The transcription factor Npas4, is thought to be exclusively expressed in neurons, while c-fos and Nr4a members which also mediate signaling in the immune and muscular system. Nspas4 has been demonstrated to control GABAergic synapse number in both cell culture systems and mouse hippocampal neurons (Maxwell and Muscat 2006, Lin, Bloodgood et al. 2008). By regulating a unique set of inhibitory-specific, late-acting target genes, Npas4 adjusts the density of dendritic- vs somatic inhibitory synapses on CA1 pyramidal neurons (Lin, Bloodgood et al. 2008, Bloodgood, Sharma et al. 2013, Spiegel, Mardinly et al. 2014). In addition, one of the downstream targets of Npas4 is BDNF, which is a critical factor for specifying the number of synapses at specific locations (Lin, Bloodgood et al. 2008, Bloodgood, Sharma et al. 2013, Spiegel, Mardinly et al. 2014). Thus, circuit-wide activity will be used to adjust both excitatory and inhibitory connections, albeit through potentially distinct pathways.

2.2.4 Molecular events identified in invertebrate studies

As mentioned in Section 1, studies on activity-dependent dendrite plasticity in the invertebrate system are relatively new compared to vertebrate studies. However, there are well-established examples of activity-induced transcriptional programs that regulate structural plasticity in the invertebrate CNS. In the larval and pupal *Drosophila* ventral nerve cord, nAchR-mediated activation of MN5 motoneuron transiently induces the expression of AP-1, the fly ortholog of c-Fos, to control dendrite arborization. Additionally, in the Mushroom Bodies (MB) of both flies and the moth *Bombyx mori*, the transcription factor Hr38, a homolog of mammalian Nr4a proteins, is upregulated by neuronal activity, sensory experience, and ethanol exposure (Fujita, Nagata et al. 2013, Adhikari, Orozco et al. 2019), although the impact of Hr38 transcription in the developing brain has yet to be characterized.

The high-throughput approaches, such as RNA sequencing, have also benefitted the study of invertebrate models. In *Drosophila*, activity-dependent changes to transcriptomic profiles have been investigated at both

the CNS-wide and tissue-specific levels, the latter including dopaminergic and circadian-related cell populations (Chen, Rahman et al. 2016). The findings revealed several key differences between mammalian and fly ARGs. Specifically, the *Drosophila* ARGs were significantly longer than their mammalian counterparts and functionally less likely to be classified as transcription factors. In a developmental study looking at how chronic upregulation of synaptic activity, achieved by rearing in constant light, alters the transcriptome in LNvs of the larval visual circuit, the resulting differentially expressed (DE) genes are enriched in functional categories related to transcriptional regulation, morphogenesis, and lipid metabolism/trafficking. Two of these, the lipophorin receptors LpR1 and LpR2, are significantly upregulated by activity and are potentially involved in the enhanced lipid shuttling induced by homeostatic responses towards chronic elevation of input activity (Yin, Gibbs et al. 2018).

Outlook: Given the rapidly evolving technologies, the logical next step for molecular studies related to dendrite plasticity is to generate cell-type specific multi-omics datasets that provide a comprehensive view of molecular pathways involved in synapse development and plasticity. These newly developed methods will be indispensable for addressing some of the current challenges and questions, including how neurons transform early phase information like synaptic activity and common IEGs into highly divergent late-phase responses, which are known to largely cell-type specific (Heinz and Bloodgood 2020). Several recent studies have already shown the potential of these approaches. For example, by analyzing single cell transcriptomes in the mouse brain during early postnatal development, Stroud and colleagues reveal that AP1-type transcription factors coordinate activation of a large array of cell-specific enhancer elements in an activity-dependent fashion (Stroud, Yang et al. 2020). Rodent barrel cortex synapses following whisker trimming, a classical paradigm discussed in Section 1, have been examined by the mass-spectrometry (MS)-based proteomics analysis. Here, reduced sensory stimulation has little impact on abundant postsynaptic proteins, such as PSD-95 and Gephyrin, but causes changes mostly to molecules implicated in dendrite spine structural maturation and synaptic strength, including glutamate receptors and proteins involved in proteasomal-dependent protein degradation (Butko, Savas et al. 2013). A related study used a specialized version of MS proteomics called BONCAT to specifically label the nascent proteome following neuronal stimulation. After pharmacologically-induced homeostatic scaling in cultured hippocampal neurons, the nascent synaptic proteome profile at 24hr post-manipulation differs from that at 2hr post-manipulation, although the functional classes broadly overlap (Schanzenbacher, Langer et al. 2018).

Lastly, in the *Xenopus* optic tectum system, visual experience produced strong changes in the RNA processing- and chromatin regulation-related proteins, a subset of which were functionally validated for their impact on cellular and behavioral plasticity (Liu, McClatchy et al. 2018).

2.3 Neuron-glia Interaction Regulates Dendritic Structural Plasticity

The heterogeneity and complexity of dendritic structural plasticity is largely determined by the intrinsic factors associated with different cell types and developmental stages, which we discussed in the previous section. At the same time, how a neuron or circuit responds to sensory experience or alterations in neural activity is strongly influenced by its cellular environment. Apart from synaptic partners, elements like the extracellular matrix, neighboring glia cells, as well as long-range neuromodulatory and network inputs, may also modify neurons' behaviors. In addition, recent studies indicate that structural changes induced by sensory deprivation are not limited to neurons, as the effect can be observed in glia and extracellular components as well (McRae, Rocco et al. 2007, Barrera, Chu et al. 2013, Chu, Abraham et al. 2018). These findings are consistent with the notion that sensory experience influences multiple cell types in the brain to elicit a coordinated response. Inspired by this concept and enabled by many technical advances, recent studies have started to reveal the significance of non-neuronal contributions to experience-dependent plasticity.

Glia have long been recognized as a critical component of the nervous system for their roles in providing neurons with metabolic support, neurotransmitter precursors and ion buffering. Studies over the past three decades have further revealed glia as active partners for neurons in synaptic transmission and essential modulators of synaptic structure and function in both invertebrate and vertebrate model systems (Eroglu and Barres 2010, Freeman 2015). When gliogenesis is inhibited genetically, mice show altered synaptogenesis, massive neuronal loss, and largely reduced motor output (Tsai, Li et al. 2012, Schreiner, Romanelli et al. 2015). In addition, neuron-glia crosstalk is crucial for neuroprotection and is implicated in human neurological diseases (Neniskyte and Gross 2017). Amongst the glial cells serving distinct roles in the nervous system, astrocytes and microglia have been directly linked to synapse development and plasticity, and both are considered integral parts of 'tripartite' or 'quad-partite' synapses (Perea, Navarrete et al. 2009, Schafer and Stevens 2013). As ramified cells, they extend numerous fine processes to the perisynaptic region, which monitor and influence local synaptic activity

and structure (Panatier, Vallee et al. 2011). While there are many exciting new studies supporting the function of glia in regulating physiological and behavioral output of neural circuits, we will focus our discussion in the following sections on the role of astrocytes and microglia in circuit development and structural plasticity.

2.3.1 Astrocytes regulate excitatory and inhibitory synapse formation and maturation

Astrocytes constitute almost one third of cells in human brains and affect many aspects of neural development and function in both vertebrate and invertebrate CNS [reviewed by (Freeman 2015, Allen and Eroglu 2017). Using a purified neuron astrocyte co-culture system, Ben Barres' group performed a series of pioneering studies that revealed essential roles of astrocytes in promoting synapse formation and maturation (Meyer-Franke, Kaplan et al. 1995, Pfrieger and Barres 1997). In recent years, molecular studies helped identify a number of glia-derived secreted molecules as either synaptogenic or anti-synaptogenic factors, which are responsible for fine-tuning synapse formation, pruning and maintenance (Allen and Eroglu 2017). Astrocyte-secreted thrombospondins 1–5 (TSP1–5) were the first group of factors found by the co-culture studies. Through their interactions with the neuronally expressed Gabapentin receptor α2δ-1, TSPs initiate excitatory synapse formation within *in vitro* and *in vivo* models (Christopherson, Ullian et al. 2005, Eroglu, Allen et al. 2009). Later studies identified additional glial secreted factors as regulators for various aspects of excitatory synapse formation, including cholesterol transported by apolipoprotein E (APOE), glypicans 4 and 6, chondroitin sulfate proteoglycans (CSPGs), Transforming Growth factor (TGF)-β and Tumor necrosis factor (TNF)-α (Mauch, Nagler et al. 2001, Stellwagen and Malenka 2006, Frischknecht, Heine et al. 2009, Pyka, Wetzel et al. 2011, Allen, Bennett et al. 2012, Fuentes-Medel, Ashley et al. 2012). Additionally, one of the most well-characterized synaptogenic factors secreted by astrocytes is Hevin (Kucukdereli, Allen et al. 2011, Singh, Stogsdill et al. 2016). Hevin acts as a bridging factor between presynaptic Neurexin-1α and dendritic Neuroligin-1 during the assembly of glutamatergic synapses and serves critical functions in the formation and plasticity of thalamocortical connections in the developing visual cortex. Notably, astrocytes also release SPARC (Secreted Protein Acidic and Rich in Cysteine), which acts as a specific antagonist of Hevin induced synaptogenesis. While Hevin knockout mice show a reduced number of excitatory synapses in the superior colliculus,

SPARC mutant mice exhibit enhanced synaptogenesis in the same brain region, supporting their cooperative functions in tuning the number of excitatory synapses during mammalian cortical development (Kucukdereli, Allen et al. 2011).

Early studies also showed that astrocytes influence GABAergic inhibitory synapse formation in neuron cultures (Elmariah, Oh et al. 2005). However, the specific factors involved were not identified and whether and how astrocyte regulate inhibition *in vivo* is unclear. To address these questions, a recent study employed a chemico-genetic proximity labeling technique to identify the proteome enriched at astrocyte-neuron junctions in the primary visual cortex and revealed the role of neuronal cell adhesion molecule (NRCAM) in regulating inhibitory synapse formation. The study demonstrated that the astrocytic NRCAM interacts with the NRCAM-gephyrin complex on inhibitory postsynapses. Eliminating NRCAM from astrocytes reduces the number and function of inhibitory synapses, while having only minor effects on excitatory synapses (Takano, Wallace et al. 2020).

Taken together, these recent studies demonstrate that astrocytes play an integral role in controlling excitatory and inhibitory synapse formation and maturation. Importantly, a diverse set of astrocytic factors with specialized functions in synapse development has been uncovered. It is likely that the differential timing and patterns of their expression are determining factors that support the proper initiation and progression of synapse development in a brain region- or circuit-specific manner.

2.3.2 Astrocytes control circuit development and plasticity

Apart from influencing synaptogenesis, astrocytes are also involved in experience-dependent circuit refinement. As discussed earlier in this chapter, a classic model for studying developmental synaptic plasticity is ocular dominance plasticity (ODP) in the mammalian visual cortex. In wild-type animals, monocular deprivation during a critical developmental period causes the rearrangement of the binocular zone, which leads to the strengthening of the input from the open eye and the weakening of the input from the closed eye (Wiesel and Hubel 1963). While there are numerous studies illustrating neuronal signaling pathways required for the ODP, recent studies also indicate critical glial contributions, a part of which is conducted through astrocytic release of the synaptogenic protein Hevin. Unlike their wild type siblings, Hevin knockout mice fail to exhibit the monocular deprivation-induced shift, while the postnatal rescue of Hevin expression, specifically in astrocytes of the visual cortex, completely restores ODP, supporting a critical function

of astrocyte-secreted proteins in the refinement of thalamocortical circuits (Risher, Patel et al. 2014, Singh, Stogsdill et al. 2016).

Experience-dependent synapse elimination is a critical process to ensure proper establishment and refinement of circuit connectivity (Sanes and Lichtman 1999). Astrocytes have been shown to directly and indirectly mediate synapse elimination (reviewed by (Chung, Allen et al. 2015)) . Using an *in vitro* engulfment assay and *in vivo* analysis of the developing retinogeniculate system, Chung *et al* demonstrated astrocytes' ability to engulf synapses (Chung, Clarke et al. 2013). This action requires the MEGF10 and MERTK phagocytic pathways and is activity dependent. Mice deficient in both pathways fail to refine retinogeniculate connections and retain ectopic synapses with reduced functionality. Importantly, astrocytes continuously engulf both excitatory and inhibitory synapses in the adult mouse brain, likely contributing to synaptic remodeling in the mature nervous system. In *Drosophila* central neurons, a similar phenomenon is observed during metamorphosis, when larval astrocytes transform into phagocytes and mediate large-scale circuit rewiring in the pupal neuropil (Tasdemir-Yilmaz and Freeman 2014). Specifically, the developmental elimination of the MB γneuron axons are performed by astrocyte engulfment through activation of Draper, a fly homolog of MEGF10, as well as Crk/Mbc/dCed-12 signaling pathways. These studies demonstrate an evolutionarily conserved function of astrocytes in synaptic pruning and remodeling.

Another conserved function of astrocytes in developmental plasticity is its involvement in regulating critical period closure, shown by two recent publications studying *Drosophila* motor circuit and mouse visual circuit. Using optogenetic manipulations, Ackerman and colleagues define a critical period in the developing *Drosophila* motor circuit, 8 hours after larval hatching, during which period the motor neuron dendrite morphology can be readily modified by changes in neural activity. Furthermore, through genetic screens, the authors identified both cellular and molecular substrates regulating the closure of this critical period, which involves direct interactions between astrocyte-derived Neuroligin and dendritic localized Neurexin, as well as changes in dendrite microtubule dynamics (Ackerman, Perez-Catalan et al. 2021). Studies performed in mouse visual circuit showed a similar function of astrocyte in critical period closure (Ribot, Breton et al. 2021). Here, the authors found that injecting immature astrocytes into the primary visual cortex (V1) of adult mice (P100) reopens the critical period for ODP in the mature circuit. By comparing the expression profiles of immature and mature astrocytes, Ribot *et al* found that a developmental upregulation of astrocyte connexin signaling inhibits the expression of matrix metalloproteinase 9

(MMP9), an extracellular matrix–degrading enzyme. This promotes interneuron maturation and triggers the closure of critical period in the visual cortex. Together, both studies provide support for a function of astrocytes in coordinating circuit maturation and regulating the duration of critical periods.

2.3.3 Microglia regulate synaptic pruning and experience-dependent plasticity

Microglia are the resident macrophages of the CNS, constituting approximately 10% of brain cells. Similar to astrocytes, microglia send processes to infiltrate the neuropil regions and serve critical functions in regulating synapse development and pruning. Additionally, as immune cells, microglia can assume a wide range of morphologies in response to changes in neuronal activity and migrate and proliferate under inflammatory conditions (Lawson, Perry et al. 1990).

Under normal physiological conditions, microglia remain in the resting state. Using transgenic mice expressing EGFP specifically in microglia (CX3CR1-GFP mice) and 2-photon live imaging, microglia are found to be constantly monitoring the microenvironment in the presynaptic region and surveying neuronal and synaptic activity, through extending and retracting their processes (Weinhard, di Bartolomei et al. 2018). To understand their function in neural plasticity, researchers generated mice specifically depleted of microglia and identified deficits in multiple learning tasks and a significant reduction in motor-learning-dependent synapse formation. Most of these deficits can be recapitulated by Cre-dependent removal of BDNF directly from microglia, supporting a specific role for microglia-secreted BDNF in synapse formation and learning-dependent structural plasticity (Parkhurst, Yang et al. 2013).

An important function of microglia in the healthy brain is mediating synaptic pruning, a critical process that helps remove excessive or weak synapses during circuit refinement and experience-dependent plasticity. During postnatal developmental, microglia prune synapses through signaling mediated by the CX3CR1 receptor and complement receptor, CR3 (Paolicelli, Bolasco et al. 2011, Xavier, Menezes et al. 2014). Due to inappropriate synaptic pruning, CX3CR1 KO mice showed a transient increase in the density of immature spines in hippocampal CA1 pyramidal neurons (Schafer, Lehrman et al. 2012). A similar delay in synapse maturation was observed in the barrel cortex of mice with CX3CR1 deficiency (Hoshiko, Arnoux et al. 2012).

Another set of molecules implicated in microglia-mediated synaptic pruning is the classical complement proteins C1q and C3, localized

to a subset of immature synapses, and the complement receptor 3 (CR3), expressed in resident microglia. Because microglia can sense neuronal communication and synaptic activity, less active presynaptic inputs are preferentially eliminated through a process mediated by the neuronal release of C1q and C3 (Stevens, Allen et al. 2007, Schafer, Lehrman et al. 2012). In the mouse visual system, C1q and its upstream regulator TGF-β as well as C3 are required for proper refinement of the retinogeniculate system (Bialas and Stevens 2013). Microglial engulfment of synapses is decreased in C3 and CR3 KO mice, consistent with the hypothesis that the complement proteins, such as C1q and C3, are activity-dependent "eat-me" signals that tag the less active synapses for targeted engulfment by phagocytic microglia (Hoshiko, Arnoux et al. 2012).

To evaluate microglial function in experience-dependent plasticity, researchers characterized microglial interactions with synapses during normal and altered sensory experience in the visual cortex of juvenile mice. In response to monocular deprivation during the critical period, microglia rapidly altered their morphology and synaptic interactions in the binocular zone of the visual cortex (Tremblay, Lowery et al. 2010). Notably, disrupting the purinergic P2Y12 receptor alters the microglial response to monocular deprivation and abrogates ocular dominance plasticity. A recent study in the somatosensory system demonstrated similar morphological changes in microglia upon sensory deprivation induced by whisker trimming (Kalambogias, Chen et al. 2020). These findings suggest that microglia actively contribute to the experience-dependent modification or elimination of a specific subset of synapses in the healthy brain (Sipe, Lowery et al. 2016).

Outlook: Glial function in circuit development, refinement and experience-dependent plasticity has been a subject of intensive research throughout the past two decades in both invertebrate and vertebrate systems. These findings indicate that not only do glia provide neuronal networks with essential structural and metabolic support, but they also modulate synaptic activity and plasticity during circuit formation and provide neuroprotection and modulation throughout the animal's lifetime. Additionally, although not described here, the significant glial involvement in regulating neurophysiology, animal behavior, as well as learning and memory are well demonstrated (Fields, Araque et al. 2014, Perea, Sur et al. 2014, Akther and Hirase 2022).

Many molecular pathways underlying neuron-glia crosstalk and their impacts on synapse development have been identified. As described above, the various glial-derived factors include secreted, membrane-bound and intracellular molecules (Summarized in Figure 2.1). For instance, Hevin, Sparc and TNF-α are secreted by astrocytes and modulate synapse number by

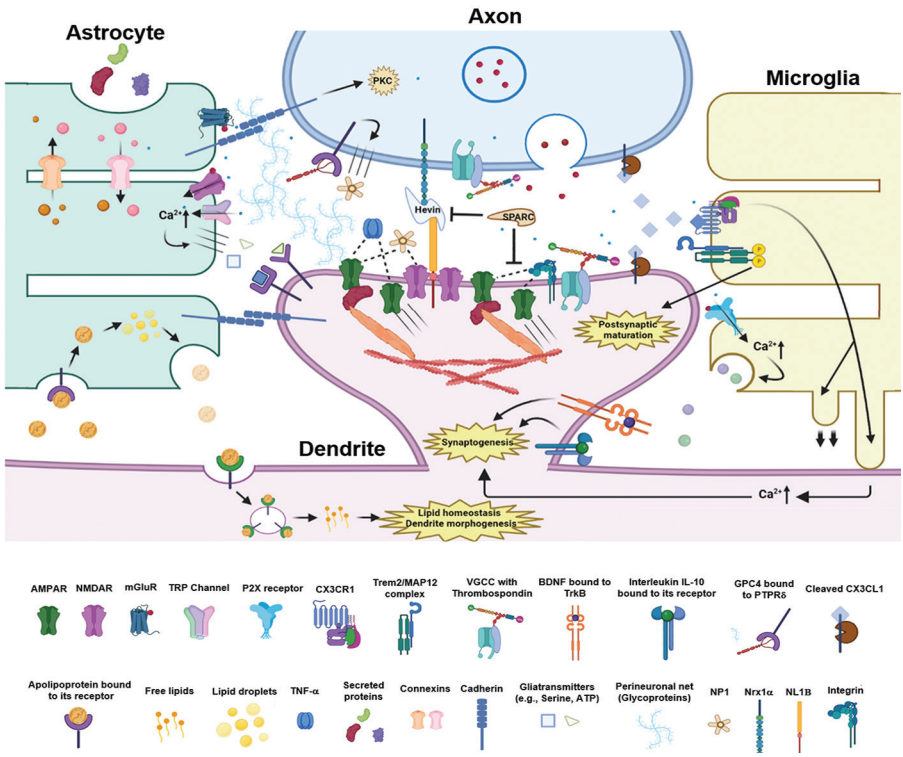

Figure 2.1 Synaptogenesis is governed by intercellular interactions between neurons and glia. Bidirectional signaling between astrocytes and microglia with proximal axon terminals and dendrites aids in the development and maturation of synapses. At this prototypical central glutamatergic synapse, neuron–glia interactions come in the form of physical contacts, such as by cell adhesion molecules, as well as secreted factors, including Hevin, Sparc, and the glycoprotein-based perineuronal network. Both microglia and astrocytes can detect nearby neuronal activity changes *via* calcium ion channels and neurotransmitter receptors and respond by releasing their own transmitters and secreted proteins in an activity-dependent manner.

interacting with glutamate receptors (i.e., AMPAR, NMDAR) and Neurexin-Neuroligin complexes directly (Jones, Bernardinelli et al. 2011). The release of these secreted molecules is often controlled by extracellular ligands or calcium entry. Stimulation of both metabotropic and ionotropic receptors, calcium channels and receptor tyrosine kinases induces astrocytes and microglia to release gliotransmitters, growth factors, and apolipoproteins (Gee and Keller 2005, Agulhon, Petravicz et al. 2008, Araque, Carmignoto et al. 2014, Yin, Spillman et al. 2021). Intracellular signaling within glia also controls these events through processes such as lipid trafficking/metabolism and Connexin-based communication between different astrocytic processes.

Finally, glia-neuron cell adhesion molecule interactions and a widely distributed glycoprotein-based perisynaptic net reinforce the structural integrity of the quadripartite synapse and regulate synaptic plasticity (Tewari, Chaunsali et al. 2022).

A number of open questions remain to be addressed in this field. There are several important areas demand further explorations, including how neurons and different types of glia communicate with each other during physiological and pathological conditions, as well as the molecular and functional heterogeneity of astrocytes and microglia (Khakh and Sofroniew 2015, Grabert, Michoel et al. 2016, Lawal, Ulloa Severino et al. 2022). In addition, both astrocytes and microglia infiltrate neuropil and cover specific territories. How their morphologies are intrinsically defined and modified by neural activity are not well understood. Recent advances in single-cell transcriptome analysis and high-resolution cellular and functional imaging in behaving animals, in combination with comparative studies using different animal models and human samples, will greatly aid researchers in solving these important questions in neurobiology (Li, Khankan et al. 2019, Farhy-Tselnicker, Boisvert et al. 2021).

2.4 Dendritic Structural Plasticity and Neurodevelopmental Disorders

Sensory experience interacts with genetic programs to shape and refine neural circuits underlying the cognitive functions of the brain. Human and animal studies suggest that altered states of neural plasticity during development are closely linked to a large spectrum of neurodevelopmental disorders. In this section, we will summarize the efforts and main findings elucidating the cellular and molecular basis of some of these disorders. While Fragile X Syndrome (FXS), Rett Syndrome and Angelman Syndrome are associated with monogenetic deficits, a large gene network has been linked to the highly prevalent autism spectrum disorders (ASD). To better understand the disease mechanisms and develop methods for detection and treatment of these complex diseases, many innovative technologies and experimental paradigms have been employed, which we will also touch upon in this section.

2.4.1 Fragile X syndrome

Fragile X Syndrome (FXS) is a common inherited cause of intellectual disability, characterized by behavioral abnormalities such as hyperactivity, emotional dysregulation, and learning deficits (Reviewed by (Garber, Visootsak

et al. 2008, Hagerman, Berry-Kravis et al. 2017)). FXS is a monogenic condition caused by the expansion of CGG triplicates in the 5' UTR region of the Fragile X messenger ribonucleoprotein 1 (FMR1) gene. The result is a hypermethylated state of the *FMR1* promoter region which leads to a strong reduction or complete absence of the protein product, Fragile X Mental Retardation Protein (FMRP). The main function of FMRP is to regulate synapse-specific gene expression through inhibiting translation until the appropriate neuronal signals ease this suppression (Garber, Visootsak et al. 2008). Due to the diversity of its mRNA targets, the neuropathological outcome of FXS is complex. In *FMR1* knockout mice used to model FXS, cellular phenotypes, including structural and dynamic phenotypes of dendrite spines, are readily observed. In barrel cortex pyramidal neurons of the mutant mice, the dynamic period of spine formation and elimination is protracted and immature dendrite filopodia fail to transition into stable mushroom-type spines as they would normally (Cruz-Martin, Crespo et al. 2010, Pan, Aldridge et al. 2010).

One of the most critical molecular changes associated with FXS is the sustained and upregulated mGluR-dependent LTD. In wild type animals, stimulation of mGluRs leads to the disinhibition of translation by FMRP withdrawal (Huber, Gallagher et al. 2002). In FMRP knockout animals, there is a continuous production of LTD-related proteins. Moreover, lack of FMRP also leads to perturbations of multiple transcription-independent signaling networks and cellular pathways. These include altered mTOR signaling and autophagy (Sharma, Hoeffer et al. 2010, Yan, Porch et al. 2018), activity-dependent translocation of mRNA granules to the dendrite (Antar, Afroz et al. 2004, Dictenberg, Swanger et al. 2008), increased ribosomal stalling (Darnell, Van Driesche et al. 2011), and cap-dependent translational initiation by the eIF4E complex (Napoli, Mercaldo et al. 2008)

In terms of factors responsible for altered postsynaptic structural plasticity associated with FXS, the activity-induced transcription factor MEF2 is implicated by recent studies. In FMR1 knockout mice, the dysregulation of Mef2 prevents PSD-95 degradation and reduces synapse elimination (Pfeiffer, Zang et al. 2010, Tsai, Wilkerson et al. 2017). The immediate early gene Arc has also been associated with FXS pathogenesis, where rapid Arc translation is observed (Park, Park et al. 2008). Furthermore, PSD-95 appears to be a common factor found in several studies. Its mRNA stability and translational activity are controlled by the level of bound FMRP (Todd, Mack et al. 2003, Muddashetty, Kelic et al. 2007, Zalfa, Eleuteri et al. 2007, Nalavadi, Muddashetty et al. 2012). Lastly, cofilin, a negative regulator of

actin polymerization, has been linked to the disruption of dendrite spine morphology, glutamatergic signaling and sensory processing in somatosensory cortical neurons in an FXS mouse model (Pyronneau, He et al. 2017).

2.4.2 Angelman syndrome

Angelman Syndrome (AS) is another neurodevelopmental disorder which causes intellectual disability, hyperactivity, severe impairment of speech, and atypical mood and disposition. The disease also features irregularities in motor control and seizures (Margolis, Sell et al. 2015). Most AS cases are associated with the improper neural expression of the maternally inherited Ubiquitin Protein Ligase E3a (UBE3A) gene, encoding the Ubiquitin ligase E6-associated protein (E6AP), which directs ubiquitinated targets for proteasomal degradation. The severity of AS symptoms occurs along a gradient that reflects its genetic etiology, including several genetic abnormalities linked to deletion, and/or methylation, of the 15q11-q13 chromosomal region that contains the E6AP locus, as well as E6AP loss-of-function mutations (Khatri and Man 2019).

Due to the large span of its protein interactions, E6AP exerts a broad effect on cellular functions, similar to the case with FMRP. Investigations of the mechanisms for the pathophysiology of AS, including defects in chronic and acute activity-dependent plasticity, have relied on mouse models as well as *in vitro* systems. In the visual cortex of E6AP knockout mice, a reduction in pyramidal neuron basal dendrite spines is observed (Yashiro, Riday et al. 2009). In addition, the E6AP-/- neurons lack normal experience-dependent maturation and have a reduced capacity for cortical plasticity, demonstrated by a mild response towards an extended period of sensory deprivation (Sato and Stryker 2010). One likely underlying molecular component is the level and activity of the immediate early gene Arc. Normally, neuronal stimulation leads to decreased Arc levels, attenuating AMPA receptor internalization and thus increasing the density of AMPA receptor inserted in the postsynaptic membrane (Greer, Hanayama et al. 2010). In the AS knockout mouse model, Arc is not degraded, leading to a host of intracellular events, including reduced CaMKII activity, persistent interaction of PSD-95 with Arc, and consequently failure of PSD-95 to associate with other postsynaptic proteins such as TrkB (Weeber, Jiang et al. 2003, Cao, Rioult-Pedotti et al. 2013). Despite a possible role for controlling Arc protein levels directly, there is evidence indicating that E6AP does not physically interact with Arc. Instead, it prevents Arc transcription (Kuhnle, Mothes et al. 2013). Additionally, studies have identified other E6AP targets, such as Ephexin5, a RhoA GEF, whose

proteolysis promotes excitatory synapse formation in young postnatal mice (Margolis, Salogiannis et al. 2010).

2.4.3 Rett syndrome

Rett Syndrome (RTT), like FSX and AS, is characterized by a spectrum of cognitive and motor deficits that appear early in development (reviewed by (Chahrour and Zoghbi 2007, Xu, Miller et al. 2014, Nakai, Takumi et al. 2018)). Despite reaching normal developmental checkpoints, such as walking and first word use, RTT individuals experience a regression in these learned skills. There is a concurrent deceleration in growth rate, including in head and brain expansion, which leads to microcephaly. Additional symptoms include social and emotional deficits, sleeping and breathing disruptions, and seizures. Physical health deteriorates later in life, commonly due to heart problems and severely restricted mobility. The syndromic features seen in RTT patients are due to deficits in the Methyl-CpG Binding Protein 2 (*Mecp2*) gene, which codes for a transcriptional regulator, and are recapitulated in Mecp2 mouse models. Protein levels of Mecp2, which is found in many cells but is enriched in neurons, rise during early postnatal development, regulating gene expression by binding to methylated DNA promoter regions and recruiting chromatin remodeling complexes and corepressors (Chahrour and Zoghbi 2007).

The neuropathology of RTT has long been known to arise, in part, from abnormal dendrite morphology and motility. In both postmortem RTT tissue (Armstrong, Dunn et al. 1995) and young postnatal Mecp2 mutant mice (Belichenko, Belichenko et al. 2009, Belichenko, Wright et al. 2009, Nguyen, Du et al. 2012), there are notable changes in dendrite spine density, motility, as well as dendrite branching pattern and complexity. This observation is seen in multiple brain regions, including visual and somatosensory cortex and hippocampus, as well as in primary hippocampal cultures (Chao, Zoghbi et al. 2007, Baj, Patrizio et al. 2014). Additional studies have directly linked these morphological aberrations to neurophysiological defects that include both reduced spontaneous excitatory drive *in vitro* and blunted evoked neurotransmission *in vivo* (Chao, Zoghbi et al. 2007, Lee, Tsytsarev et al. 2017).

The additive effect of these structural alterations to the dendrite and functional consequences to neurotransmission can lead to instances of abnormal plasticity. One clear example is the extension of the ocular dominance plasticity period in Mecp2-deficient mice, where Mecp2 is deleted specifically in PV^+ interneurons (Kuhlman, Olivas et al. 2013, Banerjee, Rikhye et al. 2016). Although the molecular basis for this permissive plasticity could

be due to any number of genes whose transcripts are regulated by Mecp2, one factor thought to be at the forefront of both the cause and treatment, is BDNF. Many reports have provided evidence to support the link between BDNF and dendrite morphology, as well as synaptic maturation and plasticity (Poo 2001, Tyler, Alonso et al. 2002). Current models, based on a variety of techniques such as chromatin immunoprecipitation, reporter assays and phosphorylation-dependent immunoblotting, propose that the Mecp2-BDNF pathway begins after depolarization, such as by visual sensory experience, induces CaMKII-dependent Mecp2 phosphorylation, dissociating its corepressors from the BDNF promoter and potentiation its expression (Chen, Chang et al. 2003, Martinowich, Hattori et al. 2003, Zhou, Hong et al. 2006). Consistently, reduced BDNF and impaired activity induced BDNF trafficking and release have been tied to RTT syndrome itself, including simplified dendrite arbors and neurological deficits mimicking RTT pathology (Chang, Khare et al. 2006, Wang, Chan et al. 2006, Ogier, Wang et al. 2007, Li, Calfa et al. 2012, Xu, Miller et al. 2014). Finally, neuronal and behavioral symptoms can be ameliorated by modulating dysfunction at the level of both Mecp2 and BDNF. Such examples include phenotypic rescue by BDNF overexpression in both Mecp2 knockout mice and hippocampal cultures subjected to shRNA mediated Mecp2 knockdown (Chang, Khare et al. 2006, Larimore, Chapleau et al. 2009). Therapies based on synthetic BDNF-like ligands have even been developed and show promise for reducing RTT symptoms *in vivo* (Massa, Yang et al. 2010, Schmid, Yang et al. 2012, Simmons, Belichenko et al. 2013, Kajiya, Takeshita et al. 2014).

2.4.4 Autism and complex neurodevelopmental disorders

In contrast to the three monogenic neurodevelopmental disorders detailed above (summarized in Figure 2.2), other neurological disorders have a more complicated etiology, which vastly complicates the pathology of the disease. Intellectual disability (ID), autism spectrum disorders (ASD) as well as psychiatric illnesses with a developmental component, such as schizophrenia (SZ), have been linked to dozens or even hundreds of genes (Ebert and Greenberg 2013, Parenti, Rabaneda et al. 2020). Interestingly, these disorders are often comorbid with each other or additional neurological symptoms, such as seizures.

Perhaps the most representative of these complex, polygenic disorders is ASD. Characterized by impaired social interaction, repetitive behaviors and narrowed interests, ASDs may be caused by spontaneous germline mutations or have a syndromic basis where, for example, an individual with FXS

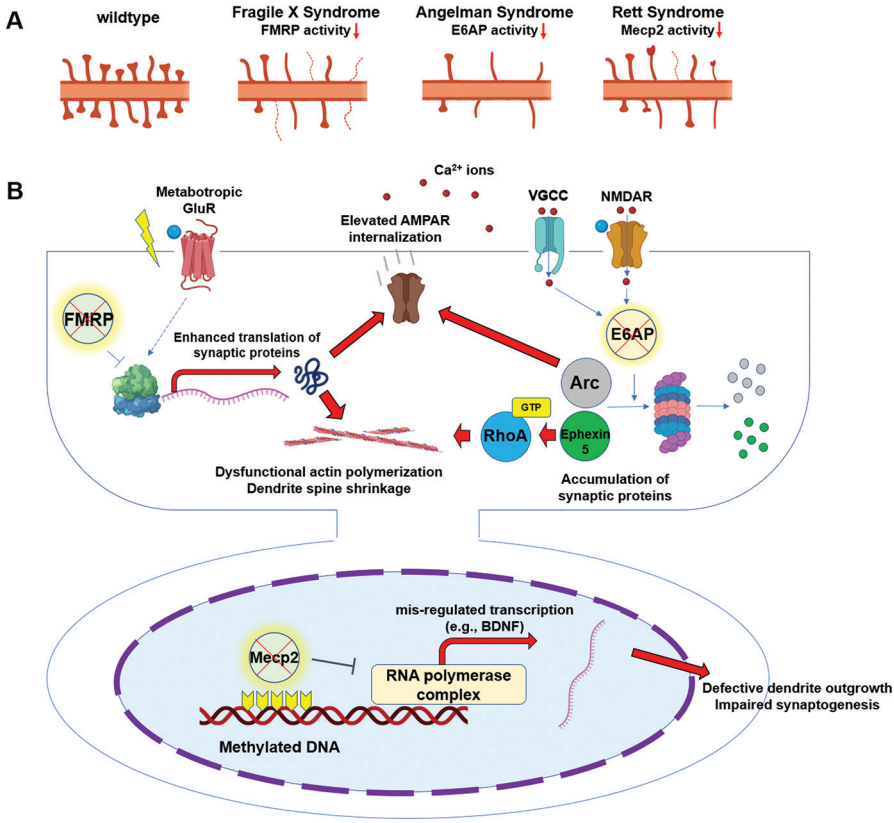

Figure 2.2 Cellular and molecular features of select monogenic neurodevelopmental disorders. (A) Stereotypical changes in dendrite and spine morphology for FXS, AS, and RTT, which include reduction of spine density and maturity. Although not pictured, RTT is also characterized by a reduced dendrite arbor complexity. **(B)** FXS, AS, and RTT arise from deficiencies of single genes. FXS results from FMRP mutations, which lead to upregulated translation of synaptic proteins. E6AP mutation reduces activity-dependent protein degradation and causes AS. Loss of Mecp2 activity observed in RTT results in unchecked transcription of synaptic proteins, such as BDNF, and impairs synapse formation and plasticity, as well as dendrite arborization.

will also be diagnosed with Autism (Ebert and Greenberg 2013). FXS, RTT and AS can all potentially result in an ASD diagnosis. In addition to these, Timothy Syndrome, stemming from dysfunctional activity of the *CACNA1C*-coding voltage-gated calcium channel, and Tuberous Sclerosis, caused by mutations in the TSC1 and TSC2 translational regulatory proteins, are common culprits of syndrome-based ASD cases ((Barrett and Tsien 2008,

Pasca, Portmann et al. 2011) and reviewed by (Han and Sahin 2011, Bhat, Dao et al. 2012)). In contrast to these more readily understood forms, there is also a great deal of evidence pointing to the Neurexin-Neuroligin cell-adhesion molecules as well as the SHANK class of PSD scaffolding proteins as the causative genes in non-syndromic instances (reviewed by (Ebert and Greenberg 2013)). One commonality between many of these genes of interest is that not only are they regulators of activity-dependent developmental plasticity, but also that their function or localization are themselves regulated by neuronal activity. For example, overexpression of Neuroligin in cultured rodent neurons results in elevated excitatory synapse numbers and enhanced NMDA receptor transmission and CaMKII activity (Chubykin, Atasoy et al. 2007).

Given the extreme heterogeneity of these neurodevelopmental disorders, online databases have been established to foster a more coherent understanding of the genetic causes for conditions like ASD and SZ (gene.sfari.org, szdb.org). SFARI Gene is one such resource which uploads candidate ASD-implicated genes from the literature as well as information on copy number variants (CNV) and genetic mouse models of ASD. The contribution of each gene is also weighted by providing a score which correlates to the strength of the experimental evidence. Gene scores are amenable to change based on new findings and heavily benefit from feedback from the research community.

2.4.5 New paradigms and technologies accelerate research on neurodevelopmental disorders

The study of developmental disorders, including those that are neurological and neuropsychiatric in origin, has undergone a transformation in the past few decades due to the implementation of genome-wide association studies, disease modeling using rodents and other animals, rational drug design, and other groundbreaking techniques. More recently, the invention of optogenetics and the discovery and rapid spread of CRISPR-based genomic editing has immensely helped to gain additional traction in cellular and genetic modeling of biological diseases. Two new technologies that have experienced a radical expansion in their use is human induced-pluripotent stem cells (iPSCs) and the related organoids (Ardhanareeswaran, Mariani et al. 2017, Shou, Liang et al. 2020). The advances made, and the tremendous potential still to be exploited, stems from the ability to directly model human disease in a human-specific biological context. The advantages of this system include bypassing the relative scarcity of patients for a given condition and confinement to postmortem

samples, fine-tuned controls over the genetic background of the tissue and generation of a completely new biological sample in several months, comparable to the amount of time taken to develop a new mouse line. The final section below will highlight how this technology has already made influential discoveries with respect to neurodevelopmental disorders, both monogenic in nature like Rett Syndrome or complex and polygenic like the autism spectrum disorders.

The information gleaned from iPSC-based research has been especially productive in studies related to Rett Syndrome (RTT). Multiple studies have demonstrated that iPSC-derived neurons from RTT individuals, or those containing *Mecp2* mutations, have similar cellular anatomical abnormalities as those seen *in vivo*. These include decreased excitatory synapse number and synaptic immaturity, as well as reduced dendrite arbor complexity and spine number (Muotri, Marchetto et al. 2010, Cheung, Horvath et al. 2011, Kim, Hysolli et al. 2011, Livide, Patriarchi et al. 2015, Tang, Kim et al. 2016) The opposite effect was also observed in cells containing the *Mecp2* duplication (Nageshappa, Carromeu et al. 2016). Using this approach, researchers were able to reproduce Mecp2-dependent BDNF expression and TRPC channel opening, corroborating earlier reports of their involvement in RTT using traditional models (Griesi-Oliveira, Acab et al. 2015).

Similar iPSC studies have also revealed activity-dependent changes at the synapse and are used to model the rare Timothy Syndrome (TS). iPSCs taken from TS individuals harboring a mutation in the *CACNA1C*, a gene encoding a calcium channel, reproduce the phenotypes seen in TS model mouse primary cortical neurons. Specifically, KCl-induced depolarization is followed by dendritic retraction, in contrast to the extension events in wildtype neurons (Krey, Pasca et al. 2013, Simms and Zamponi 2014). This atypical response is accompanied by abnormal calcium signaling and altered electrophysiology. Additionally, both studies reported large deviations in activity-dependent gene expression, particularly among constituents of the cAMP- and CREB-signaling pathways (Pasca, Portmann et al. 2011, Tian, Voineagu et al. 2014).

iPSC-based approaches are especially useful in polygenic disorders, such as autism or neuropsychiatric disease, where there are potentially hundreds of genetic mutations and polymorphisms that combinatorically shape the etiology and the severity of the disease ((Ratanatharathorn, Koenen et al. 2021) and reviewed in (Rylaarsdam and Guemez-Gamboa 2019)). In ASDs, for example, mutations at these varied loci, such as the synaptic scaffold protein gene *SHANK3,* lead to dendritic phenotypes, such as reduced complexity and length of dendrite fields, as well as decreased dendrite spine densities

(Darville, Poulet et al. 2016, Yi, Danko et al. 2016, Grunwald, Stock et al. 2019). In a second study, tissues developed from ASD patient-derived iPSCs had a disproportionate expansion of GABAergic interneurons and inhibitory synapses, lending support to the excitatory-inhibitory balance hypothesis of ASD (Mariani, Coppola et al. 2015). This approach has also been used to show that Bipolar Disorder (BD) patient-derived iPSCs produce neural stem cells which fail to completely differentiate into mature neurons, a defect which could be rescued by a WNT-signaling agonist (Madison, Zhou et al. 2015).

Finally, a particularly promising subset of iPSC research uses these induced cells to create miniature brains, termed cerebral organoids, which are layered, 3-dimensional organs with differentiated neuronal subtypes (reviewed by (Shou, Liang et al. 2020)). Organoids hold a great advantage over other model systems due to their enhanced ability to trace and analyze cellular lineages during organ development. For example, a recent study demonstrated that mutations at several loci, in isolation, abolish the normal synchronous development between excitatory and inhibitory cortical neurons, which results in physiological defects (Paulsen, Velasco et al. 2022). Additionally, although still in its infancy, i.e., cerebral organoids are still an anatomically simplified version of actual brains, the technology may be able to overcome the challenge of translating findings from isolated cellular environments to meaningful functionality in a native, *in vivo* system. Such problems have been encountered before, including the seemingly contradictory results of how Mecp2 alters BDNF levels in cell culture vs. living animals (Chahrour and Zoghbi 2007). Together with other tools like scRNA sequencing, organoids will inform us how activity-dependent changes during development impact not just the immediate downstream neuron, but also other circuit components and supporting cells, such as astrocytes and microglia.

Outlook: As a whole, the field of research focused on neurodevelopmental disorders with dendritic underpinnings has made incredible progress over the years. What initially began as observations of behavioral abnormalities and gross anatomical changes in patients evolved into a more detailed perspective of deficits at the cellular, molecular, and genetic levels (Nakai, Takumi et al. 2018). One of the many remaining obstacles is integrating information collected on any given disease, which goes beyond the causative protein(s) and the cellular compartment or cell types occupied and affected by it. While complex disorders, such as autism and schizophrenia, have the most diverse genetic and environmental etiologies, even monogenic disorders may be characterized by a spectrum of cellular and molecular deficits. Such is the case with Rett Syndrome where a single defective transcriptional repressor

leads to dysregulated expression for potentially thousands of genes (Boxer, Renthal et al. 2020). Therefore, recently developed technologies including multi-omics assays, patient-derived iPSCs and organoid-based lineage and neural circuit studies will be indispensable for elevating neurodevelopmental disease research to the next level. This shift may also advance the therapeutic sphere for neurological disorders, which has faced a disproportionate number of failures and hardships in the current era of research (Craven 2011).

Acknowledgements

We thank Anna Grigsby-Brown and Jun Yin for helpful discussions and comments on the manuscript. This work is supported by the Intramural Research Program of National Institute of Neurological Disorders and Stroke, National Institutes of Health. Project number 1ZIANS003137.

References

Abdolahi, S., A. Zare-Chahoki, F. Noorbakhsh and A. Gorji (2022). "A Review of Molecular Interplay between Neurotrophins and miRNAs in Neuropsychological Disorders." Mol Neurobiol **59**(10): 6260–6280.

Ackerman, S. D., N. A. Perez-Catalan, M. R. Freeman and C. Q. Doe (2021). "Astrocytes close a motor circuit critical period." Nature **592**(7854): 414–420.

Adhikari, P., D. Orozco, H. Randhawa and F. W. Wolf (2019). "Mef2 induction of the immediate early gene Hr38/Nr4a is terminated by Sirt1 to promote ethanol tolerance." Genes Brain Behav **18**(3): e12486.

Agulhon, C., J. Petravicz, A. B. McMullen, E. J. Sweger, S. K. Minton, S. R. Taves, K. B. Casper, T. A. Fiacco and K. D. McCarthy (2008). "What is the role of astrocyte calcium in neurophysiology?" Neuron **59**(6): 932–946.

Aizawa, H., S. C. Hu, K. Bobb, K. Balakrishnan, G. Ince, I. Gurevich, M. Cowan and A. Ghosh (2004). "Dendrite development regulated by CREST, a calcium-regulated transcriptional activator." Science **303**(5655): 197–202.

Akther, S. and H. Hirase (2022). "Assessment of astrocytes as a mediator of memory and learning in rodents." Glia **70**(8): 1484–1505.

Allen, N. J., M. L. Bennett, L. C. Foo, G. X. Wang, C. Chakraborty, S. J. Smith and B. A. Barres (2012). "Astrocyte glypicans 4 and 6 promote formation of excitatory synapses via GluA1 AMPA receptors." Nature **486**(7403): 410–414.

Allen, N. J. and C. Eroglu (2017). "Cell Biology of Astrocyte-Synapse Interactions." Neuron **96**(3): 697–708.

Alvarez, V. A. and B. L. Sabatini (2007). "Anatomical and physiological plasticity of dendritic spines." Annu Rev Neurosci **30**: 79–97.

Antar, L. N., R. Afroz, J. B. Dictenberg, R. C. Carroll and G. J. Bassell (2004). "Metabotropic glutamate receptor activation regulates fragile x mental retardation protein and FMR1 mRNA localization differentially in dendrites and at synapses." J Neurosci **24**(11): 2648–2655.

Araque, A., G. Carmignoto, P. G. Haydon, S. H. Oliet, R. Robitaille and A. Volterra (2014). "Gliotransmitters travel in time and space." Neuron **81**(4): 728–739.

Ardhanareeswaran, K., J. Mariani, G. Coppola, A. Abyzov and F. M. Vaccarino (2017). "Human induced pluripotent stem cells for modelling neurodevelopmental disorders." Nat Rev Neurol **13**(5): 265–278.

Armstrong, D., J. K. Dunn, B. Antalffy and R. Trivedi (1995). "Selective dendritic alterations in the cortex of Rett syndrome." J Neuropathol Exp Neurol **54**(2): 195–201.

Baj, G., A. Patrizio, A. Montalbano, M. Sciancalepore and E. Tongiorgi (2014). "Developmental and maintenance defects in Rett syndrome neurons identified by a new mouse staging system in vitro." Front Cell Neurosci **8**: 18.

Banerjee, A., R. V. Rikhye, V. Breton-Provencher, X. Tang, C. Li, K. Li, C. A. Runyan, Z. Fu, R. Jaenisch and M. Sur (2016). "Jointly reduced inhibition and excitation underlies circuit-wide changes in cortical processing in Rett syndrome." Proc Natl Acad Sci U S A **113**(46): E7287–E7296.

Barbagallo, B., A. Philbrook, D. Touroutine, N. Banerjee, D. Oliver, C. M. Lambert and M. M. Francis (2017). "Excitatory neurons sculpt GABAergic neuronal connectivity in the C. elegans motor circuit." Development **144**(10): 1807–1819.

Barrera, K., P. Chu, J. Abramowitz, R. Steger, R. L. Ramos and J. C. Brumberg (2013). "Organization of myelin in the mouse somatosensory barrel cortex and the effects of sensory deprivation." Dev Neurobiol **73**(4): 297–314.

Barrett, C. F. and R. W. Tsien (2008). "The Timothy syndrome mutation differentially affects voltage- and calcium-dependent inactivation of CaV1.2 L-type calcium channels." Proc Natl Acad Sci U S A **105**(6): 2157–2162.

Belichenko, N. P., P. V. Belichenko and W. C. Mobley (2009). "Evidence for both neuronal cell autonomous and nonautonomous effects of methyl-CpG-binding protein 2 in the cerebral cortex of female mice with Mecp2 mutation." Neurobiol Dis **34**(1): 71–77.

Belichenko, P. V., E. E. Wright, N. P. Belichenko, E. Masliah, H. H. Li, W. C. Mobley and U. Francke (2009). "Widespread changes in dendritic and axonal morphology in Mecp2-mutant mouse models of Rett syndrome: evidence for disruption of neuronal networks." J Comp Neurol **514**(3): 240–258.

Bhat, S., D. T. Dao, C. E. Terrillion, M. Arad, R. J. Smith, N. M. Soldatov and T. D. Gould (2012). "CACNA1C (Cav1.2) in the pathophysiology of psychiatric disease." Prog Neurobiol **99**(1): 1–14.

Bialas, A. R. and B. Stevens (2013). "TGF-beta signaling regulates neuronal C1q expression and developmental synaptic refinement." Nat Neurosci **16**(12): 1773–1782.

Biever, A., C. Glock, G. Tushev, E. Ciirdaeva, T. Dalmay, J. D. Langer and E. M. Schuman (2020). "Monosomes actively translate synaptic mRNAs in neuronal processes." Science **367**(6477).

Bloodgood, B. L., N. Sharma, H. A. Browne, A. Z. Trepman and M. E. Greenberg (2013). "The activity-dependent transcription factor NPAS4 regulates domain-specific inhibition." Nature **503**(7474): 121–125.

Borges, S. and M. Berry (1978). "The effects of dark rearing on the development of the visual cortex of the rat." J Comp Neurol **180**(2): 277–300.

Boxer, L. D., W. Renthal, A. W. Greben, T. Whitwam, A. Silberfeld, H. Stroud, E. Li, M. G. Yang, B. Kinde, E. C. Griffith, B. Bonev and M. E. Greenberg (2020). "MeCP2 Represses the Rate of Transcriptional Initiation of Highly Methylated Long Genes." Mol Cell **77**(2): 294–309 e299.

Butko, M. T., J. N. Savas, B. Friedman, C. Delahunty, F. Ebner, J. R. Yates, 3rd and R. Y. Tsien (2013). "In vivo quantitative proteomics of somatosensory cortical synapses shows which protein levels are modulated by sensory deprivation." Proc Natl Acad Sci U S A **110**(8): E726–735.

Cajigas, I. J., G. Tushev, T. J. Will, S. tom Dieck, N. Fuerst and E. M. Schuman (2012). "The local transcriptome in the synaptic neuropil revealed by deep sequencing and high-resolution imaging." Neuron **74**(3): 453–466.

Cao, C., M. S. Rioult-Pedotti, P. Migani, C. J. Yu, R. Tiwari, K. Parang, M. R. Spaller, D. J. Goebel and J. Marshall (2013). "Impairment of TrkB-PSD-95 signaling in Angelman syndrome." PLoS Biol **11**(2): e1001478.

Carvell, G. E. and D. J. Simons (1996). "Abnormal tactile experience early in life disrupts active touch." J Neurosci **16**(8): 2750–2757.

Chahrour, M. and H. Y. Zoghbi (2007). "The story of Rett syndrome: from clinic to neurobiology." Neuron **56**(3): 422–437.

Chang, J. Y., Y. Nakahata, Y. Hayano and R. Yasuda (2019). "Mechanisms of Ca(2+)/calmodulin-dependent kinase II activation in single dendritic spines." Nat Commun **10**(1): 2784.

Chang, J. Y., P. Parra-Bueno, T. Laviv, E. M. Szatmari, S. R. Lee and R. Yasuda (2017). "CaMKII Autophosphorylation Is Necessary for Optimal Integration of Ca(2+) Signals during LTP Induction, but Not Maintenance." Neuron **94**(4): 800–808 e804.

Chang, Q., G. Khare, V. Dani, S. Nelson and R. Jaenisch (2006). "The disease progression of Mecp2 mutant mice is affected by the level of BDNF expression." Neuron **49**(3): 341–348.

Chao, H. T., H. Y. Zoghbi and C. Rosenmund (2007). "MeCP2 controls excitatory synaptic strength by regulating glutamatergic synapse number." Neuron **56**(1): 58–65.

Chen, C. C. and J. C. Brumberg (2021). "Sensory Experience as a Regulator of Structural Plasticity in the Developing Whisker-to-Barrel System." Front Cell Neurosci **15**: 770453.

Chen, C. C., R. Steger and J. C. Brumberg (2009). "Barrels come of age: Barrels XXI meeting report." Somatosens Mot Res **26**(1): 25–30.

Chen, C. C., D. Tam and J. C. Brumberg (2012). "Sensory deprivation differentially impacts the dendritic development of pyramidal versus non-pyramidal neurons in layer 6 of mouse barrel cortex." Brain Struct Funct **217**(2): 435–446.

Chen, S. X., P. K. Tari, K. She and K. Haas (2010). "Neurexin-neuroligin cell adhesion complexes contribute to synaptotropic dendritogenesis via growth stabilization mechanisms in vivo." Neuron **67**(6): 967–983.

Chen, W. G., Q. Chang, Y. Lin, A. Meissner, A. E. West, E. C. Griffith, R. Jaenisch and M. E. Greenberg (2003). "Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2." Science **302**(5646): 885–889.

Chen, X., R. Rahman, F. Guo and M. Rosbash (2016). "Genome-wide identification of neuronal activity-regulated genes in Drosophila." Elife **5**.

Cheung, A. Y., L. M. Horvath, D. Grafodatskaya, P. Pasceri, R. Weksberg, A. Hotta, L. Carrel and J. Ellis (2011). "Isolation of MECP2-null Rett Syndrome patient hiPS cells and isogenic controls through X-chromosome inactivation." Hum Mol Genet **20**(11): 2103–2115.

Christopherson, K. S., E. M. Ullian, C. C. Stokes, C. E. Mullowney, J. W. Hell, A. Agah, J. Lawler, D. F. Mosher, P. Bornstein and B. A. Barres (2005). "Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis." Cell **120**(3): 421–433.

Chu, P., R. Abraham, K. Budhu, U. Khan, N. De Marco Garcia and J. C. Brumberg (2018). "The Impact of Perineuronal Net Digestion Using Chondroitinase ABC on the Intrinsic Physiology of Cortical Neurons." Neuroscience **388**: 23–35.

Chubykin, A. A., D. Atasoy, M. R. Etherton, N. Brose, E. T. Kavalali, J. R. Gibson and T. C. Sudhof (2007). "Activity-dependent validation of excitatory versus inhibitory synapses by neuroligin-1 versus neuroligin-2." Neuron **54**(6): 919–931.

Chung, W. S., N. J. Allen and C. Eroglu (2015). "Astrocytes Control Synapse Formation, Function, and Elimination." Cold Spring Harb Perspect Biol **7**(9): a020370.

Chung, W. S., L. E. Clarke, G. X. Wang, B. K. Stafford, A. Sher, C. Chakraborty, J. Joung, L. C. Foo, A. Thompson, C. Chen, S. J. Smith and B. A. Barres (2013). "Astrocytes mediate synapse elimination through MEGF10 and MERTK pathways." Nature **504**(7480): 394–400.

Cohn, J. A., E. R. Cebul, G. Valperga, L. Brose, M. de Bono, M. G. Heiman and J. T. Pierce (2020). "Long-term activity drives dendritic branch elaboration of a C. elegans sensory neuron." Dev Biol **461**(1): 66–74.

Costa, J. F., M. Dines and R. Lamprecht (2020). "The Role of Rac GTPase in Dendritic Spine Morphogenesis and Memory." Front Synaptic Neurosci **12**: 12.

Craven, R. (2011). "The risky business of drug development in neurology." Lancet Neurol **10**(2): 116–117.

Cruz-Martin, A., M. Crespo and C. Portera-Cailliau (2010). "Delayed stabilization of dendritic spines in fragile X mice." J Neurosci **30**(23): 7793–7803.

Darnell, J. C., S. J. Van Driesche, C. Zhang, K. Y. Hung, A. Mele, C. E. Fraser, E. F. Stone, C. Chen, J. J. Fak, S. W. Chi, D. D. Licatalosi, J. D. Richter and R. B. Darnell (2011). "FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism." Cell **146**(2): 247–261.

Darville, H., A. Poulet, F. Rodet-Amsellem, L. Chatrousse, J. Pernelle, C. Boissart, D. Heron, C. Nava, A. Perrier, M. Jarrige, F. Coge, M. J. Millan, T. Bourgeron, M. Peschanski, R. Delorme and A. Benchoua (2016). "Human Pluripotent Stem Cell-derived Cortical Neurons for High Throughput Medication Screening in Autism: A Proof of Concept Study in SHANK3 Haploinsufficiency Syndrome." EBioMedicine **9**: 293–305.

Del Rio, T. and M. B. Feller (2006). "Early retinal activity and visual circuit development." Neuron **52**(2): 221–222.

Dictenberg, J. B., S. A. Swanger, L. N. Antar, R. H. Singer and G. J. Bassell (2008). "A direct role for FMRP in activity-dependent dendritic mRNA transport links filopodial-spine morphogenesis to fragile X syndrome." Dev Cell **14**(6): 926–939.

Dong, W., R. H. Lee, H. Xu, S. Yang, K. G. Pratt, V. Cao, Y. K. Song, A. Nurmikko and C. D. Aizenman (2009). "Visual avoidance in Xenopus tadpoles is correlated with the maturation of visual responses in the optic tectum." J Neurophysiol **101**(2): 803–815.

Dong, X., K. Shen and H. E. Bulow (2015). "Intrinsic and extrinsic mechanisms of dendritic morphogenesis." Annu Rev Physiol **77**: 271–300.

Donlin-Asp, P. G., C. Polisseni, R. Klimek, A. Heckel and E. M. Schuman (2021). "Differential regulation of local mRNA dynamics and translation following long-term potentiation and depression." Proc Natl Acad Sci U S A **118**(13).

Duman, J. G., F. A. Blanco, C. A. Cronkite, Q. Ru, K. C. Erikson, S. Mulherkar, A. B. Saifullah, K. Firozi and K. F. Tolias (2021). "Rac-maninoff and Rho-vel: The symphony of Rho-GTPase signaling at excitatory synapses." Small GTPases: 1–34.

Ebert, D. H. and M. E. Greenberg (2013). "Activity-dependent neuronal signalling and autism spectrum disorder." Nature **493**(7432): 327–337.

Elmariah, S. B., E. J. Oh, E. G. Hughes and R. J. Balice-Gordon (2005). "Astrocytes regulate inhibitory synapse formation via Trk-mediated modulation of postsynaptic GABAA receptors." J Neurosci **25**(14): 3638–3650.

Eroglu, C., N. J. Allen, M. W. Susman, N. A. O'Rourke, C. Y. Park, E. Ozkan, C. Chakraborty, S. B. Mulinyawe, D. S. Annis, A. D. Huberman, E. M. Green, J. Lawler, R. Dolmetsch, K. C. Garcia, S. J. Smith, Z. D. Luo, A. Rosenthal, D. F. Mosher and B. A. Barres (2009). "Gabapentin receptor alpha2delta-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis." Cell **139**(2): 380–392.

Eroglu, C. and B. A. Barres (2010). "Regulation of synaptic connectivity by glia." Nature **468**(7321): 223–231.

Fagiolini, M., J. M. Fritschy, K. Low, H. Mohler, U. Rudolph and T. K. Hensch (2004). "Specific GABAA circuits for visual cortical plasticity." Science **303**(5664): 1681–1683.

Farhy-Tselnicker, I., M. M. Boisvert, H. Liu, C. Dowling, G. A. Erikson, E. Blanco-Suarez, C. Farhy, M. N. Shokhirev, J. R. Ecker and N. J. Allen (2021). "Activity-dependent modulation of synapse-regulating genes in astrocytes." Elife **10**.

Feller, M. B. (2009). "Retinal waves are likely to instruct the formation of eye-specific retinogeniculate projections." Neural Dev **4**: 24.

Fields, R. D., A. Araque, H. Johansen-Berg, S. S. Lim, G. Lynch, K. A. Nave, M. Nedergaard, R. Perez, T. Sejnowski and H. Wake (2014). "Glial biology in learning and cognition." Neuroscientist **20**(5): 426–431.

Forrest, M. P., E. Parnell and P. Penzes (2018). "Dendritic structural plasticity and neuropsychiatric disease." Nat Rev Neurosci **19**(4): 215–234.

Fox, K. and R. O. Wong (2005). "A comparison of experience-dependent plasticity in the visual and somatosensory systems." Neuron **48**(3): 465–477.

Freeman, M. R. (2015). "Drosophila Central Nervous System Glia." Cold Spring Harb Perspect Biol **7**(11).

Frischknecht, R., M. Heine, D. Perrais, C. I. Seidenbecher, D. Choquet and E. D. Gundelfinger (2009). "Brain extracellular matrix affects AMPA receptor lateral mobility and short-term synaptic plasticity." Nat Neurosci **12**(7): 897–904.

Fu, M. and Y. Zuo (2011). "Experience-dependent structural plasticity in the cortex." Trends Neurosci **34**(4): 177–187.

Fuentes-Medel, Y., J. Ashley, R. Barria, R. Maloney, M. Freeman and V. Budnik (2012). "Integration of a retrograde signal during synapse formation by glia-secreted TGF-beta ligand." Curr Biol **22**(19): 1831–1838.

Fujita, N., Y. Nagata, T. Nishiuchi, M. Sato, M. Iwami and T. Kiya (2013). "Visualization of neural activity in insect brains using a conserved immediate early gene, Hr38." Curr Biol **23**(20): 2063–2070.

Gao, M., K. Sossa, L. Song, L. Errington, L. Cummings, H. Hwang, D. Kuhl, P. Worley and H. K. Lee (2010). "A specific requirement of Arc/Arg3.1 for visual experience-induced homeostatic synaptic plasticity in mouse primary visual cortex." J Neurosci **30**(21): 7168–7178.

Garber, K. B., J. Visootsak and S. T. Warren (2008). "Fragile X syndrome." Eur J Hum Genet **16**(6): 666–672.

Gee, J. R. and J. N. Keller (2005). "Astrocytes: regulation of brain homeostasis via apolipoprotein E." Int J Biochem Cell Biol **37**(6): 1145–1150.

Gerges, N. Z., D. S. Backos and J. A. Esteban (2004). "Local control of AMPA receptor trafficking at the postsynaptic terminal by a small GTPase of the Rab family." J Biol Chem **279**(42): 43870–43878.

Gordon, J. A. and M. P. Stryker (1996). "Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse." J Neurosci **16**(10): 3274–3286.

Govek, E. E., S. E. Newey and L. Van Aelst (2005). "The role of the Rho GTPases in neuronal development." Genes Dev **19**(1): 1–49.

Grabert, K., T. Michoel, M. H. Karavolos, S. Clohisey, J. K. Baillie, M. P. Stevens, T. C. Freeman, K. M. Summers and B. W. McColl (2016). "Microglial brain region-dependent diversity and selective regional sensitivities to aging." Nat Neurosci **19**(3): 504–516.

Greer, P. L., R. Hanayama, B. L. Bloodgood, A. R. Mardinly, D. M. Lipton, S. W. Flavell, T. K. Kim, E. C. Griffith, Z. Waldon, R. Maehr, H. L.

Ploegh, S. Chowdhury, P. F. Worley, J. Steen and M. E. Greenberg (2010). "The Angelman Syndrome protein Ube3A regulates synapse development by ubiquitinating arc." Cell **140**(5): 704–716.

Griesi-Oliveira, K., A. Acab, A. R. Gupta, D. Y. Sunaga, T. Chailangkarn, X. Nicol, Y. Nunez, M. F. Walker, J. D. Murdoch, S. J. Sanders, T. V. Fernandez, W. Ji, R. P. Lifton, E. Vadasz, A. Dietrich, D. Pradhan, H. Song, G. L. Ming, X. Gu, G. Haddad, M. C. Marchetto, N. Spitzer, M. R. Passos-Bueno, M. W. State and A. R. Muotri (2015). "Modeling non-syndromic autism and the impact of TRPC6 disruption in human neurons." Mol Psychiatry **20**(11): 1350–1365.

Grueber, W. B. and Y. N. Jan (2004). "Dendritic development: lessons from Drosophila and related branches." Curr Opin Neurobiol **14**(1): 74–82.

Grunwald, L. M., R. Stock, K. Haag, S. Buckenmaier, M. C. Eberle, D. Wildgruber, H. Storchak, M. Kriebel, S. Weissgraeber, L. Mathew, Y. Singh, M. Loos, K. W. Li, U. Kraushaar, A. J. Fallgatter and H. Volkmer (2019). "Comparative characterization of human induced pluripotent stem cells (hiPSC) derived from patients with schizophrenia and autism." Transl Psychiatry **9**(1): 179.

Haas, K., J. Li and H. T. Cline (2006). "AMPA receptors regulate experience-dependent dendritic arbor growth in vivo." Proc Natl Acad Sci U S A **103**(32): 12127–12131.

Hafner, A. S., P. G. Donlin-Asp, B. Leitch, E. Herzog and E. M. Schuman (2019). "Local protein synthesis is a ubiquitous feature of neuronal pre- and postsynaptic compartments." Science **364**(6441).

Hagerman, R. J., E. Berry-Kravis, H. C. Hazlett, D. B. Bailey, Jr., H. Moine, R. F. Kooy, F. Tassone, I. Gantois, N. Sonenberg, J. L. Mandel and P. J. Hagerman (2017). "Fragile X syndrome." Nat Rev Dis Primers **3**: 17065.

Han, J. M. and M. Sahin (2011). "TSC1/TSC2 signaling in the CNS." FEBS Lett **585**(7): 973–980.

Hanover, J. L., Z. J. Huang, S. Tonegawa and M. P. Stryker (1999). "Brain-derived neurotrophic factor overexpression induces precocious critical period in mouse visual cortex." J Neurosci **19**(22): RC40.

Hartwig, C. L., J. Worrell, R. B. Levine, M. Ramaswami and S. Sanyal (2008). "Normal dendrite growth in Drosophila motor neurons requires the AP-1 transcription factor." Dev Neurobiol **68**(10): 1225–1242.

Hayashi-Takagi, A., S. Yagishita, M. Nakamura, F. Shirai, Y. I. Wu, A. L. Loshbaugh, B. Kuhlman, K. M. Hahn and H. Kasai (2015). "Labelling and optical erasure of synaptic memory traces in the motor cortex." Nature **525**(7569): 333–338.

He, H. Y., W. Shen, M. Hiramoto and H. T. Cline (2016). "Experience-Dependent Bimodal Plasticity of Inhibitory Neurons in Early Development." Neuron **90**(6): 1203–1214.

Heinz, D. A. and B. L. Bloodgood (2020). "Mechanisms that communicate features of neuronal activity to the genome." Curr Opin Neurobiol **63**: 131–136.

Hensch, T. K., M. Fagiolini, N. Mataga, M. P. Stryker, S. Baekkeskov and S. F. Kash (1998). "Local GABA circuit control of experience-dependent plasticity in developing visual cortex." Science **282**(5393): 1504–1508.

Herring, B. E. and R. A. Nicoll (2016). "Kalirin and Trio proteins serve critical roles in excitatory synaptic transmission and LTP." Proc Natl Acad Sci U S A **113**(8): 2264–2269.

Hiramoto, M. and H. T. Cline (2014). "Optic flow instructs retinotopic map formation through a spatial to temporal to spatial transformation of visual information." Proc Natl Acad Sci U S A **111**(47): E5105–5113.

Hofer, S. B., T. D. Mrsic-Flogel, T. Bonhoeffer and M. Hubener (2009). "Experience leaves a lasting structural trace in cortical circuits." Nature **457**(7227): 313–317.

Holtmaat, A., L. Wilbrecht, G. W. Knott, E. Welker and K. Svoboda (2006). "Experience-dependent and cell-type-specific spine growth in the neocortex." Nature **441**(7096): 979–983.

Hong, Y. K., S. Park, E. Y. Litvina, J. Morales, J. R. Sanes and C. Chen (2014). "Refinement of the retinogeniculate synapse by bouton clustering." Neuron **84**(2): 332–339.

Hoshiko, M., I. Arnoux, E. Avignone, N. Yamamoto and E. Audinat (2012). "Deficiency of the microglial receptor CX3CR1 impairs postnatal functional development of thalamocortical synapses in the barrel cortex." J Neurosci **32**(43): 15106–15111.

Huang, Z. J., A. Kirkwood, T. Pizzorusso, V. Porciatti, B. Morales, M. F. Bear, L. Maffei and S. Tonegawa (1999). "BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex." Cell **98**(6): 739–755.

Hubel, D. H. and T. N. Wiesel (1963). "Receptive Fields of Cells in Striate Cortex of Very Young, Visually Inexperienced Kittens." J Neurophysiol **26**: 994–1002.

Huber, K. M., S. M. Gallagher, S. T. Warren and M. F. Bear (2002). "Altered synaptic plasticity in a mouse model of fragile X mental retardation." Proc Natl Acad Sci U S A **99**(11): 7746–7750.

Huberman, A. D., D. Stellwagen and B. Chapman (2002). "Decoupling eye-specific segregation from lamination in the lateral geniculate nucleus." J Neurosci **22**(21): 9419–9429.

Ifrim, M. F., K. R. Williams and G. J. Bassell (2015). "Single-Molecule Imaging of PSD-95 mRNA Translation in Dendrites and Its Dysregulation in a Mouse Model of Fragile X Syndrome." J Neurosci **35**(18): 7116–7130.

Impey, S., M. Davare, A. Lesiak, D. Fortin, H. Ando, O. Varlamova, K. Obrietan, T. R. Soderling, R. H. Goodman and G. A. Wayman (2010). "An activity-induced microRNA controls dendritic spine formation by regulating Rac1-PAK signaling." Mol Cell Neurosci **43**(1): 146–156.

Iwai, Y., M. Fagiolini, K. Obata and T. K. Hensch (2003). "Rapid critical period induction by tonic inhibition in visual cortex." J Neurosci **23**(17): 6695–6702.

Jan, Y. N. and L. Y. Jan (2010). "Branching out: mechanisms of dendritic arborization." Nat Rev Neurosci **11**(5): 316–328.

Jin, Y. and Y. B. Qi (2018). "Building stereotypic connectivity: mechanistic insights into structural plasticity from C. elegans." Curr Opin Neurobiol **48**: 97–105.

Jones, E. V., Y. Bernardinelli, Y. C. Tse, S. Chierzi, T. P. Wong and K. K. Murai (2011). "Astrocytes control glutamate receptor levels at developing synapses through SPARC-beta-integrin interactions." J Neurosci **31**(11): 4154–4165.

Ju, W., W. Morishita, J. Tsui, G. Gaietta, T. J. Deerinck, S. R. Adams, C. C. Garner, R. Y. Tsien, M. H. Ellisman and R. C. Malenka (2004). "Activity-dependent regulation of dendritic synthesis and trafficking of AMPA receptors." Nat Neurosci **7**(3): 244–253.

Kajiya, M., K. Takeshita, M. Kittaka, S. Matsuda, K. Ouhara, K. Takeda, T. Takata, M. Kitagawa, T. Fujita, H. Shiba and H. Kurihara (2014). "BDNF mimetic compound LM22A-4 regulates cementoblast differentiation via the TrkB-ERK/Akt signaling cascade." Int Immunopharmacol **19**(2): 245–252.

Kalambogias, J., C. C. Chen, S. Khan, T. Son, R. Wercberger, C. Headlam, C. Lin and J. C. Brumberg (2020). "Development and sensory experience dependent regulation of microglia in barrel cortex." J Comp Neurol **528**(4): 559–573.

Kanamori, T., M. I. Kanai, Y. Dairyo, K. Yasunaga, R. K. Morikawa and K. Emoto (2013). "Compartmentalized calcium transients trigger dendrite pruning in Drosophila sensory neurons." Science **340**(6139): 1475–1478.

Kaneko, M. and M. P. Stryker (2017). "Homeostatic plasticity mechanisms in mouse V1." Philos Trans R Soc Lond B Biol Sci **372**(1715).

Katz, L. C. and C. J. Shatz (1996). "Synaptic activity and the construction of cortical circuits." Science **274**(5290): 1133–1138.

Keller, A. and G. C. Carlson (1999). "Neonatal whisker clipping alters intracortical, but not thalamocortical projections, in rat barrel cortex." J Comp Neurol **412**(1): 83–94.

Khakh, B. S. and M. V. Sofroniew (2015). "Diversity of astrocyte functions and phenotypes in neural circuits." Nat Neurosci **18**(7): 942–952.

Khatri, N. and H. Y. Man (2019). "The Autism and Angelman Syndrome Protein Ube3A/E6AP: The Gene, E3 Ligase Ubiquitination Targets and Neurobiological Functions." Front Mol Neurosci **12**: 109.

Kim, K. Y., E. Hysolli and I. H. Park (2011). "Neuronal maturation defect in induced pluripotent stem cells from patients with Rett syndrome." Proc Natl Acad Sci U S A **108**(34): 14169–14174.

Knott, G. W., C. Quairiaux, C. Genoud and E. Welker (2002). "Formation of dendritic spines with GABAergic synapses induced by whisker stimulation in adult mice." Neuron **34**(2): 265–273.

Koleske, A. J. (2013). "Molecular mechanisms of dendrite stability." Nat Rev Neurosci **14**(8): 536–550.

Kossel, A., S. Lowel and J. Bolz (1995). "Relationships between dendritic fields and functional architecture in striate cortex of normal and visually deprived cats." J Neurosci **15**(5 Pt 2): 3913–3926.

Krey, J. F., S. P. Pasca, A. Shcheglovitov, M. Yazawa, R. Schwemberger, R. Rasmusson and R. E. Dolmetsch (2013). "Timothy syndrome is associated with activity-dependent dendritic retraction in rodent and human neurons." Nat Neurosci **16**(2): 201–209.

Kucukdereli, H., N. J. Allen, A. T. Lee, A. Feng, M. I. Ozlu, L. M. Conatser, C. Chakraborty, G. Workman, M. Weaver, E. H. Sage, B. A. Barres and C. Eroglu (2011). "Control of excitatory CNS synaptogenesis by astrocyte-secreted proteins Hevin and SPARC." Proc Natl Acad Sci U S A **108**(32): E440–449.

Kuhlman, S. J., N. D. Olivas, E. Tring, T. Ikrar, X. Xu and J. T. Trachtenberg (2013). "A disinhibitory microcircuit initiates critical-period plasticity in the visual cortex." Nature **501**(7468): 543–546.

Kuhnle, S., B. Mothes, K. Matentzoglu and M. Scheffner (2013). "Role of the ubiquitin ligase E6AP/UBE3A in controlling levels of the synaptic protein Arc." Proc Natl Acad Sci U S A **110**(22): 8888–8893.

Lacar, B., S. B. Linker, B. N. Jaeger, S. R. Krishnaswami, J. J. Barron, M. J. E. Kelder, S. L. Parylak, A. C. M. Paquola, P. Venepally, M. Novotny, C. O'Connor, C. Fitzpatrick, J. A. Erwin, J. Y. Hsu, D. Husband, M. J. McConnell, R. Lasken and F. H. Gage (2016). "Nuclear RNA-seq of single neurons reveals molecular signatures of activation." Nat Commun **7**: 11022.

Larimore, J. L., C. A. Chapleau, S. Kudo, A. Theibert, A. K. Percy and L. Pozzo-Miller (2009). "Bdnf overexpression in hippocampal neurons prevents dendritic atrophy caused by Rett-associated MECP2 mutations." Neurobiol Dis **34**(2): 199–211.

Lawal, O., F. P. Ulloa Severino and C. Eroglu (2022). "The role of astrocyte structural plasticity in regulating neural circuit function and behavior." Glia **70**(8): 1467–1483.

Lawson, L. J., V. H. Perry, P. Dri and S. Gordon (1990). "Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain." Neuroscience **39**(1): 151–170.

Lee, K. F., C. Soares, J. P. Thivierge and J. C. Beique (2016). "Correlated Synaptic Inputs Drive Dendritic Calcium Amplification and Cooperative Plasticity during Clustered Synapse Development." Neuron **89**(4): 784–799.

Lee, L. J., V. Tsytsarev and R. S. Erzurumlu (2017). "Structural and functional differences in the barrel cortex of Mecp2 null mice." J Comp Neurol **525**(18): 3951–3961.

Lee, S. J., Y. Escobedo-Lozoya, E. M. Szatmari and R. Yasuda (2009). "Activation of CaMKII in single dendritic spines during long-term potentiation." Nature **458**(7236): 299–304.

Lefebvre, J. L., J. R. Sanes and J. N. Kay (2015). "Development of dendritic form and function." Annu Rev Cell Dev Biol **31**: 741–777.

Lemieux, M., S. Labrecque, C. Tardif, E. Labrie-Dion, E. Lebel and P. De Koninck (2012). "Translocation of CaMKII to dendritic microtubules supports the plasticity of local synapses." J Cell Biol **198**(6): 1055–1073.

Lendvai, B., E. A. Stern, B. Chen and K. Svoboda (2000). "Experience-dependent plasticity of dendritic spines in the developing rat barrel cortex in vivo." Nature **404**(6780): 876–881.

LeVay, S., T. N. Wiesel and D. H. Hubel (1980). "The development of ocular dominance columns in normal and visually deprived monkeys." J Comp Neurol **191**(1): 1–51.

Li, J., R. R. Khankan, C. Caneda, M. I. Godoy, M. S. Haney, M. C. Krawczyk, M. C. Bassik, S. A. Sloan and Y. Zhang (2019). "Astrocyte-to-astrocyte contact and a positive feedback loop of growth factor signaling regulate astrocyte maturation." Glia **67**(8): 1571–1597.

Li, W., G. Calfa, J. Larimore and L. Pozzo-Miller (2012). "Activity-dependent BDNF release and TRPC signaling is impaired in hippocampal neurons of Mecp2 mutant mice." Proc Natl Acad Sci U S A **109**(42): 17087–17092.

Li, Z., C. D. Aizenman and H. T. Cline (2002). "Regulation of rho GTPases by crosstalk and neuronal activity in vivo." Neuron **33**(5): 741–750.

Li, Z., L. Van Aelst and H. T. Cline (2000). "Rho GTPases regulate distinct aspects of dendritic arbor growth in Xenopus central neurons in vivo." Nat Neurosci **3**(3): 217–225.

Lin, Y., B. L. Bloodgood, J. L. Hauser, A. D. Lapan, A. C. Koon, T. K. Kim, L. S. Hu, A. N. Malik and M. E. Greenberg (2008). "Activity-dependent regulation of inhibitory synapse development by Npas4." Nature **455**(7217): 1198–1204.

Lisman, J., H. Schulman and H. Cline (2002). "The molecular basis of CaMKII function in synaptic and behavioural memory." Nat Rev Neurosci **3**(3): 175–190.

Liu, H. H., D. B. McClatchy, L. Schiapparelli, W. Shen, J. R. Yates, 3rd and H. T. Cline (2018). "Role of the visual experience-dependent nascent proteome in neuronal plasticity." Elife **7**.

Liu, X. F., P. K. Tari and K. Haas (2009). "PKM zeta restricts dendritic arbor growth by filopodial and branch stabilization within the intact and awake developing brain." J Neurosci **29**(39): 12229–12235.

Livide, G., T. Patriarchi, M. Amenduni, S. Amabile, D. Yasui, E. Calcagno, C. Lo Rizzo, G. De Falco, C. Ulivieri, F. Ariani, F. Mari, M. A. Mencarelli, J. W. Hell, A. Renieri and I. Meloni (2015). "GluD1 is a common altered player in neuronal differentiation from both MECP2-mutated and CDKL5-mutated iPS cells." Eur J Hum Genet **23**(2): 195–201.

Lohmann, C. and T. Bonhoeffer (2008). "A role for local calcium signaling in rapid synaptic partner selection by dendritic filopodia." Neuron **59**(2): 253–260.

Lu, H. E., H. D. MacGillavry, N. A. Frost and T. A. Blanpied (2014). "Multiple spatial and kinetic subpopulations of CaMKII in spines and dendrites as resolved by single-molecule tracking PALM." J Neurosci **34**(22): 7600–7610.

Lucic, V., G. J. Greif and M. B. Kennedy (2008). "Detailed state model of CaMKII activation and autophosphorylation." Eur Biophys J **38**(1): 83–98.

Ma, X. M., D. D. Kiraly, E. D. Gaier, Y. Wang, E. J. Kim, E. S. Levine, B. A. Eipper and R. E. Mains (2008). "Kalirin-7 is required for synaptic structure and function." J Neurosci **28**(47): 12368–12382.

Madison, J. M., F. Zhou, A. Nigam, A. Hussain, D. D. Barker, R. Nehme, K. van der Ven, J. Hsu, P. Wolf, M. Fleishman, C. O'Dushlaine, S. Rose, K. Chambert, F. H. Lau, T. Ahfeldt, E. H. Rueckert, S. D. Sheridan, D. M. Fass, J. Nemesh, T. E. Mullen, L. Daheron, S. McCarroll, P. Sklar,

R. H. Perlis and S. J. Haggarty (2015). "Characterization of bipolar disorder patient-specific induced pluripotent stem cells from a family reveals neurodevelopmental and mRNA expression abnormalities." Mol Psychiatry **20**(6): 703–717.

Maffei, A., S. B. Nelson and G. G. Turrigiano (2004). "Selective reconfiguration of layer 4 visual cortical circuitry by visual deprivation." Nat Neurosci **7**(12): 1353–1359.

Majdan, M. and C. J. Shatz (2006). "Effects of visual experience on activity-dependent gene regulation in cortex." Nat Neurosci **9**(5): 650–659.

Majewska, A. and M. Sur (2003). "Motility of dendritic spines in visual cortex in vivo: changes during the critical period and effects of visual deprivation." Proc Natl Acad Sci U S A **100**(26): 16024–16029.

Malpel, S., A. Klarsfeld and F. Rouyer (2002). "Larval optic nerve and adult extra-retinal photoreceptors sequentially associate with clock neurons during Drosophila brain development." Development **129**(6): 1443–1453.

Malun, D. and P. C. Brunjes (1996). "Development of olfactory glomeruli: temporal and spatial interactions between olfactory receptor axons and mitral cells in opossums and rats." J Comp Neurol **368**(1): 1–16.

Mameli, M., B. Balland, R. Lujan and C. Luscher (2007). "Rapid synthesis and synaptic insertion of GluR2 for mGluR-LTD in the ventral tegmental area." Science **317**(5837): 530–533.

Margolis, S. S., J. Salogiannis, D. M. Lipton, C. Mandel-Brehm, Z. P. Wills, A. R. Mardinly, L. Hu, P. L. Greer, J. B. Bikoff, H. Y. Ho, M. J. Soskis, M. Sahin and M. E. Greenberg (2010). "EphB-mediated degradation of the RhoA GEF Ephexin5 relieves a developmental brake on excitatory synapse formation." Cell **143**(3): 442–455.

Margolis, S. S., G. L. Sell, M. A. Zbinden and L. M. Bird (2015). "Angelman Syndrome." Neurotherapeutics **12**(3): 641–650.

Mariani, J., G. Coppola, P. Zhang, A. Abyzov, L. Provini, L. Tomasini, M. Amenduni, A. Szekely, D. Palejev, M. Wilson, M. Gerstein, E. L. Grigorenko, K. Chawarska, K. A. Pelphrey, J. R. Howe and F. M. Vaccarino (2015). "FOXG1-Dependent Dysregulation of GABA/Glutamate Neuron Differentiation in Autism Spectrum Disorders." Cell **162**(2): 375–390.

Marie, H., W. Morishita, X. Yu, N. Calakos and R. C. Malenka (2005). "Generation of silent synapses by acute in vivo expression of CaMKIV and CREB." Neuron **45**(5): 741–752.

Martinowich, K., D. Hattori, H. Wu, S. Fouse, F. He, Y. Hu, G. Fan and Y. E. Sun (2003). "DNA methylation-related chromatin remodeling

in activity-dependent BDNF gene regulation." Science **302**(5646): 890–893.

Massa, S. M., T. Yang, Y. Xie, J. Shi, M. Bilgen, J. N. Joyce, D. Nehama, J. Rajadas and F. M. Longo (2010). "Small molecule BDNF mimetics activate TrkB signaling and prevent neuronal degeneration in rodents." J Clin Invest **120**(5): 1774–1785.

Mauch, D. H., K. Nagler, S. Schumacher, C. Goritz, E. C. Muller, A. Otto and F. W. Pfrieger (2001). "CNS synaptogenesis promoted by glia-derived cholesterol." Science **294**(5545): 1354–1357.

Maxwell, M. A. and G. E. Muscat (2006). "The NR4A subgroup: immediate early response genes with pleiotropic physiological roles." Nucl Recept Signal **4**: e002.

McCurry, C. L., J. D. Shepherd, D. Tropea, K. H. Wang, M. F. Bear and M. Sur (2010). "Loss of Arc renders the visual cortex impervious to the effects of sensory experience or deprivation." Nat Neurosci **13**(4): 450–457.

McRae, P. A., M. M. Rocco, G. Kelly, J. C. Brumberg and R. T. Matthews (2007). "Sensory deprivation alters aggrecan and perineuronal net expression in the mouse barrel cortex." J Neurosci **27**(20): 5405–5413.

McVicker, D. P., M. M. Millette and E. W. Dent (2015). "Signaling to the microtubule cytoskeleton: an unconventional role for CaMKII." Dev Neurobiol **75**(4): 423–434.

Meyer-Franke, A., M. R. Kaplan, F. W. Pfrieger and B. A. Barres (1995). "Characterization of the signaling interactions that promote the survival and growth of developing retinal ganglion cells in culture." Neuron **15**(4): 805–819.

Miller, S., M. Yasuda, J. K. Coats, Y. Jones, M. E. Martone and M. Mayford (2002). "Disruption of dendritic translation of CaMKIIalpha impairs stabilization of synaptic plasticity and memory consolidation." Neuron **36**(3): 507–519.

Morales, B., S. Y. Choi and A. Kirkwood (2002). "Dark rearing alters the development of GABAergic transmission in visual cortex." J Neurosci **22**(18): 8084–8090.

Muddashetty, R. S., S. Kelic, C. Gross, M. Xu and G. J. Bassell (2007). "Dysregulated metabotropic glutamate receptor-dependent translation of AMPA receptor and postsynaptic density-95 mRNAs at synapses in a mouse model of fragile X syndrome." J Neurosci **27**(20): 5338–5348.

Muotri, A. R., M. C. Marchetto, N. G. Coufal, R. Oefner, G. Yeo, K. Nakashima and F. H. Gage (2010). "L1 retrotransposition in neurons is modulated by MeCP2." Nature **468**(7322): 443–446.

Murakoshi, H., H. Wang and R. Yasuda (2011). "Local, persistent activation of Rho GTPases during plasticity of single dendritic spines." Nature **472**(7341): 100–104.

Murphy, T. H., P. F. Worley and J. M. Baraban (1991). "L-type voltage-sensitive calcium channels mediate synaptic activation of immediate early genes." Neuron **7**(4): 625–635.

Nadif Kasri, N., A. Nakano-Kobayashi, R. Malinow, B. Li and L. Van Aelst (2009). "The Rho-linked mental retardation protein oligophrenin-1 controls synapse maturation and plasticity by stabilizing AMPA receptors." Genes Dev **23**(11): 1289–1302.

Nadif Kasri, N., A. Nakano-Kobayashi and L. Van Aelst (2011). "Rapid synthesis of the X-linked mental retardation protein OPHN1 mediates mGluR-dependent LTD through interaction with the endocytic machinery." Neuron **72**(2): 300–315.

Nageshappa, S., C. Carromeu, C. A. Trujillo, P. Mesci, I. Espuny-Camacho, E. Pasciuto, P. Vanderhaeghen, C. M. Verfaillie, S. Raitano, A. Kumar, C. M. Carvalho, C. Bagni, M. B. Ramocki, B. H. Araujo, L. B. Torres, J. R. Lupski, H. Van Esch and A. R. Muotri (2016). "Altered neuronal network and rescue in a human MECP2 duplication model." Mol Psychiatry **21**(2): 178–188.

Nakahata, Y. and R. Yasuda (2018). "Plasticity of Spine Structure: Local Signaling, Translation and Cytoskeletal Reorganization." Front Synaptic Neurosci **10**: 29.

Nakai, N., T. Takumi, J. Nakai and M. Sato (2018). "Common Defects of Spine Dynamics and Circuit Function in Neurodevelopmental Disorders: A Systematic Review of Findings From in Vivo Optical Imaging of Mouse Models." Front Neurosci **12**: 412.

Nalavadi, V. C., R. S. Muddashetty, C. Gross and G. J. Bassell (2012). "Dephosphorylation-induced ubiquitination and degradation of FMRP in dendrites: a role in immediate early mGluR-stimulated translation." J Neurosci **32**(8): 2582–2587.

Napoli, I., V. Mercaldo, P. P. Boyl, B. Eleuteri, F. Zalfa, S. De Rubeis, D. Di Marino, E. Mohr, M. Massimi, M. Falconi, W. Witke, M. Costa-Mattioli, N. Sonenberg, T. Achsel and C. Bagni (2008). "The fragile X syndrome protein represses activity-dependent translation through CYFIP1, a new 4E-BP." Cell **134**(6): 1042–1054.

Neniskyte, U. and C. T. Gross (2017). "Errant gardeners: glial-cell-dependent synaptic pruning and neurodevelopmental disorders." Nat Rev Neurosci **18**(11): 658–670.

Nguyen, M. V., F. Du, C. A. Felice, X. Shan, A. Nigam, G. Mandel, J. K. Robinson and N. Ballas (2012). "MeCP2 is critical for maintaining mature neuronal networks and global brain anatomy during late stages of postnatal brain development and in the mature adult brain." J Neurosci **32**(29): 10021–10034.

Nithianantharajah, J. and A. J. Hannan (2006). "Enriched environments, experience-dependent plasticity and disorders of the nervous system." Nat Rev Neurosci **7**(9): 697–709.

Ogier, M., H. Wang, E. Hong, Q. Wang, M. E. Greenberg and D. M. Katz (2007). "Brain-derived neurotrophic factor expression and respiratory function improve after ampakine treatment in a mouse model of Rett syndrome." J Neurosci **27**(40): 10912–10917.

Oswald, M. C., P. S. Brooks, M. F. Zwart, A. Mukherjee, R. J. West, C. N. Giachello, K. Morarach, R. A. Baines, S. T. Sweeney and M. Landgraf (2018). "Reactive oxygen species regulate activity-dependent neuronal plasticity in Drosophila." Elife **7**.

Pan, F., G. M. Aldridge, W. T. Greenough and W. B. Gan (2010). "Dendritic spine instability and insensitivity to modulation by sensory experience in a mouse model of fragile X syndrome." Proc Natl Acad Sci U S A **107**(41): 17768–17773.

Panatier, A., J. Vallee, M. Haber, K. K. Murai, J. C. Lacaille and R. Robitaille (2011). "Astrocytes are endogenous regulators of basal transmission at central synapses." Cell **146**(5): 785–798.

Paolicelli, R. C., G. Bolasco, F. Pagani, L. Maggi, M. Scianni, P. Panzanelli, M. Giustetto, T. A. Ferreira, E. Guiducci, L. Dumas, D. Ragozzino and C. T. Gross (2011). "Synaptic pruning by microglia is necessary for normal brain development." Science **333**(6048): 1456–1458.

Parenti, I., L. G. Rabaneda, H. Schoen and G. Novarino (2020). "Neurodevelopmental Disorders: From Genetics to Functional Pathways." Trends Neurosci **43**(8): 608–621.

Park, S., J. M. Park, S. Kim, J. A. Kim, J. D. Shepherd, C. L. Smith-Hicks, S. Chowdhury, W. Kaufmann, D. Kuhl, A. G. Ryazanov, R. L. Huganir, D. J. Linden and P. F. Worley (2008). "Elongation factor 2 and fragile X mental retardation protein control the dynamic translation of Arc/Arg3.1 essential for mGluR-LTD." Neuron **59**(1): 70–83.

Parkhurst, C. N., G. Yang, I. Ninan, J. N. Savas, J. R. Yates, 3rd, J. J. Lafaille, B. L. Hempstead, D. R. Littman and W. B. Gan (2013). "Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor." Cell **155**(7): 1596–1609.

Pasca, S. P., T. Portmann, I. Voineagu, M. Yazawa, A. Shcheglovitov, A. M. Pasca, B. Cord, T. D. Palmer, S. Chikahisa, S. Nishino, J. A. Bernstein, J. Hallmayer, D. H. Geschwind and R. E. Dolmetsch (2011). "Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy syndrome." Nat Med **17**(12): 1657–1662.

Paulsen, B., S. Velasco, A. J. Kedaigle, M. Pigoni, G. Quadrato, A. J. Deo, X. Adiconis, A. Uzquiano, R. Sartore, S. M. Yang, S. K. Simmons, P. Symvoulidis, K. Kim, K. Tsafou, A. Podury, C. Abbate, A. Tucewicz, S. N. Smith, A. Albanese, L. Barrett, N. E. Sanjana, X. Shi, K. Chung, K. Lage, E. S. Boyden, A. Regev, J. Z. Levin and P. Arlotta (2022). "Autism genes converge on asynchronous development of shared neuron classes." Nature **602**(7896): 268–273.

Penn, A. A., P. A. Riquelme, M. B. Feller and C. J. Shatz (1998). "Competition in retinogeniculate patterning driven by spontaneous activity." Science **279**(5359): 2108–2112.

Perea, G., M. Navarrete and A. Araque (2009). "Tripartite synapses: astrocytes process and control synaptic information." Trends Neurosci **32**(8): 421–431.

Perea, G., M. Sur and A. Araque (2014). "Neuron-glia networks: integral gear of brain function." Front Cell Neurosci **8**: 378.

Pfeiffer, B. E., T. Zang, J. R. Wilkerson, M. Taniguchi, M. A. Maksimova, L. N. Smith, C. W. Cowan and K. M. Huber (2010). "Fragile X mental retardation protein is required for synapse elimination by the activity-dependent transcription factor MEF2." Neuron **66**(2): 191–197.

Pfrieger, F. W. and B. A. Barres (1997). "Synaptic efficacy enhanced by glial cells in vitro." Science **277**(5332): 1684–1687.

Poo, M. M. (2001). "Neurotrophins as synaptic modulators." Nat Rev Neurosci **2**(1): 24–32.

Pyka, M., C. Wetzel, A. Aguado, M. Geissler, H. Hatt and A. Faissner (2011). "Chondroitin sulfate proteoglycans regulate astrocyte-dependent synaptogenesis and modulate synaptic activity in primary embryonic hippocampal neurons." Eur J Neurosci **33**(12): 2187–2202.

Pyronneau, A., Q. He, J. Y. Hwang, M. Porch, A. Contractor and R. S. Zukin (2017). "Aberrant Rac1-cofilin signaling mediates defects in dendritic spines, synaptic function, and sensory perception in fragile X syndrome." Sci Signal **10**(504).

Qiu, Z. and A. Ghosh (2008). "A calcium-dependent switch in a CREST-BRG1 complex regulates activity-dependent gene expression." Neuron **60**(5): 775–787.

Rajgor, D., T. M. Sanderson, M. Amici, G. L. Collingridge and J. G. Hanley (2018). "NMDAR-dependent Argonaute 2 phosphorylation regulates miRNA activity and dendritic spine plasticity." EMBO J **37**(11).

Rangamani, P., M. G. Levy, S. Khan and G. Oster (2016). "Paradoxical signaling regulates structural plasticity in dendritic spines." Proc Natl Acad Sci U S A **113**(36): E5298–5307.

Ratanatharathorn, A., K. C. Koenen, L. B. Chibnik, M. G. Weisskopf, J. W. Rich-Edwards and A. L. Roberts (2021). "Polygenic risk for autism, attention-deficit hyperactivity disorder, schizophrenia, major depressive disorder, and neuroticism is associated with the experience of childhood abuse." Mol Psychiatry **26**(5): 1696–1705.

Redmond, L., A. H. Kashani and A. Ghosh (2002). "Calcium regulation of dendritic growth via CaM kinase IV and CREB-mediated transcription." Neuron **34**(6): 999–1010.

Rial Verde, E. M., J. Lee-Osbourne, P. F. Worley, R. Malinow and H. T. Cline (2006). "Increased expression of the immediate-early gene arc/arg3.1 reduces AMPA receptor-mediated synaptic transmission." Neuron **52**(3): 461–474.

Ribot, J., R. Breton, C. F. Calvo, J. Moulard, P. Ezan, J. Zapata, K. Samama, M. Moreau, A. P. Bemelmans, V. Sabatet, F. Dingli, D. Loew, C. Milleret, P. Billuart, G. Dallerac and N. Rouach (2021). "Astrocytes close the mouse critical period for visual plasticity." Science **373**(6550): 77–81.

Richter, J. D. and E. Klann (2009). "Making synaptic plasticity and memory last: mechanisms of translational regulation." Genes Dev **23**(1): 1–11.

Risher, W. C., S. Patel, I. H. Kim, A. Uezu, S. Bhagat, D. K. Wilton, L. J. Pilaz, J. Singh Alvarado, O. Y. Calhan, D. L. Silver, B. Stevens, N. Calakos, S. H. Soderling and C. Eroglu (2014). "Astrocytes refine cortical connectivity at dendritic spines." Elife **3**.

Rosenthal, J. S., J. Yin, J. Lei, A. Sathyamurthy, J. Short, C. Long, E. Spillman, C. Sheng and Q. Yuan (2021). "Temporal regulation of nicotinic acetylcholine receptor subunits supports central cholinergic synapse development in Drosophila." Proc Natl Acad Sci U S A **118**(23).

Ruthazer, E. S., C. J. Akerman and H. T. Cline (2003). "Control of axon branch dynamics by correlated activity in vivo." Science **301**(5629): 66–70.

Rylaarsdam, L. and A. Guemez-Gamboa (2019). "Genetic Causes and Modifiers of Autism Spectrum Disorder." Front Cell Neurosci **13**: 385.

Sanes, J. R. and J. W. Lichtman (1999). "Development of the vertebrate neuromuscular junction." Annu Rev Neurosci **22**: 389–442.

Sato, M. and M. P. Stryker (2010). "Genomic imprinting of experience-dependent cortical plasticity by the ubiquitin ligase gene Ube3a." Proc Natl Acad Sci U S A **107**(12): 5611–5616.

Scarnati, M. S., R. Kataria, M. Biswas and K. G. Paradiso (2018). "Active presynaptic ribosomes in the mammalian brain, and altered transmitter release after protein synthesis inhibition." Elife **7**.

Schafer, D. P., E. K. Lehrman, A. G. Kautzman, R. Koyama, A. R. Mardinly, R. Yamasaki, R. M. Ransohoff, M. E. Greenberg, B. A. Barres and B. Stevens (2012). "Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner." Neuron **74**(4): 691–705.

Schafer, D. P. and B. Stevens (2013). "Phagocytic glial cells: sculpting synaptic circuits in the developing nervous system." Curr Opin Neurobiol **23**(6): 1034–1040.

Schanzenbacher, C. T., J. D. Langer and E. M. Schuman (2018). "Time- and polarity-dependent proteomic changes associated with homeostatic scaling at central synapses." Elife **7**.

Schmid, D. A., T. Yang, M. Ogier, I. Adams, Y. Mirakhur, Q. Wang, S. M. Massa, F. M. Longo and D. M. Katz (2012). "A TrkB small molecule partial agonist rescues TrkB phosphorylation deficits and improves respiratory function in a mouse model of Rett syndrome." J Neurosci **32**(5): 1803–1810.

Schreiner, B., E. Romanelli, P. Liberski, B. Ingold-Heppner, B. Sobottka-Brillout, T. Hartwig, V. Chandrasekar, H. Johannssen, H. U. Zeilhofer, A. Aguzzi, F. Heppner, M. Kerschensteiner and B. Becher (2015). "Astrocyte Depletion Impairs Redox Homeostasis and Triggers Neuronal Loss in the Adult CNS." Cell Rep **12**(9): 1377–1384.

Shalizi, A., B. Gaudilliere, Z. Yuan, J. Stegmuller, T. Shirogane, Q. Ge, Y. Tan, B. Schulman, J. W. Harper and A. Bonni (2006). "A calcium-regulated MEF2 sumoylation switch controls postsynaptic differentiation." Science **311**(5763): 1012–1017.

Sharma, A., C. A. Hoeffer, Y. Takayasu, T. Miyawaki, S. M. McBride, E. Klann and R. S. Zukin (2010). "Dysregulation of mTOR signaling in fragile X syndrome." J Neurosci **30**(2): 694–702.

Shen, W., J. S. Da Silva, H. He and H. T. Cline (2009). "Type A GABA-receptor-dependent synaptic transmission sculpts dendritic arbor structure in Xenopus tadpoles in vivo." J Neurosci **29**(15): 5032–5043.

Shieh, P. B., S. C. Hu, K. Bobb, T. Timmusk and A. Ghosh (1998). "Identification of a signaling pathway involved in calcium regulation of BDNF expression." Neuron **20**(4): 727–740.

Shou, Y., F. Liang, S. Xu and X. Li (2020). "The Application of Brain Organoids: From Neuronal Development to Neurological Diseases." Front Cell Dev Biol **8**: 579659.

Silva, A. J., J. H. Kogan, P. W. Frankland and S. Kida (1998). "CREB and memory." Annu Rev Neurosci **21**: 127–148.

Simmons, D. A., N. P. Belichenko, T. Yang, C. Condon, M. Monbureau, M. Shamloo, D. Jing, S. M. Massa and F. M. Longo (2013). "A small molecule TrkB ligand reduces motor impairment and neuropathology in R6/2 and BACHD mouse models of Huntington's disease." J Neurosci **33**(48): 18712–18727.

Simms, B. A. and G. W. Zamponi (2014). "Neuronal voltage-gated calcium channels: structure, function, and dysfunction." Neuron **82**(1): 24–45.

Sin, W. C., K. Haas, E. S. Ruthazer and H. T. Cline (2002). "Dendrite growth increased by visual activity requires NMDA receptor and Rho GTPases." Nature **419**(6906): 475–480.

Singh, A. P., K. VijayRaghavan and V. Rodrigues (2010). "Dendritic refinement of an identified neuron in the Drosophila CNS is regulated by neuronal activity and Wnt signaling." Development **137**(8): 1351–1360.

Singh, S. K., J. A. Stogsdill, N. S. Pulimood, H. Dingsdale, Y. H. Kim, L. J. Pilaz, I. H. Kim, A. C. Manhaes, W. S. Rodrigues, Jr., A. Pamukcu, E. Enustun, Z. Ertuz, P. Scheiffele, S. H. Soderling, D. L. Silver, R. R. Ji, A. E. Medina and C. Eroglu (2016). "Astrocytes Assemble Thalamocortical Synapses by Bridging NRX1alpha and NL1 via Hevin." Cell **164**(1–2): 183–196.

Sipe, G. O., R. L. Lowery, M. E. Tremblay, E. A. Kelly, C. E. Lamantia and A. K. Majewska (2016). "Microglial P2Y12 is necessary for synaptic plasticity in mouse visual cortex." Nat Commun **7**: 10905.

Smith, G. B., A. J. Heynen and M. F. Bear (2009). "Bidirectional synaptic mechanisms of ocular dominance plasticity in visual cortex." Philos Trans R Soc Lond B Biol Sci **364**(1515): 357–367.

Smith, S. L. and J. T. Trachtenberg (2007). "Experience-dependent binocular competition in the visual cortex begins at eye opening." Nat Neurosci **10**(3): 370–375.

Smith, W. B., S. R. Starck, R. W. Roberts and E. M. Schuman (2005). "Dopaminergic stimulation of local protein synthesis enhances surface expression of GluR1 and synaptic transmission in hippocampal neurons." Neuron **45**(5): 765–779.

Soderling, S. H., E. S. Guire, S. Kaech, J. White, F. Zhang, K. Schutz, L. K. Langeberg, G. Banker, J. Raber and J. D. Scott (2007). "A WAVE-1 and

WRP signaling complex regulates spine density, synaptic plasticity, and memory." J Neurosci **27**(2): 355–365.

Spiegel, I., A. R. Mardinly, H. W. Gabel, J. E. Bazinet, C. H. Couch, C. P. Tzeng, D. A. Harmin and M. E. Greenberg (2014). "Npas4 regulates excitatory-inhibitory balance within neural circuits through cell-type-specific gene programs." Cell **157**(5): 1216–1229.

Sprecher, S. G., A. Cardona and V. Hartenstein (2011). "The Drosophila larval visual system: high-resolution analysis of a simple visual neuropil." Dev Biol **358**(1): 33–43.

Staiger, J. F., I. Flagmeyer, D. Schubert, K. Zilles, R. Kotter and H. J. Luhmann (2004). "Functional diversity of layer IV spiny neurons in rat somatosensory cortex: quantitative morphology of electrophysiologically characterized and biocytin labeled cells." Cereb Cortex **14**(6): 690–701.

Stankiewicz, T. R. and D. A. Linseman (2014). "Rho family GTPases: key players in neuronal development, neuronal survival, and neurodegeneration." Front Cell Neurosci **8**: 314.

Stellwagen, D. and R. C. Malenka (2006). "Synaptic scaling mediated by glial TNF-alpha." Nature **440**(7087): 1054–1059.

Stellwagen, D. and C. J. Shatz (2002). "An instructive role for retinal waves in the development of retinogeniculate connectivity." Neuron **33**(3): 357–367.

Stevens, B., N. J. Allen, L. E. Vazquez, G. R. Howell, K. S. Christopherson, N. Nouri, K. D. Micheva, A. K. Mehalow, A. D. Huberman, B. Stafford, A. Sher, A. M. Litke, J. D. Lambris, S. J. Smith, S. W. John and B. A. Barres (2007). "The classical complement cascade mediates CNS synapse elimination." Cell **131**(6): 1164–1178.

Stroud, H., M. G. Yang, Y. N. Tsitohay, C. P. Davis, M. A. Sherman, S. Hrvatin, E. Ling and M. E. Greenberg (2020). "An Activity-Mediated Transition in Transcription in Early Postnatal Neurons." Neuron **107**(5): 874–890 e878.

Sun, Y. J., J. S. Espinosa, M. S. Hoseini and M. P. Stryker (2019). "Experience-dependent structural plasticity at pre- and postsynaptic sites of layer 2/3 cells in developing visual cortex." Proc Natl Acad Sci U S A **116**(43): 21812–21820.

Suzuki, S., H. Zhou, J. F. Neumaier and T. A. Pham (2007). "Opposing functions of CREB and MKK1 synergistically regulate the geometry of dendritic spines in visual cortex." J Comp Neurol **503**(5): 605–617.

Takano, T., J. T. Wallace, K. T. Baldwin, A. M. Purkey, A. Uezu, J. L. Courtland, E. J. Soderblom, T. Shimogori, P. F. Maness, C. Eroglu and

S. H. Soderling (2020). "Chemico-genetic discovery of astrocytic control of inhibition in vivo." Nature **588**(7837): 296–302.

Tang, X., J. Kim, L. Zhou, E. Wengert, L. Zhang, Z. Wu, C. Carromeu, A. R. Muotri, M. C. Marchetto, F. H. Gage and G. Chen (2016). "KCC2 rescues functional deficits in human neurons derived from patients with Rett syndrome." Proc Natl Acad Sci U S A **113**(3): 751–756.

Tasdemir-Yilmaz, O. E. and M. R. Freeman (2014). "Astrocytes engage unique molecular programs to engulf pruned neuronal debris from distinct subsets of neurons." Genes Dev **28**(1): 20–33.

Tatavarty, V., M. F. Ifrim, M. Levin, G. Korza, E. Barbarese, J. Yu and J. H. Carson (2012). "Single-molecule imaging of translational output from individual RNA granules in neurons." Mol Biol Cell **23**(5): 918–929.

Tewari, B. P., L. Chaunsali, C. E. Prim and H. Sontheimer (2022). "A glial perspective on the extracellular matrix and perineuronal net remodeling in the central nervous system." Front Cell Neurosci **16**: 1022754.

Tian, N. and D. R. Copenhagen (2003). "Visual stimulation is required for refinement of ON and OFF pathways in postnatal retina." Neuron **39**(1): 85–96.

Tian, Y., I. Voineagu, S. P. Pasca, H. Won, V. Chandran, S. Horvath, R. E. Dolmetsch and D. H. Geschwind (2014). "Alteration in basal and depolarization induced transcriptional network in iPSC derived neurons from Timothy syndrome." Genome Med **6**(10): 75.

Todd, P. K., K. J. Mack and J. S. Malter (2003). "The fragile X mental retardation protein is required for type-I metabotropic glutamate receptor-dependent translation of PSD-95." Proc Natl Acad Sci U S A **100**(24): 14374–14378.

Trachtenberg, J. T., B. E. Chen, G. W. Knott, G. Feng, J. R. Sanes, E. Welker and K. Svoboda (2002). "Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex." Nature **420**(6917): 788–794.

Tremblay, M. E., R. L. Lowery and A. K. Majewska (2010). "Microglial interactions with synapses are modulated by visual experience." PLoS Biol **8**(11): e1000527.

Tripodi, M., J. F. Evers, A. Mauss, M. Bate and M. Landgraf (2008). "Structural homeostasis: compensatory adjustments of dendritic arbor geometry in response to variations of synaptic input." PLoS Biol **6**(10): e260.

Tropea, D., A. K. Majewska, R. Garcia and M. Sur (2010). "Structural dynamics of synapses in vivo correlate with functional changes during experience-dependent plasticity in visual cortex." J Neurosci **30**(33): 11086–11095.

Tropea, D., A. Van Wart and M. Sur (2009). "Molecular mechanisms of experience-dependent plasticity in visual cortex." Philos Trans R Soc Lond B Biol Sci **364**(1515): 341–355.

Tsai, H. H., H. Li, L. C. Fuentealba, A. V. Molofsky, R. Taveira-Marques, H. Zhuang, A. Tenney, A. T. Murnen, S. P. Fancy, F. Merkle, N. Kessaris, A. Alvarez-Buylla, W. D. Richardson and D. H. Rowitch (2012). "Regional astrocyte allocation regulates CNS synaptogenesis and repair." Science **337**(6092): 358–362.

Tsai, N. P., J. R. Wilkerson, W. Guo and K. M. Huber (2017). "FMRP-dependent Mdm2 dephosphorylation is required for MEF2-induced synapse elimination." Hum Mol Genet **26**(2): 293–304.

Tu, S., M. W. Akhtar, R. M. Escorihuela, A. Amador-Arjona, V. Swarup, J. Parker, J. D. Zaremba, T. Holland, N. Bansal, D. R. Holohan, K. Lopez, S. D. Ryan, S. F. Chan, L. Yan, X. Zhang, X. Huang, A. Sultan, S. R. McKercher, R. Ambasudhan, H. Xu, Y. Wang, D. H. Geschwind, A. J. Roberts, A. V. Terskikh, R. A. Rissman, E. Masliah, S. A. Lipton and N. Nakanishi (2017). "NitroSynapsin therapy for a mouse MEF2C haploinsufficiency model of human autism." Nat Commun **8**(1): 1488.

Tyler, W. J., M. Alonso, C. R. Bramham and L. D. Pozzo-Miller (2002). "From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning." Learn Mem **9**(5): 224–237.

Udagawa, T., S. A. Swanger, K. Takeuchi, J. H. Kim, V. Nalavadi, J. Shin, L. J. Lorenz, R. S. Zukin, G. J. Bassell and J. D. Richter (2012). "Bidirectional control of mRNA translation and synaptic plasticity by the cytoplasmic polyadenylation complex." Mol Cell **47**(2): 253–266.

Van der Loos, H. and T. A. Woolsey (1973). "Somatosensory cortex: structural alterations following early injury to sense organs." Science **179**(4071): 395–398.

Vaughn, J. E. (1989). "Fine structure of synaptogenesis in the vertebrate central nervous system." Synapse **3**(3): 255–285.

Vaughn, J. E., R. P. Barber and T. J. Sims (1988). "Dendritic development and preferential growth into synaptogenic fields: a quantitative study of Golgi-impregnated spinal motor neurons." Synapse **2**(1): 69–78.

Volkmar, F. R. and W. T. Greenough (1972). "Rearing complexity affects branching of dendrites in the visual cortex of the rat." Science **176**(4042): 1445–1447.

Wang, G. Y., L. C. Liets and L. M. Chalupa (2001). "Unique functional properties of on and off pathways in the developing mammalian retina." J Neurosci **21**(12): 4310–4317.

Wang, H., S. A. Chan, M. Ogier, D. Hellard, Q. Wang, C. Smith and D. M. Katz (2006). "Dysregulation of brain-derived neurotrophic factor expression and neurosecretory function in Mecp2 null mice." J Neurosci **26**(42): 10911–10915.

Watson, J. R., D. Owen and H. R. Mott (2017). "Cdc42 in actin dynamics: An ordered pathway governed by complex equilibria and directional effector handover." Small GTPases **8**(4): 237–244.

Weeber, E. J., Y. H. Jiang, Y. Elgersma, A. W. Varga, Y. Carrasquillo, S. E. Brown, J. M. Christian, B. Mirnikjoo, A. Silva, A. L. Beaudet and J. D. Sweatt (2003). "Derangements of hippocampal calcium/calmodulin-dependent protein kinase II in a mouse model for Angelman mental retardation syndrome." J Neurosci **23**(7): 2634–2644.

Weinhard, L., G. di Bartolomei, G. Bolasco, P. Machado, N. L. Schieber, U. Neniskyte, M. Exiga, A. Vadisiute, A. Raggioli, A. Schertel, Y. Schwab and C. T. Gross (2018). "Microglia remodel synapses by presynaptic trogocytosis and spine head filopodia induction." Nat Commun **9**(1): 1228.

Weller, W. L. and J. I. Johnson (1975). "Barrels in cerebral cortex altered by receptor disruption in newborn, but not in five-day-old mice (Cricetidoe and Muridae)." Brain Res **83**(3): 504–508.

West, A. E. and M. E. Greenberg (2011). "Neuronal activity-regulated gene transcription in synapse development and cognitive function." Cold Spring Harb Perspect Biol **3**(6).

Whitford, K. L., P. Dijkhuizen, F. Polleux and A. Ghosh (2002). "Molecular control of cortical dendrite development." Annu Rev Neurosci **25**: 127–149.

Wiesel, T. N. and D. H. Hubel (1963). "Effects of Visual Deprivation on Morphology and Physiology of Cells in the Cats Lateral Geniculate Body." J Neurophysiol **26**: 978–993.

Wiesel, T. N. and D. H. Hubel (1963). "Single-Cell Responses in Striate Cortex of Kittens Deprived of Vision in One Eye." J Neurophysiol **26**: 1003–1017.

Withers, G. S. and W. T. Greenough (1989). "Reach training selectively alters dendritic branching in subpopulations of layer II-III pyramids in rat motor-somatosensory forelimb cortex." Neuropsychologia **27**(1): 61–69.

Wong, R. O. and A. Ghosh (2002). "Activity-dependent regulation of dendritic growth and patterning." Nat Rev Neurosci **3**(10): 803–812.

Woolsey, T. A., M. L. Dierker and D. F. Wann (1975). "Mouse SmI cortex: qualitative and quantitative classification of golgi-impregnated barrel neurons." Proc Natl Acad Sci U S A **72**(6): 2165–2169.

Wu, B., C. Eliscovich, Y. J. Yoon and R. H. Singer (2016). "Translation dynamics of single mRNAs in live cells and neurons." Science **352**(6292): 1430–1435.

Wu, G., R. Malinow and H. T. Cline (1996). "Maturation of a central glutamatergic synapse." Science **274**(5289): 972–976.

Wu, G. Y. and H. T. Cline (1998). "Stabilization of dendritic arbor structure in vivo by CaMKII." Science **279**(5348): 222–226.

Wu, J. I., J. Lessard, I. A. Olave, Z. Qiu, A. Ghosh, I. A. Graef and G. R. Crabtree (2007). "Regulation of dendritic development by neuron-specific chromatin remodeling complexes." Neuron **56**(1): 94–108.

Xavier, A. L., J. R. Menezes, S. A. Goldman and M. Nedergaard (2014). "Fine-tuning the central nervous system: microglial modelling of cells and synapses." Philos Trans R Soc Lond B Biol Sci **369**(1654): 20130593.

Xie, Z., M. E. Cahill and P. Penzes (2010). "Kalirin loss results in cortical morphological alterations." Mol Cell Neurosci **43**(1): 81–89.

Xie, Z., D. P. Srivastava, H. Photowala, L. Kai, M. E. Cahill, K. M. Woolfrey, C. Y. Shum, D. J. Surmeier and P. Penzes (2007). "Kalirin-7 controls activity-dependent structural and functional plasticity of dendritic spines." Neuron **56**(4): 640–656.

Xu, H., A. S. Khakhalin, A. V. Nurmikko and C. D. Aizenman (2011). "Visual experience-dependent maturation of correlated neuronal activity patterns in a developing visual system." J Neurosci **31**(22): 8025–8036.

Xu, X., E. C. Miller and L. Pozzo-Miller (2014). "Dendritic spine dysgenesis in Rett syndrome." Front Neuroanat **8**: 97.

Yan, J., M. W. Porch, B. Court-Vazquez, M. V. L. Bennett and R. S. Zukin (2018). "Activation of autophagy rescues synaptic and cognitive deficits in fragile X mice." Proc Natl Acad Sci U S A **115**(41): E9707–E9716.

Yang, G., F. Pan and W. B. Gan (2009). "Stably maintained dendritic spines are associated with lifelong memories." Nature **462**(7275): 920–924.

Yap, E. L. and M. E. Greenberg (2018). "Activity-Regulated Transcription: Bridging the Gap between Neural Activity and Behavior." Neuron **100**(2): 330–348.

Yashiro, K., T. T. Riday, K. H. Condon, A. C. Roberts, D. R. Bernardo, R. Prakash, R. J. Weinberg, M. D. Ehlers and B. D. Philpot (2009). "Ube3a is required for experience-dependent maturation of the neocortex." Nat Neurosci **12**(6): 777–783.

Yi, F., T. Danko, S. C. Botelho, C. Patzke, C. Pak, M. Wernig and T. C. Sudhof (2016). "Autism-associated SHANK3 haploinsufficiency causes Ih channelopathy in human neurons." Science **352**(6286): aaf2669.

Yin, J., M. Gibbs, C. Long, J. Rosenthal, H. S. Kim, A. Kim, C. Sheng, P. Ding, U. Javed and Q. Yuan (2018). "Transcriptional Regulation of Lipophorin Receptors Supports Neuronal Adaptation to Chronic Elevations of Activity." Cell Rep **25**(5): 1181–1192 e1184.

Yin, J., E. Spillman, E. S. Cheng, J. Short, Y. Chen, J. Lei, M. Gibbs, J. S. Rosenthal, C. Sheng, Y. X. Chen, K. Veerasammy, T. Choetso, R. Abzalimov, B. Wang, C. Han, Y. He and Q. Yuan (2021). "Brain-specific lipoprotein receptors interact with astrocyte derived apolipoprotein and mediate neuron-glia lipid shuttling." Nat Commun **12**(1): 2408.

Yoon, Y. J., B. Wu, A. R. Buxbaum, S. Das, A. Tsai, B. P. English, J. B. Grimm, L. D. Lavis and R. H. Singer (2016). "Glutamate-induced RNA localization and translation in neurons." Proc Natl Acad Sci U S A **113**(44): E6877–E6886.

Younts, T. J., H. R. Monday, B. Dudok, M. E. Klein, B. A. Jordan, I. Katona and P. E. Castillo (2016). "Presynaptic Protein Synthesis Is Required for Long-Term Plasticity of GABA Release." Neuron **92**(2): 479–492.

Yuan, Q., Y. Xiang, Z. Yan, C. Han, L. Y. Jan and Y. N. Jan (2011). "Light-induced structural and functional plasticity in Drosophila larval visual system." Science **333**(6048): 1458–1462.

Zalfa, F., B. Eleuteri, K. S. Dickson, V. Mercaldo, S. De Rubeis, A. di Penta, E. Tabolacci, P. Chiurazzi, G. Neri, S. G. Grant and C. Bagni (2007). "A new function for the fragile X mental retardation protein in regulation of PSD-95 mRNA stability." Nat Neurosci **10**(5): 578–587.

Zhang, G., Z. Gao, S. Guan, Y. Zhu and J. H. Wang (2013). "Upregulation of excitatory neurons and downregulation of inhibitory neurons in barrel cortex are associated with loss of whisker inputs." Mol Brain **6**: 2.

Zhou, Z., E. J. Hong, S. Cohen, W. N. Zhao, H. Y. Ho, L. Schmidt, W. G. Chen, Y. Lin, E. Savner, E. C. Griffith, L. Hu, J. A. Steen, C. J. Weitz and M. E. Greenberg (2006). "Brain-specific phosphorylation of MeCP2 regulates activity-dependent Bdnf transcription, dendritic growth, and spine maturation." Neuron **52**(2): 255–269.

Zuo, Y., G. Yang, E. Kwon and W. B. Gan (2005). "Long-term sensory deprivation prevents dendritic spine loss in primary somatosensory cortex." Nature **436**(7048): 261–265.