Viewpoints

Activity Shapes Neural Circuit Form and Function: A Historical Perspective

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The brilliant and often prescient hypotheses of Ramon y Cajal have proven foundational for modern neuroscience, but his statement that “In adult centers the nerve paths are something fixed, ended, immutable . . .” is an exception that did not stand the test of empirical study. Mechanisms of cellular and circuit-level plasticity continue to shape and reshape many regions of the adult nervous system long after the neurodevelopmental period. Initially focused on neurons alone, the field has followed a meteoric trajectory in understanding of activity-regulated neurodevelopment and ongoing neuroplasticity with an arc toward appreciating neuron–glial interactions and the role that each neural cell type plays in shaping adaptable neural circuitry. In this review, as part of a celebration of the 50th anniversary of Society for Neuroscience, we provide a historical perspective, following this arc of inquiry from neuronal to neuron–glial mechanisms by which activity and experience modulate circuit structure and function. The scope of this consideration is broad, and it will not be possible to cover the wealth of knowledge about all aspects of activity-dependent circuit development and plasticity in depth.

Introduction

Neuronal activity, the electrical activity of neurons, governs neural circuit formation during prenatal/perinatal neurodevelopment and neural circuit function/plasticity during adulthood (LoTurco et al., 1995; Leclerc et al., 2001; Luk et al., 2003; Deisseroth et al., 2004; Luk and Sadikot, 2004; Tozuka et al., 2005; Song et al., 2013; Paez-Gonzalez et al., 2014). Establishment of synaptic connectivity begins as a diffuse process that is refined in an activity-dependent manner during development (for review, see Shatz, 1990; Katz and Shatz, 1996). Ongoing adaptive changes to dynamic circuit function are then mediated throughout life by plasticity in the strength and number of individual synapses, the establishment and elimination of synaptic connections, and alterations to spike timing. Over the past several decades of research, it has become increasingly clear that mechanisms of neuronal connectivity and circuit function require the cooperative activities of neurons together with each class of glial cells: astrocytes, oligodendrocytes, and microglia. Herein, we review the role of neuronal activity in neural circuit assembly and function throughout neurodevelopment and adulthood, with additional focus on roles of glial cells in this process.

Principles of activity-dependent circuit development

Spontaneous neuronal activity in early neurodevelopment

The critical role of neuronal activity in neurodevelopment was first appreciated in the beautifully patterned visual system, with

highly ordered synaptic connections. The initial neuron migration, differentiation, and synaptic connections of the visual system are guided by molecular cues. These processes lead to excessive neuronal arborization and synaptic connections that are refined by spontaneous and then visually evoked activity-dependent mechanisms. Herein, we define activity-dependent as the dependence on neuronal activity. Retinal ganglion cells (RGCs) from the retina project to the lateral geniculate nucleus (LGN) in the visual thalamus, and from LGN to layer 4 of the primary visual cortex (Fig. 1). Many early studies of spontaneous neuronal activity focused on segregation of axonal projections from the eyes, a process that is initiated before birth when visual experience-dependent neuronal activity is absent. During the prenatal period, the input from two eyes is segregated into distinct layers in the LGN by remodeling the axon branches and synaptic connections of RGCs (Sretavan and Shatz, 1984, 1986; Campbell and Shatz, 1992). Similarly, in the visual cortex, neurons that respond preferentially to one eye are segregated from neurons that respond preferentially to the other eye in structures called ocular dominance columns, a phenomenon discovered by Hubel and Wiesel (1969) around the time of the first Society for Neuroscience (SfN) conference. Contemporaneously, Hubel and Wiesel (1969) reported another organized visual cortex structure, orientation columns that respond to a specific line orientation. Both eye segregation and the formation of orientation columns happen before vision-induced neuronal activity is possible (Horton and Hocking, 1996b), indicating the existence of experience-independent mechanisms for early circuit assembly.

Even before eye opening, when photoreceptors cannot transmit information about incoming light, RGCs (the output neurons of the retina) exhibit spontaneous activity that drives neurodevelopment (Galli and Maffei, 1988; Maffei and Galli-Resta, 1990; Meister et al., 1991; Wong et al., 1993). Spontaneous activity is the firing of action potentials without external stimuli

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Figure 1. Illustration of segregation of projections from the eye. The retinal input from two eyes (blue represents left; red represents right) is segregated into distinct layers in the LGN by remodeling the axon branches and synaptic connections of RGCs. In the layer IVC of the primary visual cortex (V1), LGN neurons that respond preferentially to one eye segregate from neurons that respond preferentially to the other eye in structures called ocular dominance columns. Illustration by Sigrid Knemeyer.

and was first recorded in retinal neurons in rat fetuses by Galli and Maffei (1988). Discovery of retinal spontaneous activity was not surprising because its presence in the embryonic retina has long been suspected. In 1990, retinal waves, the synchronized spontaneous activity of neighboring RGCs, were recorded by the same group (Maffei and Galli-Resta, 1990). Retinal waves occur in gap junction-coupled clusters formed by immature retinal neurons that exhibit synchronized membrane depolarization and consequent intracellular calcium waves (Wong et al., 1995; Feller et al., 1996; Pearson et al., 2004).

Spontaneous neuronal activity is required for development of appropriate connectivity. In prenatal cats, infusion of tetrodotoxin (TTX) (a neurotoxin that blocks voltage-gated sodium channels and prevents action potentials) into RGC axons prevents normal arborization and segregation of RGC terminal synapses in the LGN (Shatz and Stryker, 1988; Sretavan et al., 1988). Spontaneous activity similarly shapes development of the visual cortex. Infusion of TTX into the thalamocortical visual pathway before eye opening results in abnormal thalamic axon arborization in the visual cortex of cats (Herrmann and Shatz, 1995), and inhibiting early spontaneous retinal activity leads to abnormal development of ocular dominance columns in visual cortex of ferrets (Huberman et al., 2006).

In the 1950s–1960s, Hubel and Wiesel (1959, 1962) also described the receptive fields of single cells in the visual cortex. Consistent with the findings that most visual pathway circuits are established before visual experience, the receptive fields of cortical

cells responding to patterned light are similar in kittens with no prior experience and those in adult experienced cats (Hubel and Wiesel, 1963), as is the selectivity for stimulus orientation in kitten visual cortex (Sherk and Stryker, 1976), underscoring the role of spontaneous activity during early neurodevelopment.

Such spontaneous activity has been demonstrated in other developing brain regions, such as the auditory pathway (Moore and Kitzes, 1985; Kitzes et al., 1995; Russell and Moore, 1995), hippocampus (Ben-Ari et al., 1989; Garaschuk et al., 1998), cerebellum (Watt et al., 2009), and somatosensory cortex (Anton-Bolano et al., 2019) in many mammalian species (Anderson et al., 1985; Yuste et al., 1992; Horton and Hocking, 1996a; Lamblin et al., 1999; Khazipov et al., 2001, 2004; Leinekugel et al., 2002; Moreno-Juan et al., 2017). In the auditory system, spontaneous activity of auditory neurons is present before the onset of hearing and may contribute to circuit development (for review, see Wang and Bergles, 2015). During this period, inner hair cells generate spontaneous periodic bursts of action potentials, and cochlear ablation/deafferentation results in abnormal synaptic connections in the developing auditory pathway (Moore and Kitzes, 1985; Kitzes et al., 1995; Russell and Moore, 1995). In the immature somatosensory cortex, a recent study demonstrates that spontaneous activity from prenatal thalamic neurons drives the development of functional columnar structures (Anton-Bolano et al., 2019), furthering the concept that spontaneous neuronal activity is required for early neuronal circuit assembly throughout the CNS.

Figure 2. Evolving view of circuit establishment and plasticity. **A**, Neural circuit establishment involves synaptogenesis between appropriate presynaptic (red) and postsynaptic (orange) neurons and subsequent refinement of synaptic connectivity. **B**, Astrocytes (green) promote synaptogenesis and modulate synaptic function. Microglia (purple) prune less active synapses, and oligodendrocytes, generated by OPCs (blue), ensheath axons to modulate spike timing and overall circuit dynamics. Together, the major classes of glia promote, support, and alter neural circuit function. Circuit activity influences each process. Illustration by Sigrid Knemeyer.

Experience-dependent neuronal activity in neurodevelopment

Spontaneous activity is critical for early neurodevelopment; however, it is not sufficient for mature circuit formation. Around the time of the first SfN meeting, seminal work began to reveal that experience is critical for circuit refinement (Wiesel and Hubel, 1963a,b). For example, visual experience is required for refinement of synaptic connections at thalamic axon terminals that form the ocular dominance columns in the visual cortex (Hubel et al., 1977; LeVay et al., 1980). Monocular deprivation or strabismus after eye opening leads to a stark increase in neuronal representation of the normal eye in the visual cortex (Hubel and Wiesel, 1965, 1970; Hubel et al., 1977). This shift in ocular dominance induced by monocular deprivation is prevented by intracortical infusion of TTX (Reiter et al., 1986).

Importantly, a critical period exists during which experience-dependent neuronal activity regulates visual system neurodevelopment (Wiesel and Hubel, 1963a,b; Hubel and Wiesel, 1970; Daw et al., 1992). For example, monocular deprivation in kittens during the critical period results in LGN atrophy and diminished cortical response to the deprived eye. However, no such changes are observed in kittens that underwent monocular deprivation outside of the critical period or in adult cats that underwent monocular deprivation, illustrating a critical period for visual experience-dependent development (Wiesel and Hubel, 1963a,b). Together, these studies demonstrated that experience-dependent neuronal activity modulates visual cortex development.

Astrocytes in circuit establishment during neurodevelopment

Understandably, studies of circuit establishment and function were initially focused on neurons. In the 1990s, attention was drawn to glia, which include astrocytes, microglia, and oligodendrocytes in the central nervous system (CNS). Originally thought of as “glue” and as interstitial cells simply playing a supporting role to neurons, glial cells are now understood to be indispensable

for proper neurodevelopment and plasticity (the ability of neural cells and circuit function to change continuously) (Fig. 2). The focus was initially on astrocytes, star-shaped glial cells with extensive processes. In the 1980s–1990s, a role for glial cells in sensing neuronal activity was proposed based on the discoveries that glial cells express many neurotransmitter receptors (Pearce et al., 1988; Gallo and Bertolotto, 1990; Barres, 1991). In 1990, attention was drawn to the observation that neurotransmitters, such as glutamate, can elevate intracellular calcium concentration ($[Ca^{2+}]_i$) of astrocytes (Cornell-Bell et al., 1990; Cornell-Bell and Finkbeiner, 1991). Several groups later observed activity-induced $[Ca^{2+}]_i$ elevation in astrocytes using hippocampal slice preparations (Dani et al., 1992; Porter and McCarthy, 1996; Pasti et al., 1997). Kriegler and Chiu (1993) and demonstrated an activity-dependent neuron–glia interaction during which activity of axons triggers $[Ca^{2+}]_i$ elevation in nonsynaptically associated glial cells.

A massive wave of synaptogenesis occurs in early postnatal life, followed by a period of synapse elimination and circuit refinement, and the onset of this synaptogenic developmental period coincides with the early postnatal maturation of astrocytes (for review, see Chung et al., 2015). Advances in neuronal cell culture techniques enabled direct evaluations of the role astrocytes play in synaptogenesis. In RGC cultures (Meyer-Franke et al., 1995), RGC neurites establish contact with each other, but few synapses form. Addition of astrocytes or astrocyte-conditioned medium results in a massive increase in RGC synapse formation *in vitro*, indicating that astrocytes secrete synaptogenic factors required for appropriate connectivity (Mauch et al., 2001; Nägler et al., 2001; Ullian et al., 2001; Christopherson et al., 2005; for review, see Ullian et al., 2004). Subsequent work showed that astrocytes promote the formation of both excitatory and inhibitory synapses in various organisms (Elmariyah et al., 2005;

Colón-Ramos et al., 2007; Hughes et al., 2010; Muthukumar et al., 2014). Concordantly, glial ablation during synaptogenesis in *Drosophila* results in 50% reduction in synapse number (Muthukumar et al., 2014). Furthermore, a large number of astrocytic genes are regulated by synaptic activity (Hasel et al., 2017). For example, the activity of GABAergic neurons is required for increased expression of astrocytic GABA transporters during *Drosophila* synaptogenesis (Muthukumar et al., 2014). Astrocytes in turn mediate synaptogenesis via both secreted [e.g., hevin and secreted protein acidic and rich in cysteine (SPARC)] and membrane-bound factors (e.g., protocadherin and ephrin) (for review, see Eroglu, 2009; Risher and Eroglu, 2012). Despite these important findings, the role of neuronal activity in astrocyte-mediated circuit assembly remains to be determined.

Microglia and astrocytes in pruning synapses for circuit precision

As Hubel and Weisel demonstrated 50 years ago, circuits, once established, require refinement for precise connectivity. Elimination of extraneous synapses (synaptic pruning) is critical for proper circuit function. Synaptic pruning is regulated by neuronal activity and experience (for review, see Katz and Shatz, 1996; Hua and Smith, 2004). Microglia, brain resident immune cells, are major players in this activity-dependent synaptic pruning (for review, see Michell-Robinson et al., 2015; Schafer and Stevens, 2015; Salter and Stevens, 2017; Li and Barres, 2018). Microglia, which comprise 5%–15% of CNS cells, colonize the brain during early CNS development (Ginhoux et al., 2010). Microglia dynamically interact with synapses and prune immature/inappropriate synapses (Fig. 2) (for review, see Wake et al., 2013; Schafer and Stevens, 2015).

The role of microglia as a major player in synapse pruning was first identified in 2007, when Beth Stevens and Ben Barres revealed the microglial complement immune pathway as the molecular mediator of synapse elimination (for review, see Schafer and Stevens, 2010; Stephan et al., 2012). This area of research was primarily conducted in the visual system because of the beautifully organized eye-segregation process, which occurs during an active period for synaptic pruning. In the developing LGN, synaptic input (RGC axons) from both eyes initially forms overlapping synaptic fields, which are later pruned to eye-specific regions (Rakic, 1976; Hubel et al., 1977; LeVay et al., 1978; Chen and Regehr, 2000; Hooks and Chen, 2006; for review, see Huberman, 2007). Components of the classical complement immune pathway, such as C1q and its downstream effector C3, are expressed at synapses in developing, but not mature, LGN (Stevens et al., 2007; Schafer et al., 2012). During the developmental period in which active synaptic pruning occurs, microglia are the only cell type that expresses complement receptor 3 (CR3, CD11b) (Akiyama and McGeer, 1990), which mediates microglial engulfment of RGC axon terminals in the LGN (Schafer et al., 2012). Mice lacking C1q, C3, or CR3 exhibit similar phenotypes in which RGC axon terminals fail to form eye-specific regions in LGN, indicating defective synaptic pruning (Stevens et al., 2007; Schafer et al., 2012). Consistent with this, microglial engulfment of RGC presynaptic terminals is decreased and synaptic connectivity is compromised in CR3/C3 knockout (KO) mice (Schafer et al., 2012).

Microglia-mediated synaptic pruning is regulated by activity. In the visual system, reducing neuronal activity through light deprivation increases the number of microglia positioned at dendritic spines that eventually diminish in size. This implies a role for microglia in eliminating synapses that are less active (Tremblay et al., 2010). Consistent with the regulatory role of neuronal activity in microglia-mediated synaptic pruning, reintroducing

dark-reared mice to light is sufficient to reverse the effect (Tremblay et al., 2010). Schafer et al. (2012, 2014) later established an *in vivo* engulfment assay and directly demonstrated the relationship between neuronal activity and microglial engulfment of synapses. During eye segregation in the LGN, silent (TTX-treated) RGC terminals are more likely to be engulfed by microglia, relative to normal (vehicle-treated) RGC terminals. In contrast, activated (forskolin-treated) RGC terminals are less likely to be eliminated by microglia (Schafer et al., 2012). Together, mounting evidence indicates that microglia are indispensable for proper synaptic pruning/refinement.

Like microglia, astrocytes participate in synaptic pruning by phagocytosis of unwanted synapses, in this case via the MERTK/MEGF10 pathway (Chung et al., 2013). Studies in the visual system demonstrate that astrocytes also regulate synaptic pruning indirectly by secreting transforming growth factor (TGF)- β , which stimulates neuronal expression of C1q and consequently triggers microglial phagocytosis (Rakic, 1976; Stevens et al., 2007; Schafer et al., 2012; Bialas and Stevens, 2013). Thus, synaptic pruning is mediated by an interplay among astrocytes, neurons, and microglia. Future studies are needed to determine whether and how neuronal activity contributes to astrocyte-mediated synaptic pruning.

Oligodendrocytes in developmental myelination

Neuronal activity also has profound effects on oligodendrocyte lineage cells, which form myelin and thus strongly influence the timing of action potential conduction and neural circuit dynamics, as well as providing metabolic support to axons (Saab et al., 2013). Myelinating oligodendrocytes are generated by oligodendrocyte precursor cells (OPCs), a unipotent stem cell population that self-renews to maintain a homeostatic precursor population density and generates new oligodendrocytes throughout life (Fig. 2) (Tripathi et al., 2017; Hill et al., 2018; Hughes et al., 2018).

Developmental myelination in the CNS begins perinatally and spans nearly three decades of human life (Yakovlev and Lecours, 1967; Lebel et al., 2012), allowing ample opportunity for experience to modulate developmental myelination. In the 1940s, formation of myelin with “ideal” geometric proportions was proposed to promote maximal action potential speed for a given axonal diameter (Huxley and Stampfli, 1949). At that time, it was unclear to what extent developmental myelination may be influenced by experience.

The idea that neurons may regulate the degree to which their axons are myelinated again emerged from early observations in the visual system. In the 1960s, Gyllenstein and Malmfors (1963) discovered that dark rearing, which decreases retinal activity, delays myelination of RGC axons in the optic nerve; and conversely, premature eye opening results in accelerated myelination in the optic nerve (Tauber et al., 1980). It is now clear that, during development, axonal activity influences selection of axons for ensheathment in a manner dependent on vesicular release (Hines et al., 2015; Mensch et al., 2015). However, the idea that neuronal activity can influence myelination was brought into question by the observations that myelination can also proceed in a neuronal activity-independent manner, evidenced by myelination of fixed axons or inert nanofibers of appropriate diameter *in vitro* (Bullock and Rome, 1990; Lee et al., 2012) and of silenced optic nerve axons *in vivo* (Mayoral et al., 2018). These findings led to a two-phase model of myelination: intrinsic myelination occurs independent of activity, and adaptive myelination that is regulated by neuronal activity/experience (Bechler et al., 2015). This is discussed in more detail below.

Activity-dependent plasticity of form and function

Neuronal activity in synaptic plasticity and circuit function

In the adult brain, the number, shape, and strength of synapses change over time in response to neuronal activity (for review, see Katz and Shatz, 1996; Citri and Malenka, 2008; Ho et al., 2011). In general, this activity-dependent synaptic plasticity is hypothesized to be a central cellular correlate of learning and memory. The rules and mechanisms governing these changes are diverse and depend upon the type of synapse, type of presynaptic and postsynaptic cell, relative timing of spikes or depolarization in these cells, brain region, developmental stage, and recent activity history, among many other factors. Synaptic function can be modulated by vesicle release probability and quantal composition on the presynaptic side, and by trafficking of neurotransmitter receptors to and from the postsynaptic membrane (Malenka and Bear, 2004). For example, neuronal activity during experience, such as motor skill learning, sensory experience, and fear conditioning, can alter synaptic receptor composition and synapse numbers in behavior-relevant circuits (Trachtenberg et al., 2002; Holtmaat et al., 2006; De Roo et al., 2008; Xu et al., 2009; Yang et al., 2009; Lai et al., 2012). In addition, activity can change the morphology of postsynaptic dendritic spines, which can be associated with functional changes to the synapses (Van Harreveld and Fikova, 1975; Engert and Bonhoeffer, 1999; Maletic-Savatic et al., 1999; Grutzendler et al., 2002; Trachtenberg et al., 2002). For example, repetitive activation of hippocampal CA1 pyramidal neurons may lead to sustained enlargement of originally small dendritic spines, and this spine enlargement can be associated with increased AMPA receptor (AMPA)-mediated currents (Matsuzaki et al., 2004).

Two important forms of activity-dependent synaptic modification are long-term potentiation (LTP) the persistent enhancement of synaptic strength, and long-term depression (LTD), the persistent reduction of synaptic strength (for review, see Malenka and Bear, 2004). In 1949, Donald Hebb proposed a theory for synaptic plasticity (Hebb's rule), according to which the repeated successful activation of one neuron (B) by another (A) will increase the efficacy (i.e., the strength) of the synapse connecting A to B (Hebb, 1949). Hebb's rule was confirmed by the discovery of LTP in the late 1960s (Lømo, 1966; Bliss and Lømo, 1970; Bliss and Gardner-Medwin, 1973), around the time of the first SfN meeting, although not all plastic synapses follow this rule. In the early 1990s, a debate over whether LTP is presynaptic or postsynaptic spurred intense research into the underlying mechanisms of LTP. Although some synapse types express presynaptic LTP and others express postsynaptic LTP, one question in the debate was whether LTP at the hippocampal CA3/CA1 synapse is due to increased presynaptic neurotransmitter release probability or to increased/altered postsynaptic receptors. Addressing this controversy inspired development and application of new tools, such as 2-photon glutamate uncaging (Matsuzaki et al., 2004) and optical quantal analysis allowing for single-synapse resolution (Emptage et al., 2003; Enoki et al., 2009). These efforts resulted in profound new knowledge about synaptic biology, such as regulation of postsynaptic receptor trafficking by neuronal activity (for review, see Malenka and Nicoll, 1999; Malinow and Malenka, 2002; Brecht and Nicoll, 2003).

Many forms of LTP and LTD exist depending on the type of synapse, developmental stages, and postsynaptic receptors involved. Here, we summarize key steps in hippocampal CA3/CA1 LTP and LTD (for review in various forms and mechanisms of LTP and LDP, see Malinow and Malenka, 2002; Malenka and Bear, 2004). Hippocampal LTP consists of two main phases: early

(E) and late (L) LTP. Generally speaking, E-LTP can be induced by high-frequency stimulation of a synapse, which triggers calcium influx through neuronal NMDA receptors (NMDARs) or L-type voltage-gated calcium channels (VGCCs) (Lynch et al., 1983; Malenka et al., 1988, 1992; Grover and Teyler, 1990). This rise in calcium levels within dendritic spines leads to persistent activation of Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC) which phosphorylate AMPARs to increase channel activity and/or postsynaptic trafficking (Barria et al., 1997; Benke et al., 1998; Deisseroth et al., 1998; Strack and Colbran, 1998; Lee et al., 2003). Unlike E-LTP, which is independent of protein synthesis, L-LTP involves transcriptional (Frey et al., 1996) and translational (Frey et al., 1988) changes (for review, see Abraham and Williams, 2003; Pittenger and Kandel, 2003; Lynch, 2004). Activation of the transcription factor cAMP response element-binding protein (CREB) is critical for the transcriptional changes (Dash et al., 1990; Bourtschuladze et al., 1994; Yin et al., 1994; Deisseroth et al., 1998). The MAPK/ERK and mTOR pathways are important in translational control during L-LTP (Casadio et al., 1999; Tang et al., 2002; Kelleher et al., 2004; Kovács et al., 2007).

In 1992, Bear and Malenka demonstrated that low-frequency stimulation induces LTD in hippocampal slices (Dudek and Bear, 1992; Mulkey and Malenka, 1992). As for LTP, this form of LTD involves NMDAR activation and increases in postsynaptic calcium concentration; however, the downstream pathways elicited are distinct. The lower-intensity stimulation that induces LTD leads to moderate calcium influx and downstream activation of the calcineurin/inhibitor-1/protein phosphatases cascade (Mulkey and Malenka, 1992; Mulkey et al., 1993, 1994), dephosphorylation of AMPARs (Lee et al., 1998, 2000, 2003) and endocytosis of AMPARs from the postsynaptic density (Lüthi et al., 1999; Beattie et al., 2000; Ehlers, 2000; Lin et al., 2000; Man et al., 2000; Lee et al., 2002; for review, see Carroll et al., 2001; Brecht and Nicoll, 2003).

A wealth of work over the past two decades has advanced our understanding of activity-dependent synaptic plasticity, LTP, LTD, and the roles of these processes in learning, memory, and neurological diseases. We suggest interested readers see excellent reviews on this important topic (Turriano, 1999; Lamprecht and LeDoux, 2004; Malenka and Bear, 2004; Sutton and Schuman, 2006; Blundon and Zakharenko, 2008; Bourne and Harris, 2008; Alberini, 2009; Makino and Malinow, 2009; Bagetta et al., 2010; Collingridge et al., 2010; Kasai et al., 2010; Caroni et al., 2012; Pozueta et al., 2013).

Astrocytes in modulating circuit function

Astrocytes modulate synaptic function, influencing both presynaptic and postsynaptic mechanisms (for review, see Allen and Eroglu, 2017). In 1998, Kang et al., demonstrated that the activity of hippocampal interneurons increases the $[\text{Ca}^{2+}]_i$ in surrounding astrocytes, which in turn potentiates inhibitory transmission (Kang et al., 1998). The next year, Ventura and Harris (1999) described the fine structure of synapses and revealed their "tripartite" nature, specifically, that they are composed of not only a presynaptic axon and postsynaptic dendrite, but also a perisynaptic astrocyte process (PAP) (for review, see Araque et al., 1999). PAPs assist fast clearance of extracellular neurotransmitters and stabilize synaptic connections. PAPs are highly motile; and in response to neuronal activity, individual PAPs exhibit localized morphological changes (for review, see Theodosis et al., 2008), and altered neurotransmitter transporter expression (Genoud et al., 2006; Haber et al., 2006; Bernardinelli et al., 2014). For exam-

ple, activation of synaptic terminals *in situ* enhances the motility of PAPs within synaptic regions (Hirrlinger et al., 2004). Consistent with this, neuronal activation that induces LTP leads to increased PAP motility (Bernardinelli et al., 2014). Similar increased PAP motility, as well as increased glutamate transporter expression and increased astrocytic coverage on synapses, was observed in the somatosensory cortex following whisker stimulation of adult mice (Genoud et al., 2006; Bernardinelli et al., 2014). These neuronal activity-dependent PAP changes often happen at a slow timescale (hours to days) and are mediated partly by astrocytic metabotropic glutamate receptors and intracellular calcium signaling (Porter and McCarthy, 1996; Pasti et al., 1997; Hirase et al., 2004; Wang et al., 2006; Bernardinelli et al., 2014). However, the downstream events mediating changes in PAP motility and protein expression, and how these changes affect activity-dependent circuit function require future investigation.

Myelin plasticity in circuit function

Neural circuit function requires not only precise connectivity but also regulation of signal timing and metabolic support for axons. Myelination can robustly influence neural circuit dynamics (for review, see Mount and Monje, 2017). The geometric properties of myelinated internodes, including sheath thickness and internode length, contribute to conduction velocity, together with the diameter of the axon itself. The “ideal” ratio of sheath thickness relative to axon diameter (g-ratio) may maximize conduction velocity, although it is important to note that, in terms of complex circuit function, faster is not necessarily better. Rather, subtle changes in spike arrival time can influence synchronicity of signals and spike timing-dependent synaptic plasticity (for review, see Bi and Poo, 2001). Relatively small variations in myelin profiles can exert large changes in conduction velocity, which may substantially influence circuit dynamics and thereby alter neural function (Pajevic et al., 2014; Steadman et al., 2019).

While some CNS structures, such as the optic nerve and spinal cord, exhibit complete myelination with close to the “ideal” g-ratio, the neocortex and subcortical projection fibers involved in associative cognitive function exhibit myelination patterns and profiles that are far from “ideal.” Cortical axons exhibit variable myelin profiles along the length of a given axon, with some axonal regions lacking internodes (Tomassy et al., 2014) and a significant proportion of corpus callosum axons are unmyelinated (Sturrock, 1980). The opportunity for “tuning” myelination over the lifespan exists, particularly in regions with available unmyelinated axonal territory, such as the neocortex and intercortical projections. Concordantly, oligodendrocytes (Tripathi et al., 2017; Hill et al., 2018; Hughes et al., 2018) and myelin (Yakovlev and Lecours, 1967) accumulate over the lifespan.

In the 1990s, Barres and Raff extended the idea that axonal activity may influence myelin beyond the developmental period and demonstrated that neuronal activity may influence OPC behavior in the adult optic nerve (Barres and Raff, 1993). Both transecting the optic nerve and intravitreal injection of TTX inhibited OPC proliferation, whereas TTX did not alter OPC proliferation in the absence of neurons (Barres and Raff, 1993). Consistent with this, later studies demonstrated that enhancing neuronal firing with α -scorpion toxin promotes optic nerve myelination (Demerens et al., 1996). It was discovered in 2000 that OPCs form “axon–glial” synapses with neurons (Bergles et al., 2000; Karadottir et al., 2005; Kougioumtzidou et al., 2017), and the influence of neuronal activity on oligodendrogenesis and my-

elination was shown *in vitro* (Stevens et al., 2002; Ishibashi et al., 2006; Wake et al., 2011, 2015).

Recently, advances in neuroscience techniques enabled *in vivo* studies of adaptive myelination with spatiotemporal resolution. Several recent studies demonstrated the direct role of neuronal activity in promoting myelination and modulating behavior *in vivo*. Optogenetic stimulation of cortical projection neurons in mouse premotor cortex results in circuit-specific increases in OPC proliferation, oligodendrogenesis, and changes in cortical projection axon myelination, both during the juvenile period and in adulthood (Gibson et al., 2014). This neuronal-activity-regulated myelination in the premotor circuit requires neuronal-activity-regulated brain-derived neurotrophic factor (BDNF) signaling to the Tropomyosin receptor kinase B (TrkB) on OPCs (Geraghty et al., 2019) and is associated with improved motor function that depends on new oligodendrocyte generation (Gibson et al., 2014). Similarly, chemogenetic stimulation of somatosensory cortical neurons results in circuit-specific increases in OPC proliferation, oligodendrogenesis, and myelination of the stimulated axons (Mitew et al., 2018). Using *in vivo* 2-photon imaging, Hughes et al. (2018) conducted a longitudinal study that tracked oligodendrocytes in the mouse somatosensory superficial cortex. Sensory enrichment (whisker stimulation) triggered a robust increase in new oligodendrocyte generation and new myelin sheath formation in somatosensory (barrel) cortex.

Further supporting an adaptive role for activity-dependent changes in myelin-forming cells, Richardson and colleagues demonstrated that new oligodendrocyte generation is also required for learning new motor skills in adulthood (McKenzie et al., 2014). Mice trained to run on a complex wheel exhibited increased oligodendrogenesis in the premotor circuit, and motor skill learning in this task was blocked by preventing new oligodendrogenesis through conditional, inducible KO of myelin regulatory factor (Myrf), which is required for oligodendrocyte maturation, in OPCs during adulthood (McKenzie et al., 2014). If the conditional KO was introduced after the skill was learned, oligodendrogenesis was no longer required for performing this task, indicating a role for oligodendrocytes in the learning process. Consistent with this principle that neuronal activity can influence ongoing plasticity of myelin, experience-dependent changes in myelin structure have been demonstrated in humans using diffusion tensor imaging. Individuals who trained in specific tasks, such as juggling (Scholz et al., 2009) and piano practicing (Bengtsson et al., 2005), exhibited myelin structure changes evident on diffusion tensor imaging in circuits relevant to hand-eye coordination and to motor function.

Myelin plasticity contributes to nonmotor cognitive function as well. Ongoing activity-regulated myelination is required for normal cognitive behavioral function in a test of attention and short-term memory in mice (Geraghty et al., 2019). Water-maze learning induces OPC proliferation, oligodendrogenesis, and *de novo* myelination in hippocampal-frontal circuitry, and oligodendrogenesis is required for spatial learning (Steadman et al., 2019). Importantly, spatial learning-induced oligodendrogenesis continues through the consolidation phase and is required for memory consolidation (Steadman et al., 2019). Concordantly, disruption of myelin plasticity contributes to cognitive impairment observed in a mouse model of chemotherapy-related cognitive impairment (Geraghty et al., 2019). The influence of experience on myelin structure and thus circuit dynamics may be bidirectional, with experiential deprivation in the form of social isolation leading to reduced myelin sheath thickness in the prefrontal cortex of both juvenile and adult mice; these myelin struc-

tural changes are associated with impairments in social function upon reintroduction to social interactions (Liu et al., 2012; Maki-nodan et al., 2012). Promoting oligodendrogenesis in socially isolated mice normalizes myelin and rescues social avoidance behavior (Liu et al., 2016). Collectively, adaptive myelination is emerging as a versatile process by which experience influences circuit dynamics and behavior.

In conclusion, our understanding of neuronal activity-regulated circuit establishment and plasticity has advanced tremendously in the past 50 years. Starting from an intense period of neuron-centric investigations, the field is marching into a new area of studying glial contributions to activity-dependent events. The entire neuroscience field has advanced exponentially with the development of neuromodulatory tools (e.g., optogenetics and chemogenetics), circuit mapping tools (e.g., transsynaptic viral mapping), and imaging techniques (e.g., 2-photon imaging, tissue clearing, and large-volume imaging). With the enormous leap in our knowledge about the CNS, much remains unknown. Mapping of neuron–neuron and neuron–glia (e.g., OPCs) communication will promote understanding of how the brain functions as a cellular society in health and diseases. The role of astrocytes in activity-dependent synaptic pruning and the role of microglia in synaptic plasticity remain to be fully explored. In addition, how glial cells affect activity-dependent neurodevelopment and plasticity in disease states is largely unknown. Adding another layer of complexity is the heterogeneity of each glial cell type. For example, different subtypes or states of astrocytes or microglia may perform diverse functions (Zhang and Barres, 2010; Liddel and Barres, 2017; Hammond et al., 2019; Masuda et al., 2019; Spitzer et al., 2019). Recent advances in spatially resolved single-cell sequencing will aid in determining how glial heterogeneity contributes to neurodevelopment and circuit function. In addition, there is a pressing need for tools that allow simultaneous profiling of neural cell transcriptome and function. Aided by the tools of modern neuroscience, the cellular and molecular mechanisms underlying activity-dependent neurodevelopment and circuit function are coming to light. Yet much remains to be elucidated in the next 50 years.

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