

REVIEW ARTICLE

An evolving view of retinogeniculate transmission

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Abstract

The thalamocortical (TC) relay neuron of the dorsoLateral Geniculate Nucleus (dLGN) has borne its imprecise label for many decades in spite of strong evidence that its role in visual processing transcends the implied simplicity of the term “relay”. The retinogeniculate synapse is the site of communication between a retinal ganglion cell and a TC neuron of the dLGN. Activation of retinal fibers in the optic tract causes reliable, rapid, and robust postsynaptic potentials that drive postsynaptic spikes in a TC neuron. Cortical and subcortical modulatory systems have been known for decades to regulate retinogeniculate transmission. The dynamic properties that the retinogeniculate synapse itself exhibits during and after developmental refinement further enrich the role of the dLGN in the transmission of the retinal signal. Here we consider the structural and functional substrates for retinogeniculate synaptic transmission and plasticity, and reflect on how the complexity of the retinogeniculate synapse imparts a novel dynamic and influential capacity to subcortical processing of visual information.

Keywords: Retinogeniculate synapse, Short-term plasticity, Developmental refinement, Visual circuit, Synaptic transmission

More than a relay

The retinogeniculate synapse has been an invaluable workhorse for neuroscience research. In recent years, it has served as a powerful model for understanding the molecular and circuit-level mechanisms that influence normal development and disease (Bishop et al., 1959; Sengpiel & Kind, 2002; Kastner et al., 2006; Guido, 2008; Kano & Hashimoto, 2009; Hong & Chen, 2011; Stephan et al., 2012; Kaplan, 2014). The ability to independently label Retinal Ganglion Cells (RGCs) from opposite eyes has enabled the identification of cellular and molecular mechanisms of axon mapping, arbor pruning, and synapse elimination that drive the refinement of retinotopic maps and eye-specific lamination (Wong, 1999; Luo & O'Leary, 2005; Huberman et al., 2008a; Feller, 2009; Kano & Hashimoto, 2009; Hong & Chen, 2011). *In vitro*, the easily accessible bundle of RGC axons in the optic nerve provides a convenient means of selectively activating presynaptic inputs in studies of synaptic physiology and plasticity, and is also an excellent system for uncovering mechanisms of axon regeneration (Guido, 2008; Hong & Chen, 2011; Benowitz et al., 2017). *In vivo*, the retinogeniculate synapse has been a prominent model system for the study of subcortical visual processing. Numerous studies have capitalized on the ease of manipulating visual stimulation, combined with the ability to simultaneously monitor the activity patterns of inputs

and outputs of the thalamus to reliably demonstrate that the transfer of information from the retina to the visual cortex is the major function of the retinogeniculate synapse (Sherman, 2005; Usrey & Alitto, 2015; Weyand, 2016).

Despite the tenacity of the term “relay” to describe the function of the dLGN, the retinogeniculate synapse does not simply transfer a copy of RGC activity patterns to the cortex. Over the past few decades, a number of retinogeniculate attributes have been shown to play a role in modifying visual information before conveying it to the cortex (Blitz et al., 2004; Sherman, 2007; Usrey & Alitto, 2015; Weyand, 2016). Simultaneous recording of the firing patterns of RGC inputs and TC target neurons *in vivo* has shown that the reliability of action potential generation in TC neurons depends on the local activity context, such as neuromodulatory signaling or the membrane potential. These factors can dictate or modulate the firing pattern (“tonic” or “burst”) of a TC neuron (McCormick & Bal, 1994; Usrey et al., 1998; Sherman & Guillery, 2002; Wang et al., 2007). In some cases, a TC neuron is much more likely to generate a response to the second of a pair of visually-driven potentials arriving in quick succession (separated by less than 30 ms, Mastronarde, 1987; von Krosigk et al., 1993; Usrey et al., 1998; Levine & Cleland, 2001; Rowe & Fischer, 2001; Carandini et al., 2007; Weyand, 2007; Sincich et al., 2007, 2009; Alitto et al., 2011). This integrative function increases the amount of information encoded in thalamic spiking (Wang et al., 2010). In other cases, a single RGC impulse can result in a post-synaptic burst of multiple action potentials (Usrey et al., 1998; Blitz & Regehr, 2003).

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Recent work is revealing new receptive field complexity and plasticity in the dLGN that further demonstrates significant thalamic processing of visual information en route to the cortex, at least in some species. Stimulus orientation selectivity is one salient example of a complex feature encoded in subpopulations of dLGN neurons in a variety of species: mouse (Marshall et al., 2012; Piscopo et al., 2013; Scholl et al., 2013; Zhao et al., 2013) and rabbit (Levick et al., 2010; Hei et al., 2014), with weaker orientation or direction bias occurring in the cat (Hubel & Wiesel, 1961; Daniels et al., 1977; Levick & Thibos, 1980; Vidyasagar & Urbas, 1982; Soodak et al., 1987; Shou & Leventhal, 1989; Thompson et al., 1994), squirrel (Zaltsman et al., 2015), and primate (Lee et al., 1979; Smith et al., 1990; Cheong et al., 2013). Complex feature selectivity persists in TC neurons after inactivation of the primary visual cortex, suggesting that the dLGN may compute orientation or direction selectivity rather than inherit it from cortical feedback (cat Vidyasagar & Urbas, 1982; mouse Zhao et al., 2013; Scholl et al., 2013). Furthermore, cat TC neurons have a higher stimulus contrast sensitivity than their individual inputs, suggesting TC neurons can functionally integrate information from multiple RGC inputs (Rathbun et al., 2016). The presence of binocularly innervated dLGN neurons in mice, cats, and primates further supports the possibility of convergence of multiple RGCs onto single geniculate neurons in mice, cat, and primate dLGN (Sanderson et al., 1971; Howarth et al., 2014; Zeater et al., 2015; Rompani et al., 2017). Here, we explore synaptic mechanisms and structural attributes that could support the diversity of features and functions now emerging in studies of the dLGN. In this review, we describe the structural properties of RGC axons and TC neurons, together with their biophysical features and plasticity mechanisms. These properties may combine to impart novel and adaptive functionality to the dLGN, and to dynamically regulate information flow between retina and cortex.

Retinogeniculate synaptic structure

To appreciate the functional complexity in retinogeniculate processing, we first describe the underlying synaptic structure. The architecture of the retinogeniculate synapse is conserved across species. Glutamate is the excitatory neurotransmitter packed into numerous round vesicles contained in large synaptic terminals along the axon (Montero & Wenthold, 1989). A single retinal axon terminal can span ~1–4 microns in diameter and contain multiple spatially distinct neurotransmitter release sites (cat and mouse studies: Famiglietti & Peters, 1972; Rafols & Valverde, 1973; Sur & Sherman, 1982; Hamos et al., 1987; Robson, 1993; Bickford et al., 2010; Budisantoso et al., 2012; Morgan et al., 2016). RGC boutons contact a TC neuron near its cell body, synapsing directly onto the dendritic shaft or dendritic appendages that protrude from the proximal shaft or primary dendritic branch points (Rafols & Valverde, 1973; Robson & Mason, 1979; Wilson et al., 1984; Hamos et al., 1987; Bickford et al., 2010; Morgan et al., 2016). Retinal inputs account for only 5–10% of a TC neuron's synaptic input, whereas cortical feedback projections from Layer 6 occupy the distal dendrites, providing as much as 50% of synaptic input (Wilson et al., 1984; Montero, 1991; Van Horn et al., 2000). Nonetheless, the proximal position of retinogeniculate synapses along the dendrite, their synaptic structure with multiple release sites, and their large number of synaptic contacts drives powerful and reliable transmission that has earned the retinal input the moniker of “driver” to all other inputs’ “modulator” (Guillery & Sherman, 2002).

The fine details of retinogeniculate connectivity reveal potential heterogeneity of circuit organization and, thereby, of function. A RGC axon contacts a TC neuron with as many as 59 terminals in cat or mouse (Fig. 1A–1C; Hamos et al., 1987; Robson, 1993; Morgan et al., 2016). The morphology of these numerous synaptic contacts between a single RGC axon and its target TC neuron can range from the simple to the complex (Jones & Powell, 1969; Famiglietti & Peters, 1972; Hammer et al., 2015; for finer categorization, see Lund & Cunningham, 1972; Robson & Mason, 1979; Morgan et al., 2016). Simple retinogeniculate contacts consist of one small or large crenulated bouton contacting a dendrite or dendritic appendage. Complex contacts comprise a glomerular structure containing multiple boutons from retinal, inhibitory, and neuromodulatory inputs (Robson & Mason, 1979; Koch, 1985; Sherman & Guillery, 1996; Sherman, 2004). Although it is not known whether differences in bouton morphology correlate with specializations for retinogeniculate information transfer, work on cerebellar parallel fibers shows that bouton size can predict sensitivity to neuromodulation, and induction of LTP or LTD can induce plasticity in the size of hippocampal presynaptic boutons (Toni et al., 1999; Becker et al., 2008; Zhang & Linden, 2009). Furthermore, the morphology of synaptic contacts is optimized to the requirements of sensory transmission in the retina, inner ear, and central auditory synapses (Taschenberger et al., 2002; Matthews & Fuchs, 2010; Freche et al., 2011; Graydon et al., 2014). It is therefore likely that the diversity of retinogeniculate contact morphologies reflects differences in their contribution to transmission. Indeed, different TC neuron types in cats exhibit biases in presynaptic morphology. Cat RGCs and TC neurons are distinguished into three categories (X, Y, W) based on the properties of their responses to visual stimuli, including the size of the receptive field and the degree of linearity of spatial summation, as well as morphological markers. The X and Y classifications refer to relatively homogeneous populations (and are often compared to primate M and P pathways), whereas the W (compared to K in primates) encompasses a more diverse set of cells with rarely-encountered physiological responses (Wilson et al., 1976; Fukuda et al., 1984; Felch & Van Hooser, 2012). Simple contacts dominate retinal input onto cat Y cells, whereas X cell dendritic appendages preferentially participate in complex synaptic structures (Robson & Mason, 1979; Hamos et al., 1985; Koch, 1985; Sherman & Guillery, 1996; Sherman, 2004). Similar distinctions among TC neurons have been observed in the mice by morphological analysis, but have not been associated with distinct patterns of synaptic structures nor delineated by physiology (Krahe et al., 2011; El-Danaf et al., 2015; Sriram et al., 2016).

In addition to potential functional differences reflected in the morphology of presynaptic geniculate boutons, the close proximity of clustered multisynaptic boutons in the mature synapse makes possible novel interactions between glutamate transients originating in separate RGC inputs. Large simple boutons in the rat contain an average of 27 independent release sites, whereas each of the boutons in a glomerulus has approximately 6 (Hamos et al., 1987; Budisantoso et al., 2012; Hammer et al., 2015). Notably, multiple RGCs may contribute to the same cluster or glomerulus of boutons (Hammer et al., 2015; Morgan et al., 2016). At other CNS synapses, glia ensheath individual boutons and interdigitate into the synaptic cleft, preventing glutamate from diffusing, or “spilling over,” to neighboring boutons, in part through the action of glutamate transporters, which clear glutamate from the extracellular space (Diamond & Jahr, 1997; Danbolt, 2001; Tzingounis & Wadiche, 2007; Hauser et al., 2013; Rimmelé & Rosenberg, 2016). In contrast, glia do not interdigitate into the cleft of single RGC boutons

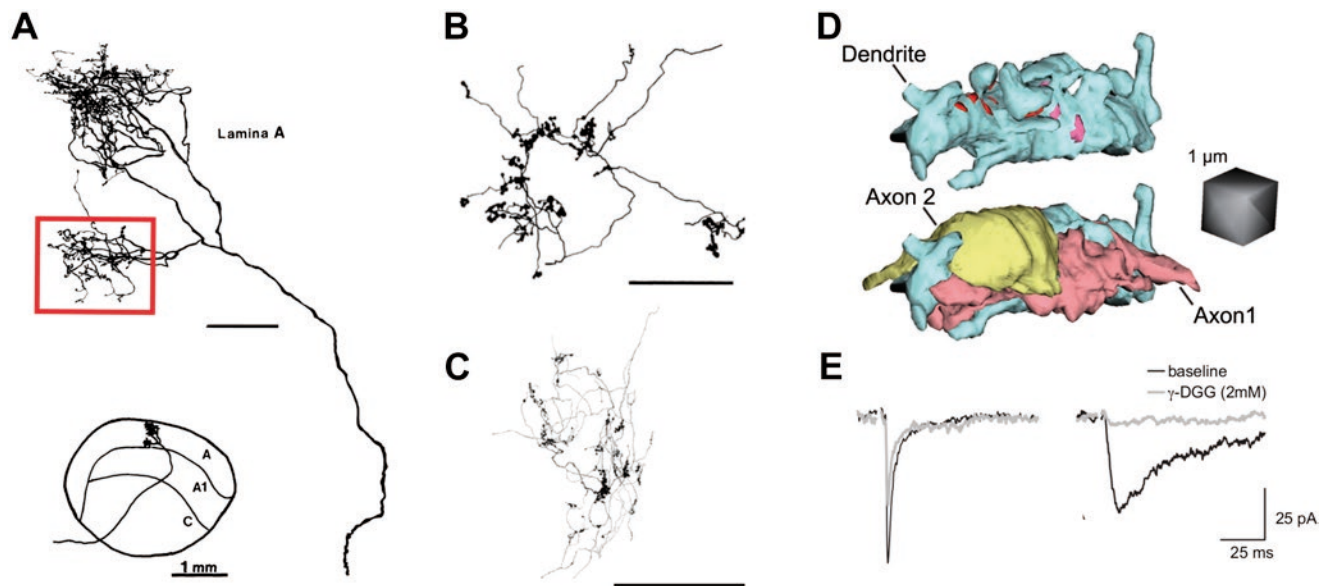


Fig. 1. Synaptic structure shapes retinogeniculate transmission. (A) Tracing of an HRP-filled X-RGC arbor in the cat dLGN shows the location and morphology of a single branch (red box) of the X-RGC arbor used for EM reconstruction. This branch of the axon contacts 4 TC neurons out of 40 available neurons in the territory of the arbor. The remainder of the axon was not reconstructed, and likely contacts several other TC neurons. Bottom inset shows the location of the axonal arbor in the context of the cat LGN. Figure modified from Hamos et al. (1987). Unmarked scale bar = 100 μm . (B, C) Reconstructed arbors of single RGC axons showing distribution of presynaptic boutons into dense clusters in the LGN of (B) an adult cat and (C) a p20 mouse. Note the clustering of boutons along the arbor. Image in B is modified from Robson et al. (1993), showing a segment of a RGC axon; Image in C is from Hong et al. (2014), showing a BD-RGC axon. Scales bars are 100 μm . (D) A 3D reconstruction of a TC neuron dendrite and sites of contact between two neighboring RGC boutons from Budisantoso et al. (2012). In the top image, the dendrite and its appendages are depicted in blue, whereas pink and red sites label the postsynaptic densities of the two axons. In the bottom image, the structure of the terminals of two axons has been added. Spillover can occur between these two nearby terminals. (E) Evidence of spillover-mediated responses to the stimulation of a single RGC axon before eye opening. Two different synaptic responses were observed in response to single retinal fiber stimulation. Shown are recordings from TC neurons in whole cell voltage clamp at -70 mV in a dLGN slice in the presence of the NMDAR blocker, 20 μM CPP. On the left is an example of a retinogeniculate AMPAR EPSC with characteristic rapid rise time and decay kinetics (black trace). On the right is an atypical AMPAR EPSC response notable for significantly slower rise time and decay kinetics (black trace). The two types of EPSCs differ in their sensitivity to the low-affinity AMPAR antagonist, γ -DGG. Low affinity antagonists can be used to assess the relative concentration of glutamate in the synaptic cleft (Clements et al., 1992; Diamond & Jahr, 1997). As γ -DGG competes with glutamate for binding to AMPAR, its efficacy of inhibition decreases with increasing glutamate concentration. γ -DGG has only a small effect on the amplitude of the fast EPSC, but dramatically reduces the amplitude of the slow EPSC (overlaid gray traces), consistent with lower peak glutamate concentration in the synaptic cleft of the slow EPSC. Because the EPSCs are evoked by minimal stimulation, the rapid EPSC represents a direct input from a single RGC axon that forms a direct synapse onto the voltage-clamped relay neuron, whereas the slow EPSC corresponds to the activation of a RGC axon that does not directly synapse onto the voltage-clamped neuron. Modified from Hauser et al. (2014). All figures reprinted with permission.

nor within geniculate glomeruli, making the retinogeniculate connection conducive to glutamate spillover within and between individual boutons (Famiglietti & Peters, 1972; Robson & Mason, 1979; Winfield et al., 1980; Mason, 1982; Bickford et al., 2010). Although interbouton spillover has not been experimentally assessed in the mature dLGN, a simulation that demonstrated the likelihood of spillover between distant synapses within the same bouton also implies the possibility of spillover of glutamate between closely spaced boutons. Fig. 1D shows an example of two such close retinogeniculate boutons along one TC neuron dendrite, highlighting that glutamate released from one bouton can diffuse to postsynaptic release sites of the neighboring bouton (Budisantoso et al., 2012). At a developmental phase when boutons are less clustered (Sur et al., 1984; Hong et al., 2014) and glomeruli have not yet formed, retinogeniculate transmission exhibits extensive glutamate spillover between neighboring boutons. In fact, glutamate from the bouton of one RGC axon can spill over to the synaptic cleft of a neighboring RGC axon before eye opening (Hauser et al., 2014).

Glutamate spillover can be distinguished from direct retinogeniculate synaptic activation by the slower kinetics of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)-mediated Excitatory Postsynaptic Current (EPSC) and increased sensitivity to γ -DGG (gray traces), a low affinity AMPAR antagonist (Fig. 1E). These characteristics indicate that the receptors mediating the spillover current are exposed to a lower glutamate concentration than those mediating the direct EPSC. Glutamate spillover can therefore diminish synaptic specificity, but also result in complex and graded integration of information transmitted from different RGC inputs. This mechanism of transmission may be particularly relevant for high-frequency presynaptic activity (RGCs can reach up to 500 Hz, Nirenberg & Meister, 1997), which would promote the pooling and spillover of glutamate. Therefore, the intricate morphology of retinogeniculate contacts presents the possibility for a diversity of modes of retinogeniculate information transfer, which could vary as a function of preceding sensory or modulatory activity.

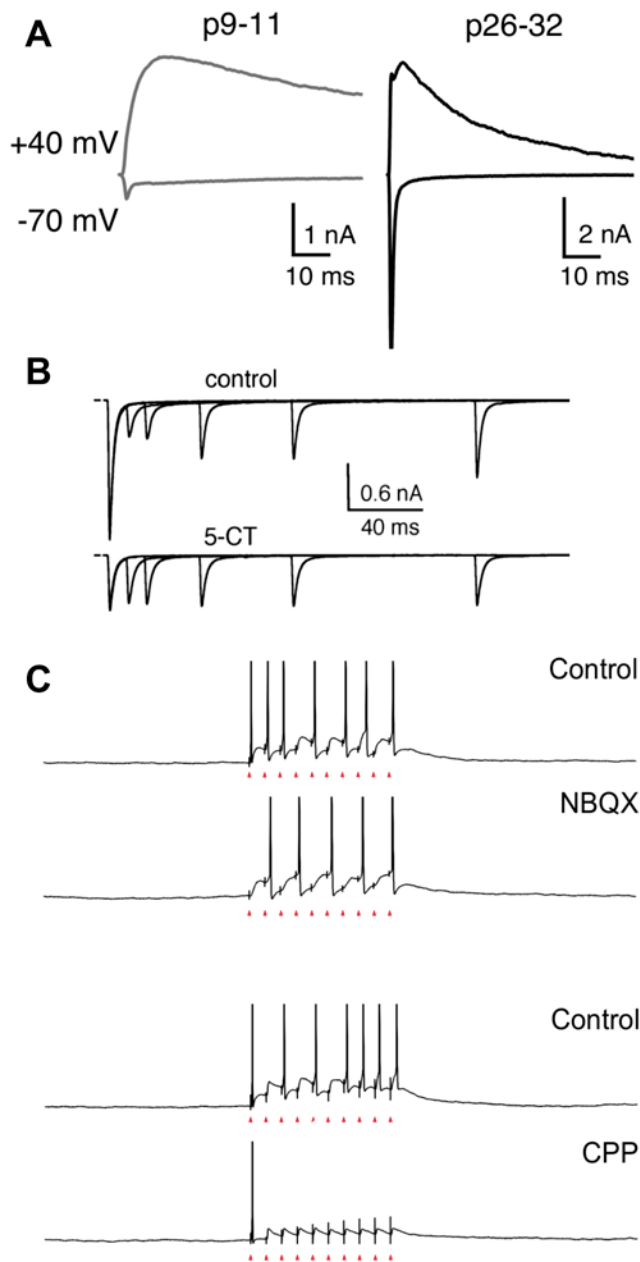


Fig. 2. Contributions of retinogeniculate short-term plasticity. (A) Representative traces of AMPAR and NMDAR mediated currents recorded before eye opening (left) and in a mature mouse (right) in response to the stimulation of the optic tract. Whole-cell voltage clamp recordings were performed with bicuculline to block GABA_A-receptor mediated currents. At -70 mV holding potential, AMPARs mediate the fast activating and decaying current. AMPAR and NMDAR currents both contribute to the EPSCs recorded at +40 mV with AMPARs contributing to the rapid rise and the NMDAR currents contributing to the slow decay of the EPSC. The average amplitude of AMPAR currents increases over development. (B) 5-CT-mediated activation of serotonin receptors alters retinogeniculate short-term plasticity. Experiments were performed in retinogeniculate slices from mature mice. Top and bottom traces overlay pairs of retinogeniculate EPSCs evoked with varying ISI before (top) and after (bottom) the application of 5-CT to activate 5HT-1 receptors expressed in presynaptic retinogeniculate boutons. Application of 5-CT reduces the amplitude of the first EPSC and relieves short-term depression, increasing the amplitude of the second EPSC preferentially at short interstimulus interval. (C) Physiologically relevant stimulation frequencies preferentially diminish the contribution of AMPARs to relay neuron firing. Current clamp recordings of action potential firing in

Short-term plasticity

The mature retinogeniculate synapse boasts multiple bouton contacts, each with many release sites, leading to a high probability of release (Yeow & Peterson, 1991; Chen & Regehr, 2000; Budisantos et al., 2012). Combined with the proximity of retinal contacts to the cell body that minimizes potential dendritic filtering of the synaptic signal, these structural features give rise to an EPSC characterized by rapid kinetics (time constant of decay ~2 ms) and large amplitudes *in vitro* (Chen & Regehr, 2000; example recording in Fig. 2A, p26–32). Studies in slices have identified several pre and postsynaptic mechanisms of short-term plasticity that modulate these EPSCs to further shape transmission based on the activity of the RGC input itself as well as other retinal and nonretinal inputs to that neuron. In shaping retinogeniculate transmission, these short-term plasticity mechanisms provide the means to dynamically modify the information transmitted from RGC to TC neuron output.

A prominent feature of retinogeniculate transmission studied *in vitro* is short-term depression: the second of two impulses separated by a short interval generates a weaker response than the first. Both presynaptic mechanisms involving vesicle depletion and postsynaptic mechanisms including AMPAR desensitization and *N*-methyl-D-aspartate receptor (NMDAR) saturation contribute to this plasticity (Chen et al., 2002; Blitz et al., 2004; Budisantos et al., 2012). In contrast to the short-term depression observed *in vitro* in mice, extracellular recordings of TC neuron activity *in vivo* in cats and primates consistently show paired-stimulus enhancement, such that the second of two retinal impulses separated by a brief (<30 ms) interval is more effective at driving a postsynaptic action potential (Mastronarde, 1987; Usrey et al., 1998; Levine & Cleland, 2001; Rowe & Fischer, 2001; Carandini et al., 2007; Rathbun et al., 2007; Sincich et al., 2007, 2009). In part, this contradiction is due to the dependence of short-term depression on the recent history of activity at the synapse. Activation of the retinogeniculate synapse in slice usually follows a period of quiescence, whereas baseline spontaneous activity maintains synaptic transmission in a chronically depressed state *in vivo* (Levick & Williams, 1964; Stoelzel et al., 2015). A train of spikes preceding optic tract stimulation *in vitro* attenuates the degree of synaptic depression (Seeburg et al., 2004; Augustinaite & Heggelund, 2007; Liu & Chen, 2008). Further, neurotransmitter inputs from the brainstem and inhibitory neurons can modulate retinogeniculate transmission in a context-dependent manner *in vivo*. To understand the relationship between *in vitro* and *in vivo* manifestations of short-term plasticity, we review the prominent sources of modulation of retinogeniculate transmission.

Presynaptic modulation

Retinogeniculate transmission is known to be modulated presynaptically by a number of neurotransmitter receptors, including GABA_B, serotonin 5HT_{1B} (Chen & Regehr, 2003; Seeburg et al., 2004),

response to trains of optic tract stimulation in the presence of AMPAR (NBQX) or NMDAR (CPP) antagonists. Holding potential -50 mV. Blockade of AMPARs alters the latency to first spike but only minimally reduces the overall number of spikes. In contrast, blockade of NMDARs abolished EPSC summation toward action potential firing; only the first stimulus evokes an action potential, reflecting the contribution of AMPARs that rapidly desensitize after the first pulse. Therefore, NMDAR currents can sustain action potential generation without AMPAR contribution. Adapted from (A) Chen and Regehr (2000), (B) Liu and Chen (2008) and (C) Augustinaite and Heggelund (2007). All figures reprinted with permission.

as well as adenosine A1 (Yang et al., 2014) and metabotropic glutamate receptors (Hauser et al., 2013; Lam & Sherman, 2013). Activation of the GABA_B or 5-HT_{1B} receptors strongly depresses neurotransmitter release and relieves short-term depression by decreasing the entry of calcium into the presynaptic terminal (see Fig. 2B; Chen & Regehr, 2003; Seeburg et al., 2004). While these modulators decrease the strength of the retinogeniculate EPSC, they also alter the pattern of action potentials transmitted from the pre- to post-synaptic neuron. For example, activation of presynaptic 5-HT_{1B} receptors leads to preferential transmission of high-frequency over low-frequency activity, essentially acting as a high-pass filter (Seeburg et al., 2004). In some cases, presynaptic modulation can be additive. The combined activation of 5HT_{1B} and adenosine A1 receptors, can convert presynaptic depression into facilitation (Yang et al., 2014). Therefore, the activity of neuromodulatory inputs *in vivo* can dynamically shape retinogeniculate information transfer by modulating the degree of short-term plasticity. It is not known whether the expression of presynaptic receptors differs between RGC types or RGC bouton morphologies. However, any such differences would add an additional layer of modularity to retinogeniculate transmission.

Postsynaptic modulation

In addition to presynaptic depression, postsynaptic glutamate receptor properties also contribute to short-term depression and shape the efficacy of retinogeniculate transmission. Postsynaptic AMPA and NMDA receptors both exhibit short-term depression, and perform complementary functions in retinogeniculate transmission.

AMPA channel gating properties and the high density of their expression contribute to the large, rapid activation, and decay kinetics of the retinogeniculate EPSC (Tarusawa et al., 2009). Because AMPARs readily conduct at negative potentials, they are effective at initiating postsynaptic spiking, even from a relatively hyperpolarized membrane potential (Blitz & Regehr, 2003; Augustinaite & Heggelund, 2007; Liu & Chen, 2008). However, AMPARs desensitize upon exposure to glutamate and recover with a time constant of ~100 ms (Chen et al., 2002; Kielland & Heggelund, 2002). These properties lead to short-term depression of the AMPAR EPSC. Therefore, AMPARs contribute to the onset of an action potential train transmitted from a RGC, initiating robust short-latency spikes during low frequency activity, but cannot sustain the robust transmission of high-frequency retinogeniculate activity (Blitz & Regehr, 2003). Fig. 2C demonstrates that pharmacological blockade of AMPAR with NBQX reduces the initial spikes in response to a stimulus train (Turner et al., 1994; Augustinaite & Heggelund, 2007).

NMDA receptor-mediated currents have distinct kinetics and voltage dependence from AMPAR (Fig. 3A and 3B). At the retinogeniculate synapse, NMDARs exhibit short-term depression due to their high affinity to glutamate and receptor saturation (Traynelis et al., 2010). Recovery from NMDAR saturation occurs more quickly than from AMPAR desensitization (Chen et al., 2002; Kielland & Heggelund, 2002). TC neuron NMDARs experience incomplete Mg²⁺ block at hyperpolarized potentials, and therefore conduct significant current at negative potentials (Liu & Chen, 2008). Fig. 3B and 3C illustrates the contribution of NMDAR to transmission over development. NMDARs conduct current for many tens of milliseconds during a prolonged decay, which permits the summation of closely timed EPSCs, especially within the range of interstimulus intervals (ISIs) that exhibit paired-pulse enhancement *in vivo*, and

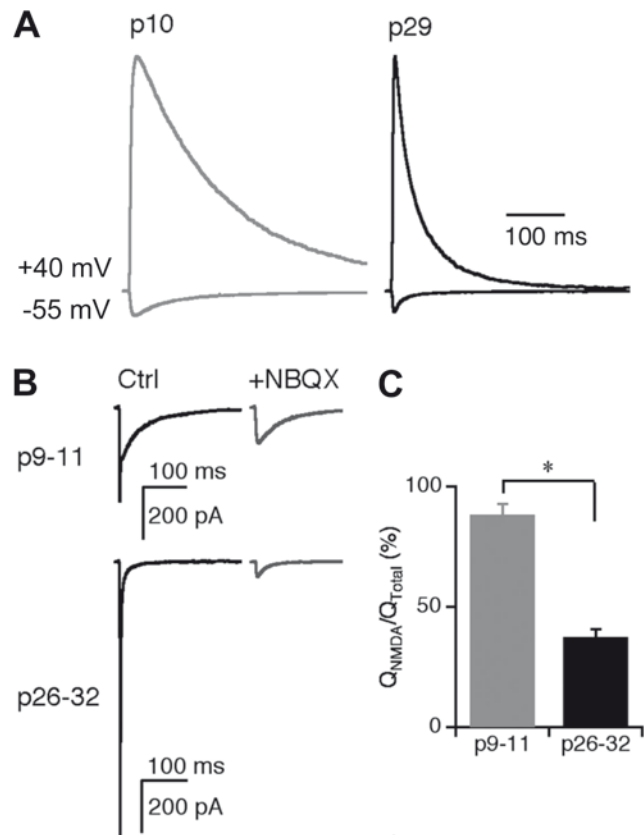


Fig. 3. Contribution of NMDAR-currents to retinogeniculate transmission over development. (A) NMDAR EPSCs recorded in the presence of the AMPAR blocker, NBQX, at +40 and -55 mV holding potentials in a p10 (left) and a p29 (right) retinogeniculate slice. Normalized traces are shown. Note the acceleration in NMDAR current decay time over development. (B) Example EPSCs recorded in young (top) and mature (bottom) TC neuron in slice before (left) and during (right) the application of NBQX. Holding potential, -55 mV. (C) NMDAR currents contribute more to the total retinogeniculate charge transfer at p9-11 than p26-32; however, even at the mature synapse, NMDARs contribute nearly half of the total charge transfer. Figure adapted from Liu and Chen (2008). All figures reprinted with permission.

supports multiple TC neuron spikes even in “tonic” mode (Chen et al., 2002; Blitz & Regehr, 2003; Augustinaite & Heggelund, 2007; Liu & Chen, 2008; Budisantoso et al., 2012). Blockade of NMDAR dramatically reduces retinogeniculate transmission *in vivo* (Sillito et al., 1990; Kwon et al., 1991), and NMDAR current summation *in vitro* can even drive action potential firing in the presence of AMPAR blockers, though with less temporal precision (Fig. 2C; Chen et al., 2002; Blitz & Regehr, 2003; Augustinaite & Heggelund, 2007; Budisantoso et al., 2012). In fact, the NMDAR component of the first EPSC may sufficiently depolarize a TC neuron to spike threshold, such that a small or depressed AMPAR current can shorten the latency to first spike (Kielland & Heggelund, 2002; Augustinaite & Heggelund, 2007; Budisantoso et al., 2012). Therefore, summation of NMDAR currents enhances the probability of TC neuron spiking in response to the second and later RGC action potentials during a train. Together with modulation and postsynaptic integration (Carandini et al., 2007), the properties of NMDA and AMPA receptor currents can reconcile the robust short-term depression seen *in vitro* with paired-pulse enhancement observed *in vivo*.

An additional factor that could contribute to differences in *in vitro* and *in vivo* short-term plasticity is the expression of

calcium-permeable AMPARs. The retinogeniculate synapse differs from other synapses in that the expression of calcium-permeable AMPARs increases over development (see Fig. 4A and 4B; Budisantoso et al., 2012; Hauser et al., 2014; Louros et al., 2014; compare to Kumar et al., 2002; Soto et al., 2007). Calcium permeable AMPARs (those lacking the GluA2 subunit) exhibit stronger desensitization-mediated paired pulse depression (Budisantoso et al., 2012). However, depolarization-mediated reduction of polyamine block may partly rescue this effect (Rozov et al., 1998; Soto et al., 2007), increasing the contribution from AMPARs to transmission later in a train of high frequency activity.

The *in vitro* retinogeniculate preparation has permitted the identification of mechanisms regulating retinogeniculate synaptic transmission at an unmatched resolution. The synaptic mechanisms discussed above are part of a larger array of factors that affect retinogeniculate information transfer, including circuit elements that influence postsynaptic integration in the TC neuron: local and extrageniculate GABAergic circuits, reciprocal connectivity with the cortex, and brainstem modulatory inputs (reviewed in Sherman & Guillery, 2002). Together, these synaptic and circuit mechanisms impart the dynamic features that regulate transmission of information at the retinogeniculate synapse. Interestingly, the paired-stimulus enhancement of retinogeniculate transmission *in vivo* acts not only to increase the signal-to-noise of retino-geniculo-cortical information transfer, but also encode emergent features in the spike code (Sincich et al., 2009; Rathbun et al., 2010; Wang et al., 2010). Thus these synaptic mechanisms may also impart novel functionality at the level of dLGN. Further, as these mechanisms can rapidly alter the contribution of a particular retinal input to postsynaptic spiking, they may regulate the contribution of strong *versus* weak RGC inputs to visual processing (discussed below).

Neurotransmission before eye-opening

The distinct features of the immature retinogeniculate synapse suggest that the immature dLGN carries out a different set of computations on incoming retinal information than the mature dLGN. Many of the modulatory circuits that shape transmission in the adult dLGN begin to innervate TC neurons shortly before eye-opening: corticogeniculate innervation is not complete in mice until p14 (Jacobs et al., 2007; Seabrook et al., 2013; Grant et al., 2016), and cholinergic innervation develops over several postnatal weeks in cats (Carden et al., 2000). GABAergic interneurons continue to be recruited into the dLGN at the end of the first postnatal week in mice, and GABAergic innervation in rodents and carnivores occurs gradually (Shatz and Kirkwood, 1984; Ramoa & McCormick, 1994a; Pirchio et al., 1997; Ziburkus et al., 2003; Golding et al., 2014). In addition, presynaptic ultrastructural morphology and TC dendritic arbor complexity are immature at eye-opening (Bickford et al., 2010). Therefore, retinogeniculate transmission before eye-opening occurs in a very different environment than after circuits have matured.

Whereas mature TC neurons receive and integrate information from one or several strong retinal inputs that can reach several nA in amplitude, numerous weak inputs, measuring on average ~40 pA in amplitude (peak AMPAR EPSC) innervate a TC neuron before eye opening (*in vitro* in mice; Hooks and Chen, 2006). Remarkably, retinogeniculate transmission to cortex does occur before input refinement: both the spontaneous patterns of activity (retinal waves) that prominently feature in the developing retina, and visually-evoked stimuli detectable through the closed eyelid

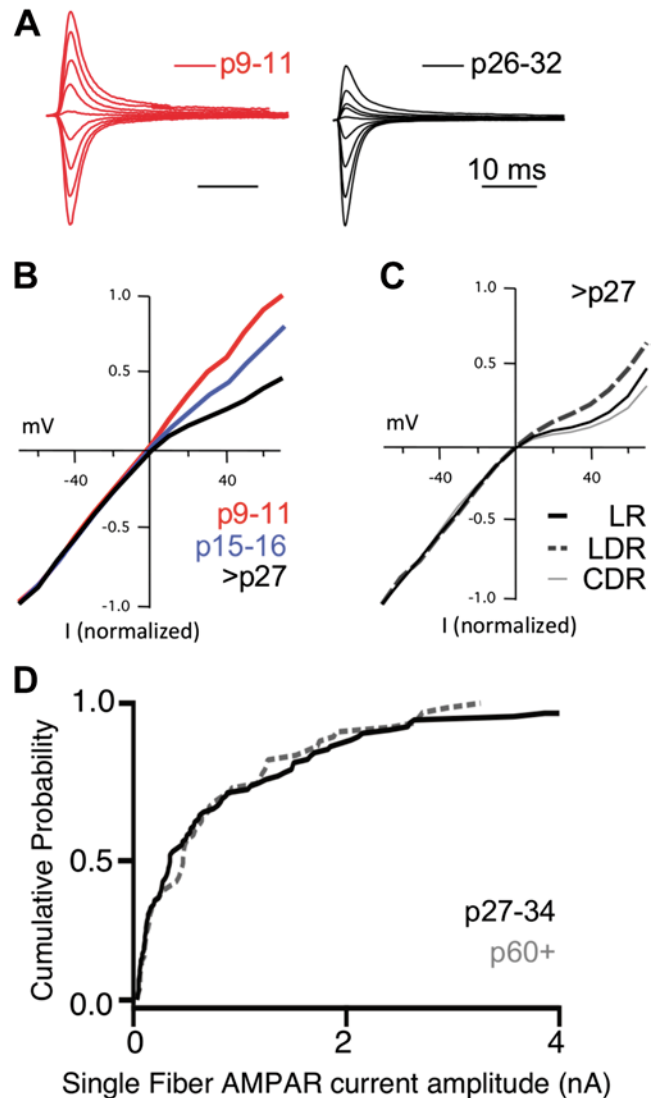


Fig. 4. Substrates for retinogeniculate plasticity. (A) Overlaid AMPAR current traces recorded from different holding potentials to assess the current voltage (I - V) relationship. Currents in the presence of CPP to block NMDAR currents and with spermine in the internal solution to examine the degree of I - V rectification. Calcium-permeable AMPARs exhibit a rectifying I - V relationship. Traces were recorded at 20 mV increments from -60 to $+60$ mV holding potentials. Left-example obtained before eye opening; right, example from a mature slice. From Hauser et al. (2014). (B) Change in the average AMPAR EPSC I - V relationship over development. Rectification of I - V currents increases significantly from p9-11 to maturity, indicating a gradual increase in the contribution of CP-AMPARs to AMPAR-mediated currents. Modified from Hauser et al. (2014). Red: p9-11; blue: p15-16; black: p27-32. (C) Changes in AMPAR subunit composition in response to visual experience. The effect of visual deprivation from p20 (late-dark rear, LDR) or dark rearing from birth (chronic dark reared, CDR) on the AMPAR EPSC I - V relationship. Rectification of AMPAR currents is reduced in LDR but not in chronically dark reared (CDR) mice when compared to normally reared mice (light rear, LR) mice. $P = 0.03$. Recordings performed at p27-32. Modified from Louros et al. (2014). (D) Comparison of the distribution of amplitudes of single fiber RGC inputs in juvenile (p27-34) and adult (p60+) mice show the persistence of weak (small-amplitude) inputs with age. Modified from Hong et al. (2014). All figures reprinted with permission.

influence the activity of the visual cortex (Katz & Shatz, 1996; Mooney et al., 1996; Feller, 1999; Akerman et al., 2002; Hanganu et al., 2006; Ackman et al., 2012). In slice, the synaptic charge transfer needed to drive TC neuron spiking before eye-opening is relatively small: an AMPAR EPSC with a peak amplitude of 120 pA is adequate (Liu & Chen, 2008). The coincident activation of a subset of the dozen or more converging RGC inputs, perhaps relying on synchronous activity that dominates retinal activity during this period of development, can achieve this amplitude (Wong et al., 1993; Wong, 1999; Butts & Rokhsar, 2001; Feller, 2009).

Multiple mechanisms contribute to the efficacy of neurotransmission at the immature weak retinogeniculate synapse. A study using the slow calcium chelator, EGTA-AM, suggested that the distance between the presynaptic release machinery and calcium channels at retinal terminals is greater at immature presynaptic specializations, resulting in delayed or asynchronous release (Borst & Sakmann, 1996; Hauser et al., 2014). Additionally, the immature nervous system produces a slower action potential waveform (Taschenberger & von Gersdorff, 2000; Murphy & du Lac, 2001) and a lower density of glutamate transporters in surrounding astrocytes (Thomas et al., 2011). These properties of the immature synapse lead to the prolonged exposure of postsynaptic receptors to glutamate, promoting the integration of retinal EPSCs over a longer time scale than after maturation.

Several postsynaptic mechanisms also improve the integration of weak RGC inputs at young ages. The temporal window for postsynaptic summation is much greater before eye opening (Liu & Chen, 2008). This is due in part to the higher input resistance in immature neurons (Ramoia & McCormick, 1994b; Macleod et al., 1997; Pirchio et al., 1997), as well as enhanced conduction through NMDA receptors at negative potentials because of a greater contribution of both NR2B as well as NR2C/D subunits at young synapses (Ramoia & McCormick, 1994a; Liu & Chen, 2008). These receptors exhibit slower decay kinetics and a lower sensitivity to magnesium block (compare between ages in Fig. 3), and their contribution declines over development in an activity-regulated manner (Ramoia & Prusky, 1997; Chen & Regehr, 2000; Liu & Chen, 2008).

AMPA current amplitudes at the immature retinogeniculate synapse are much smaller than later in life (Figs. 2A and 3B). In fact, a substantial fraction (22%) of immature RGC inputs are “silent” (lacking detectable AMPA currents; Isaac et al., 1995; Liao et al., 1995; Chen & Regehr, 2000). Transmission before eye opening therefore seems to rely almost entirely on NMDAR transmission, with AMPARs influencing the latency to spike (Liu & Chen, 2008). Finally, immature neurons also exhibit calcium plateau potentials (Jaubert-Miazza et al., 2005; Lo et al., 2013), and more depolarized resting membrane potentials that are closer to firing threshold (Ramoia & McCormick, 1994b; Macleod et al., 1997; Pirchio et al., 1997), increasing the efficacy of individual inputs.

In summary, the developing retinogeniculate synapse exhibits numerous adaptations that permit it to integrate and transfer visual signals to cortex even while it undergoes dramatic synaptic rearrangement. As these signals arise from the summation of multiple weak convergent RGC inputs, the computations that the immature dLGN performs, and therefore its role in visual processing, is substantially different from that of the mature dLGN. In addition to a role in conveying visual information, retinogeniculate transmission is important for cortical map formation (Huberman et al., 2008b; Cang & Feldheim, 2013; Owens et al., 2015), though its precise computational role is not yet understood.

Retinogeniculate connectivity

Developmental refinement of retinogeniculate connectivity

Retinogeniculate refinement is thought to lead to the maturation of receptive field properties in the dLGN. Before eye opening, RGC axons from the two eyes segregate into eye-specific layers: segments of the axon arbor that occupy the inappropriate layer are pruned, while the appropriately positioned portion of the arbor becomes more elaborate in a number of species (Robson, 1981; Mason, 1982; Sretavan & Shatz, 1984, 1986; Campbell & Shatz, 1992; Garraghty & Sur, 1993; Dhande et al., 2011; Hong et al., 2014). *In vitro* studies of the dLGN in rodents show that each TC neuron receives weak inputs from more than a dozen RGCs. Some of these inputs are subsequently pruned while others strengthen to become dominant drivers of postsynaptic activity (reviewed in Guido, 2008; Huberman et al., 2008a; Hong & Chen, 2011; Thompson et al., 2017). This refinement occurs over several weeks following eye opening in mice. The earliest phases depend on spontaneous input from the retina, while visual experience maintains the mature configuration and modifies connectivity *via* feedback from the cortex during a critical period (Hooks & Chen, 2006; Thompson et al., 2016).

The robust refinement of retinogeniculate connectivity demonstrated *in vitro* in mice corresponds temporally to the developmental transformation of initially broad, irregularly-shaped or temporally imprecise receptive fields to smaller, sharper, or temporally precise ones that closely match the receptive field of the dominant retinal inputs *in vivo* (cat: Wiesel & Hubel, 1963; Daniels et al., 1978; Tootle & Friedlander, 1989; Gary-Bobo et al., 1995; Cai et al., 1997; Ferret: Tavazoie & Reid, 2000, Akerman et al., 2002, Davis et al., 2015; primate: Blakemore & Vital-durand, 1985; mouse *in vitro*: Chen & Regehr, 2000; Jaubert-Miazza et al., 2005). Surprisingly, there is a disconnect between structure and function—studies in cats, mice, and primates fail to show large-scale pruning of the axon arbor during this later window of development (Sur et al., 1984, 1987; Lachica & Casagrande, 1988; Hong et al., 2014). A recent study that examined individually reconstructed axon arbors of a subtype of mouse RGCs, the BD-RGC (ON–OFF direction-selective RGC, Kim et al., 2010), found that their size and branching complexity remain stable in the 2–3 weeks following eye opening. Instead, during the period of robust functional refinement, changes occur in bouton size and distribution along the arbor structure (Hong et al., 2014). Before eye-opening, boutons are distributed broadly along the terminal arbor in mice, but gradually form tight clusters over the later window of development (for examples of mouse and cat RGC axon bouton clustering, see Fig. 1B and 1C). This development suggests that an immature axon makes transient contacts with a large number of potential postsynaptic targets, but redistributes its inputs onto a few targets during the period of activity-dependent refinement. Final pruning of the arbor skeleton, however, does not occur until well after the end of the geniculate and cortical critical periods (Hong et al., 2014). These findings are consistent with observations in cat and primate studies of the complexity of mature RGC axon morphology (Fig. 1A), with multiple segments that can branch off the primary axon within the optic tract (Sur & Sherman, 1982; Hamos et al., 1987; Sur et al., 1987; Garraghty et al., 1988; Dhande et al., 2011; Hong et al., 2014), although the arbors may be more restricted in the primate dLGN (Glees & Le Gros Clark, 1941; Lachica & Casagrande, 1988; Michael, 1988; Conley & Fitzpatrick, 1989). In cat, one RGC axon arbor spans the territory of far more postsynaptic neurons than it

contacts (Hamos et al., 1987). Reduction of the X-RGC axon arbor occurs between 4 and 12 weeks postnatal, after the peak of ocular dominance plasticity (Hubel & Wiesel, 1970; Sur et al., 1984).

Therefore, while retinogeniculate development yields a circuit with appreciable functional specificity, the anatomical correlates of this process suggests latent complexity in the mature system. The breadth of the RGC axon arbor, which may impart the potential to synapse onto new TC partners even in the adult, together with short-term plasticity mechanisms that modulate the efficacy of existing contacts, provide the scaffold for dynamic computation beyond the relay of retinal firing patterns to the cortex (Alonso et al., 2006; Martinez et al., 2014; Usrey & Alitto, 2015).

Convergence at the retinogeniculate synapse

Retinogeniculate convergence (and divergence) add complexity to visual processing in the dLGN. The simplest circuit, where 1 RGC contacts 1 TC neuron, is most consistent with the concept of a thalamic “relay” (Glees & Le Gros Clark, 1941; Sherman & Guillery, 1996). More complex circuits with converging RGC inputs and/or diverging single RGC axons onto multiple target TC neurons increase the likelihood of the emergence of novel visual features or receptive field properties (Dan et al., 1998; Alonso et al., 2006; Koepsell et al., 2009; Usrey & Alitto, 2015; Sherman, 2016; Weyand, 2016). For these reasons, studies quantifying connectivity, and in particular, the degree of retinogeniculate convergence, is an active area of research.

A tour-de-force serial electron microscopy (EM) reconstruction of the synaptic contacts of one branch of an X-type retinal axon in the cat dLGN demonstrated that a RGC axon makes connections selectively rather than randomly. The reconstructed portion of the axon (reproduced in Fig. 1A) innervated three X-cells and one Y-cell, and its inputs accounted for as much as 33, 49, and 100% of total innervation to the X-cells, and as little as <6% to the Y-cell. This study concluded simultaneously that a TC neuron can receive inputs from multiple RGCs (convergence), and that some of those inputs can also contact other TC neurons (divergence/multiplexing; Hamos et al., 1987). However, the single X-cell that received all of its inputs from the labeled axon remains the best-recognized result, serving as exemplary anatomical evidence for low retinogeniculate convergence. In contrast, Robson (1993) estimated that cat Y-cells receive upwards of 10 inputs per cell, suggesting that convergence varies depending on cell type.

Recent studies using new anatomical methods in p30 mice, however, came to a conclusion that counters the general view of low convergence. Morgan and colleagues used an approach that combines serial section EM with circuit tracing, to identify the presynaptic RGC axons that connect to reconstructed postsynaptic TC neurons in the dLGN. They observed at least 40 RGC axon segments contacting one of these TC neurons (Morgan et al., 2016). Many axons also promiscuously diverged to innervate numerous other TC neurons. Hammer and colleagues reached a number closer to 10 inputs per cell from observations of bouton clustering of multi-color fluorescently labeled RGC axons (Brainbow labeling) in the mouse LGN (Hammer et al., 2015). However, these studies were not able to trace the axon segments to the primary axon, raising the possibility that they were overestimating the number of inputs to a given TC neuron. Overcoming this limitation, and despite low efficiency of rabies tracing, Rompani and colleagues showed that 1–36 RGCs innervate monocular neurons, and up to 91 RGCs from both eyes converge onto binocularly innervated neurons in the mouse

dLGN. The three anatomical studies made no distinctions between X- and Y-cells, but the rabies tracing identified three different patterns of convergence in the binocular dLGN region (Rompani et al., 2017). Importantly, these studies cannot determine whether all the identified contacts are functional; many convergent inputs could be nonfunctional remnants of refinement, as final pruning of the axon arbor occurs between p30 and p60 (Hong et al., 2014). Nonetheless, these independent studies using disparate anatomical methods demonstrate that tens of RGCs may converge onto mature mouse TC neurons.

To date, most functional studies have yielded a more conservative estimate of convergence than the ultrastructural literature. In the rodent slice prep, estimates of the number of afferent inputs obtained by varying the intensity of optic tract stimulation yield numbers ranging from 1 to 5 (Chen & Regehr, 2000; Jaubert-Miazza et al., 2005; Ziburkus & Guido, 2006; Hooks & Chen, 2007; Chung et al., 2013; Lee et al., 2014; Dilger et al., 2015). However, this approach likely underestimates convergence due to the severing of axons in slice. It also averages across the population of TC neurons accessible with this method, with no distinction between TC neuron subtypes with different input convergence that may exist in the mouse dLGN (Krahe et al., 2011).

Estimates of retinogeniculate connectivity from carnivores and nonhuman primates have largely utilized recordings that assess the correlation of spiking activity of RGC-TC neuron pairs *in vivo* (Cleland et al., 1971; Levick et al., 1972; Kaplan & Shapley, 1984; Mastronarde, 1987, 1992; Usrey et al., 1998; Rowe & Fischer, 2001; Carandini et al., 2007; Sincich et al., 2007; Rathbun et al., 2010). Many of these experiments show that a geniculate X-cell (cat) or M or P cell (primate) receives at least one dominant input that reliably drives EPSCs preceding all or most of a TC neuron’s spikes (Cleland et al., 1971; Cleland & Lee, 1985; Soodak et al., 1987; Sincich et al., 2007). Others, however (especially those focusing on Y cells in cats), show that the contribution from individual RGCs exhibits greater variability, and the activity of a single retinal input rarely accounts for the entirety of the activity of its TC neuron partner (Hubel & Wiesel, 1961; Cleland & Levick, 1971; Cleland et al., 1971; Levick et al., 1972; Mastronarde, 1992). Interestingly, one study using paired recordings across both X- and Y-cells yielded examples of RGCs that drove as few as ~1% to as many as 82% of a TC neuron’s action potentials (Usrey et al., 1999); similar results later emerged in the Y pathway (Yeh et al., 2009; Rathbun et al., 2016; considered in detail in; Weyand, 2016). Furthermore, several studies corroborate anatomical observations of divergence, such that neurons with most closely matching receptive fields exhibit the greatest correlation among their firing patterns (Alonso et al., 1996; Usrey et al., 1998).

The variability in the contribution of a single RGC to postsynaptic spiking in cat dLGN is consistent with anatomical studies, if the number of contacts between a single RGC axon and TC cell relates to the functional strength of the individual input (Hamos et al., 1987). The findings in cat are also consistent with *in vitro* functional data from mice. Even in adult mice (p60), the distribution of single RGC input amplitudes ranges from a tens of pA to several nA in strength (Fig. 4D; Hooks & Chen, 2008; Hong et al., 2014; Thompson et al., 2016). The fact that weak convergent inputs persist into adulthood, in both cats and mice, suggest that they have relevance for retinogeniculate function (Alonso et al., 1996; Dan et al., 1998; Usrey et al., 1999).

Taken together, the retinogeniculate circuit exhibits organization that is set up to actively tune, select, or elaborate information that is being conveyed from the retina to the cortex, suggesting that the dLGN participates in complex processing of visual information

(Sherman, 2016). While similarities across species support this view, insight into the function of dLGN should come from further elucidation of the differences between mice, cat and primates.

Retinogeniculate plasticity

In addition to short-term plasticity, the retinogeniculate circuit exhibits long-term plasticity of synaptic weights. The finding that both weak and strong inputs innervate mature TC neurons and contribute to their spiking activity highlights the possibility that experience-dependent plasticity of RGC input strength and number relies on the balancing of synaptic weights in the adult circuit (Thompson et al., 2016). The retinogeniculate connectivity map remodels to experience during development, and may also do so in mature animals. Depriving juvenile mice of visual experience for a week starting at p20 (late dark rearing) disrupts retinogeniculate connectivity, decreasing the amplitude of the average retinal input and increasing the overall number of RGC inputs onto TC neurons (Hooks & Chen, 2006, 2008; Narushima et al., 2016). This manipulation also reduces the clustering of RGC axon boutons without significantly altering the size of the arbor or the number of boutons (Hong et al., 2014). Together, these observations suggest that while connectivity between axons and targets is selective, the large size of the arbor builds flexibility into the system: dramatic change in visual experience, such as late dark rearing can resculpt connectivity by rearranging boutons and adjusting input strength (Louros et al., 2014) without investing into remodeling the entire axonal arbor. Because excess branches of RGC arbors do not prune down until at least p60 in mice, retinogeniculate connectivity may exhibit substantial plasticity until at least this age (Hong et al., 2014).

A well-established mechanism for altering synaptic strength in response to activity or experience is through changes in AMPAR content of the post-synaptic density (Huganir & Nicoll, 2013). Several studies link the regulation of AMPAR trafficking and function to modulation of the strength of juvenile retinogeniculate synapses. The retinogeniculate synapse is one among several synapses that recruit GluA1-containing AMPARs in response to sensory stimulation (Clem & Barth, 2006; Kielland et al., 2009; Louros et al., 2014), suggesting that GluA1-dependent AMPAR-driven forms of transmission play an important role in the development and plasticity at this synapse (Fig. 4A–4C; activity-dependent changes in AMPAR subunit composition reviewed in Cull-Candy et al., 2006; Liu & Zukin, 2007; Lee et al., 2014). AMPAR subunit content is sensitive to visual experience: mice subjected to late dark rearing exhibited a decrease in AMPAR current rectification, a measure of the fraction of calcium-permeable to calcium-impermeable AMPARs in the postsynaptic density. In contrast, mice that never had any visual experience (chronically dark reared from birth) exhibited normal rectification (Fig. 4C; Louros et al., 2014). Experience-dependent changes in AMPAR content and function at the retinogeniculate synapse rely in part on stargazin, a transmembrane AMPA regulatory protein that modifies the trafficking and channel kinetics of AMPARs (Straub & Tomita, 2012). Indeed, late dark rearing increases the expression and phosphorylation of stargazin, which can in turn regulate the composition of postsynaptic AMPARs in both a Hebbian (Tomita et al., 2005) or homeostatic manner (Louros et al., 2014). Finally, changes in AMPAR expression also mediate the role of MHC class I molecule H2-D^b in retinogeniculate developmental refinement (Lee et al., 2014). H2-D^b is one of a series of immune-related molecules that shape retinogeniculate

development (Shatz, 2009; Schafer & Stevens, 2010). Mice lacking H2-D^b expression exhibit an increase in calcium-permeable AMPARs at retinogeniculate synapses, corresponding to a deficit in LTD. Together, these studies bespeak a critical role of AMPAR regulation in retinogeniculate synaptic plasticity, which may persist into adulthood.

Both Hebbian and homeostatic mechanisms of synaptic plasticity have been shown to alter retinogeniculate synaptic strength during development (Mooney et al., 1993; Butts et al., 2007; Ziburkus et al., 2009; Krahe & Guido, 2011; Lin et al., 2014; Louros et al., 2014). High frequency stimulation of the optic tract, or low frequency stimulation coincident with postsynaptic depolarization in slices from immature ferret dLGN result in long-term enhancement of the EPSC, with contribution from NMDAR activation (Mooney et al., 1993). However, in rat, the same high-frequency stimulus results in long-term depression in dLGN explants before eye-opening, but long-term potentiation later in development (Ziburkus et al., 2009). Finally, plasticity rules based on burst timing have been identified before eye-opening (Butts et al., 2007 in rat), but these plasticity rules have not been examined in more mature slices. On the other hand, the contribution of homeostatic plasticity in retinogeniculate plasticity has been suggested through studies involving monocular deprivation, chronic dark rearing, manipulation of stargazin, and deletion of *Mecp2* (a transcription factor necessary for homeostatic scaling up in the visual cortex; Blackman et al., 2012; Noutel et al., 2011; Krahe & Guido, 2011; Lin et al., 2014; Louros et al., 2014). Similar paradigms likely also drive synaptic plasticity at the fully mature retinogeniculate synapse.

Recently described instances of rapid plasticity across species could also engage Hebbian or homeostatic mechanisms at the retinogeniculate synapse and cause a shift in the strength of individual retinogeniculate inputs (Moore et al., 2011; Aguila et al., 2017). In fact, dLGN neurons readily adapt to changes in visual input. For example, pharmacologic blockade of On-center RGC activity in adult cats rapidly uncovers Off-center responses in dLGN neurons previously exhibiting On-center responses, instead of silencing them (Moore et al., 2011). Further, acute suppression of cortical feedback in awake monkeys shifted the receptive field position of a subset of TC neurons (Aguila et al., 2017). Finally, rabbit geniculate neurons exhibit bidirectional sensory adaptation that improves signal detection (Stoelzel et al., 2015). While modulatory mechanisms could shape the response of the TC neuron to rapid changes in upstream inputs, the specificity that TC neuron responses exhibit in these studies indicates instead a role for rapid shifts in the synaptic efficacy of retinogeniculate connections. These changes occur too rapidly to rely on structural rearrangements of retinogeniculate connections, their timecourse is consistent with possible unsilencing or strengthening of functionally silent or weak sub-threshold inputs *via* the insertion of postsynaptic receptors at dormant synaptic sites. Of course, local inhibitory circuits may also contribute to rapid shifts in RGC input efficacy (Fisher et al., 2017). Changes that occur over days rather than hours may also recruit the redistribution of presynaptic boutons along the broad RGC axon arbor. The capacity of the diverse types of retinogeniculate synaptic contacts for functional plasticity remains unexplored.

The expression of a variety of mechanisms for modification of synaptic weights is layered on top of a potentially densely interconnected network that is evident in considerable retinogeniculate divergence and convergence. Combined with the observation that both weak and strong inputs innervate mature TC neurons, these plasticity mechanism may endow the dLGN with a role in visual learning on multiple time scales (Ramos et al., 1976; Albrecht et al., 1990).

Conclusion

Recent work is revealing new complexities of retinogeniculate transmission and circuit organization that further expand the potential role of the dLGN in visual processing beyond its classic attributes (Steriade et al., 1997; Sherman & Guillery, 2001). The morphological diversity of synaptic motifs and complex connectivity patterns, combined with short- and long-term plasticity mechanisms of the retinogeniculate circuit demonstrate that the retinogeniculate synapse makes substantial and dynamic contributions to the processing of visual information. Weak or non-dominant retinogeniculate inputs in the mature dLGN, which have repeatedly been dismissed as insignificant, as errors of development or leftovers from developmental plasticity with no functional relevance (Sur et al., 1984; Garraghty et al., 1985; Hamos et al., 1987), likely enhance extraction of visual features in the geniculate and visual cortex, and serve as strategic reserves of plasticity. Moreover, the convergence of potentially heterogeneous RGC inputs onto single geniculate neurons could give rise to new receptive field features such as orientation selectivity in mouse dLGN, as recently proposed (Stafford & Huberman, 2017). Finally, the interplay between the strength and short-term plasticity properties of RGC inputs in the context of convergence and divergence adds to the richness of the dLGN circuitry.

Much is still left to understand about the extent and underlying basis of plasticity in the dLGN. However, the idea that the mature geniculate system can utilize activity-dependent plasticity mechanisms to fine-tune the contribution of its individual inputs in response to novel visual challenges, experiences, changes in modulatory state, or retinal degeneration appears to be rapidly gaining experimental support. Future studies are needed to clarify the differences in the number of inputs that converge onto TC neurons between species, because the results may correlate with the degree by which new receptive field features emerge at the level of dLGN. Elucidation of whether and how weak inputs contribute to visual processing in different species will also uncover the richness of thalamic function.

The continually expanding toolbox for interrogating diversity in neuronal circuits is already uncovering nuances in the contribution of different RGC types to TC neuron function (Storchi et al., 2015; Denman et al., 2016). Advances in methods for labeling, activating, and measuring the activity of different neuronal populations that have been deployed extensively in mice may also reveal underappreciated subtleties of retinogeniculate transmission in other species (Scholl et al., 2013; Zaltsman et al., 2015; Zeater et al., 2015; Suresh et al., 2016). Shifting models of the organization of the visual system that take into account the important nuances of retinogeniculate functional organization and plasticity are certain to provide new models of visual system development and function.

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