delaying or speeding up onset would be an important experimental twist. Similarly, it would also be interesting to probe whether other subtle stressors (immune challenge, brief exposure to stress, or an environmental toxin) could trigger collapse in a similar way. Detailed studies also will need to elucidate the functional state of each of the components of the dopamine-signaling pathway following transient pre/perinatal reductions of *Disc1*. Electrophysiology studies could directly address whether dopamine D1 and D2 receptors are responding normally to both dopaminergic and PFC circuit-specific challenges. Based on the morphological and neurochemical results, pyramidal and parvalbumin interneuron functions, dopamine transporter activity, and receptor trafficking should be examined directly. As the authors note, it also is important to determine how transiently decreasing *Disc1* leads to alterations in dendritic morphology of pyramidal neurons, which further disrupts the mesocortical DA projections, ultimately creating an allostatic load on the PFC that causes altered behavioral phenotypes.

Finally, this report illustrates the necessity of examining the progression of prenatal disruptions in a temporal fashion. Furthermore, these results highlight the possibility of long-lasting consequences by subtly and selectively disturbing a circuit early in its assembly. Underlying mechanisms driving this phenomenon together with the development of novel strategies for buffering the impact of developmentally induced allostatic load have the capacity to generate novel clinical prevention and intervention strategies prior to disease onset—a noble goal that is occurring more frequently through the translation of basic neurobiological studies.

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Layers upon Layers: MHC Class I Acts in the Retina to Influence Thalamic Segregation

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Recent research has introduced the major histocompatibility complex class I (MHCI) genes as unexpected players in structural and synaptic plasticity in the central nervous system. In this issue of *Neuron*, Xu et al. redirect current theory by providing strong evidence for the inner retina as a site of action of MHCI proteins in retinogeniculate refinement.

Although very well studied for their role in antigen presentation in the immune system, major histocompatibility complex class I (MHCI) genes have only recently been highlighted for their role in developmental plasticity (reviewed in Boulanger, 2009). Corriveau et al. (1998) first demonstrated the expression of MHCI proteins in the normal brain and revealed that their

expression was strongly regulated by neural activity. Subsequently, several MHCI proteins and immunoreceptors were found to be expressed in the retina and dorsal lateral geniculate nucleus of the thalamus (dLGN) of the mouse during the first two postnatal weeks, a period of intense activity-dependent refinement of retinal efferents (Huh et al., 2000).

The projections from the eyes to the dLGN are initially diffuse, but segregate into eye-specific layers early in postnatal development in the mouse (reviewed in Huberman et al., 2008). The location of the domain innervated by each eye is guided in part by ephrin-A signaling, and the refinement of the initially exuberant projections is subsequently dependent on patterned activity by the retinal ganglion cells (RGC) in the eyes. Although light does not drive visual responses in RGCs until a few days before eye opening (around P12 in mouse), spontaneous waves of bursting in the retina are thought to contribute the patterned activity that helps guide early segregation in the dLGN (Galli and Maffei, 1988). During the first postnatal week in mice, spontaneous retinal waves driving correlated firing in neighboring RGCs are mediated by acetylcholine (ACh) released from starburst amacrine cells, which acts on nicotinic ACh receptors (nAChRs) on RGCs and other starburst amacrine cells (Blankenship and Feller, 2010). In mutant mice lacking the β2 nAChR subunit, spontaneous activity persists, but the waves of patterned retinal activity are replaced by abnormally patterned RGC firing. Normal eye-specific segregation does not occur in the dLGNs of β2 *nAChR*$^{-/-}$ mice, nor in animals with pharmacological blockade of retinal nAChRs, arguing for an important role of early patterned activity in retinogeniculate refinement (Penn et al., 1998; Rossi et al., 2001).

Starting around P10 in normal mice, retinal waves begin to be driven by glutamate released from bipolar cells. During this late phase of glutamate receptor-mediated spontaneous activity, the ipsilateral and contralateral eye inputs continue to segregate by further sharpening the boundaries of eye-specific layers. Interestingly, although the dLGN fails to laminate by P8 in β2 nAChR knockout mice, the glutamate-driven waves appear to be sufficient for segregation into widespread, patchy eye-specific regions by the time of eye opening (Muir-Robinson et al., 2002). Furthermore, the maintenance of segregation also requires appropriate spontaneous, and later evoked, retinal activity (Chapman, 2000; Demas et al., 2006).

Meanwhile, back in the retina, stratification of RGC dendrites into sublaminae within the inner plexiform layer (IPL) is also taking place. RGCs can be classified as having ON, OFF, or ON-OFF response properties depending on whether they respond, respectively, to light stimulus onset, offset, or both. The dendritic arbors of ON RGCs ramify exclusively within sublamina b of the IPL where the axons of ON bipolar cells terminate, while OFF RGCs extend within sublamina a to contact the terminals of OFF bipolar cells. On the other hand, ON-OFF RGC dendrites are bistratified (i.e., arborize in both sublaminae of the IPL) to receive inputs from both types of bipolar cell. Between the time of eye opening and full maturity, the fraction of RGCs functionally classified as ON-OFF type decreases dramatically from nearly 40% to just 20% of the total population, and this transformation is accompanied by a corresponding decrease in the fraction of RGCs with bistratified dendritic morphologies. As this shift in the RGC population does not take place in dark-reared mice, it appears to be dependent on visual experience rather than just spontaneous activity (Tian and Copenhagen, 2003).

How might MHCI proteins participate in retinogeniculate refinement? The expression of MHCI proteins and their immunoreceptors has been found to be important for developmental plasticity in several visual structures. Disruption of eye-specific segregation in the dLGN has been demonstrated in mice lacking two specific MHCI proteins, H2-K^b and H2-D^b, as well as in animals deficient for β2-microglobulin and TAP1, which are required for general MHCI expression at the cell surface (Huh et al., 2000; Datwani et al., 2009). Mice mutant for the CD3ζ subunit of the T cell antigen receptor (an MHCI immunoreceptor) have abnormal thalamic segregation (Huh et al., 2000), and H2-K^b and H2-D^b knockout mice, as well as animals lacking PirB (another MHCI immunoreceptor), show enhanced ocular dominance plasticity in the cortex (Boulanger, 2009; Datwani et al., 2009).

In addition to the defect in thalamic segregation, Huh et al. (2000) linked loss of CD3ζ with a lack of hippocampal LTD and enhanced LTP. These functional results led them to hypothesize that CD3ζ/MHCI signaling was required for the elimination of branches from opposite-eye thalamic territory through activity-dependent weakening of retinogeniculate synapses, though plasticity at this synapse was never directly tested in these mice. A study by Xu et al. in this issue (Xu et al., 2010) offers an alternative explanation: that MHCI proteins may be necessary for the normal development of retinal connectivity and function, and thus the defect in retinogeniculate refinement may result from altered activity of RGCs.

Xu et al. took advantage of a mouse line lacking CD3ζ crossed with mice that sparsely express YFP in RGCs to examine the effects of knocking out CD3ζ on RGC form and function. First, CD3ζ was confirmed to be expressed in RGCs, as well as displaced amacrine cells, and shown to colocalize with synaptic markers. Mice mutant for CD3ζ exhibited increased RGC dendritic density at P12, which the authors used time-lapse imaging to attribute to a large decrease in the motility of dendritic protrusions resulting in longer branch lifetimes. Furthermore, at P30 the stratification of *CD3ζ*$^{-/-}$ RGC dendrites was found to be disrupted, with cells having expanded dendritic widths (i.e., the thickness of their dendritic projections as a fraction of the IPL) and many cells extending into both ON and OFF sublaminae of the IPL in the retina. Using multielectrode array recording of light-evoked responses, they functionally confirmed that cells with compromised retinal stratification indeed were acting as ON-OFF RGCs. Moreover, electroretinography from CD3ζ mutants indicated that the oscillatory potentials (which reflect inner retina function) but not the a-wave (photoreceptors) or b-wave (ON bipolar cells) were reduced at P14, designating the inner retina as the site of change in retinal function due to loss of CD3ζ.

The frequency of cholinergic retinal waves in CD3ζ mutants was normal at P3, consistent with previous reports that retinal waves in these animals were

unaltered (Huh et al., 2000). However by P10, when retinal waves should be driven by glutamatergic transmission, the frequency of waves in the retina had decreased sharply. This timeline closely paralleled the deficits seen in retinogeniculate refinement, in which retinal axons established normal patterns in the dLGN in P8 animals, but had projections that were significantly less segregated than wild-type mice at P16. The decrease in frequency of glutamate waves provides strong evidence for modulation of glutamate transmission by CD3ζ, and indeed both the deficits in dendritic motility and LGN refinement in *CD3*$\zeta^{-/-}$ animals could be phenocopied by intraocular application of glutamate receptor blockers NBQX and AP5 from P7 until P12. Significantly, these drugs had no additive effect on dendritic motility in *CD3*$\zeta^{-/-}$ mice, suggesting that the putative defects in glutamatergic transmission due to loss of CD3ζ could account for much of the phenotype.

The observation that improper development of retinal circuitry and function may be the root cause of visual system defects in *CD3*$\zeta^{-/-}$ mice raises important questions about the extent to which MHCI signaling in the dLGN may also participate in retinogeniculate segregation. Although clearly present in the dLGN during the period of segregation, details of the contribution of CD3ζ in the dLGN itself have yet to be clarified. Bulk labeling of retinal axons in CD3ζ mutants indicates deficits in eye-specific segregation, but reconstruction of single RGC axonal arbors in the dLGN would allow for visualization of parameters such as arbor coverage area and branch density that might help distinguish between the consequences of retinal activity blockade and CD3ζ loss of function in the thalamus. Given the enhanced LTP and lack of LTD in the hippocampus of *CD3*$\zeta^{-/-}$ mice, investigating the effects of CD3ζ on synaptic plasticity mechanisms at the retinogeniculate synapse will naturally be an important future experiment to clarify the role of MHCI in visual system plasticity. Other MHCI proteins, as well as members of the innate immune complement cascade like C1q, that are developmentally expressed in the inner retina and play important roles in visual system development should be re-examined with these additional functions in mind. Understanding the exact mechanisms by which MHCI proteins influence dendritic motility, restrict arbor density, and potentially regulate glutamatergic transmission in the eye offers a new set of targets for experiments to help explain how MHCI functions in CNS development. The suggested role for MHCI family members as putative chaperones for V2R receptors in the accessory olfactory system raises the possibility of a direct interaction with glutamate receptors, and perhaps offers a clue as to how they might regulate glutamatergic transmission in the eye and hippocampus (Olson et al., 2006).

Along with the reduced frequency of glutamatergic retinal waves, Xu et al. also reported a decreased firing frequency of RGCs at P3, when retinal waves are cholinergic. Although *CD3*$\zeta^{-/-}$ animals do not show deficits in eye-specific segregation when spontaneous retinal activity is mediated by acetylcholine, it would be interesting to assess the motility and dendritic branch density of *CD3*$\zeta^{-/-}$ RGCs at these young ages when segregation is occurring. It is possible that the decreased firing rate seen in acetylcholine-mediated retinal waves of *CD3*$\zeta^{-/-}$ mice has early effects on morphology or motility that were not revealed using bulk labeling of the retinogeniculate projection.

Evidence for a role of MHCI signaling in retinal development calls for a broadening of our thinking about the sites of action of proteins for synaptic and structural plasticity in the visual system. Future studies will need to be mindful that an effect of disrupted signaling in the retina could be carried throughout the visual system and could have effects in any visual structure downstream. Use of conditional gene deletions and local targeted rescue should help distinguish between potential sites of action. The perspective provided by Xu et al. should "immunize" us against ignoring the potential contributions of retinal plasticity in future studies of visual system development.

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