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Neuron
Previews

Shaping sight: Novel thalamic plasticity channels dLGN feature preference during visual critical period

Chuying Zhou,[1,2,3] Xiang Gao,[1,2,3] and Liming Tan[1,2,3,4,*]
[1]Shenzhen Key Laboratory of Neuropsychiatric Modulation, Shenzhen-Hong Kong Institute of Brain Science, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China
[2]CAS Key Laboratory of Brain Connectome and Manipulation, the Brain Cognition and Brain Disease Institute, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China
[3]Guangdong Provincial Key Laboratory of Brain Connectome and Behavior, the Brain Cognition and Brain Disease Institute, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China
[4]University of Chinese Academy of Sciences, Beijing 100049, China
*Correspondence: lm.tan@siat.ac.cn
https://doi.org/10.1016/j.neuron.2025.04.001

Sonoda et al.[1] showed that dLGN neurons exhibit long-lasting shifts of tuning preference toward selective features experienced during the classical critical period. They demonstrated that this plasticity results from feedforward-input refinement, revealing a different form of experience-dependent plasticity compared to V1.

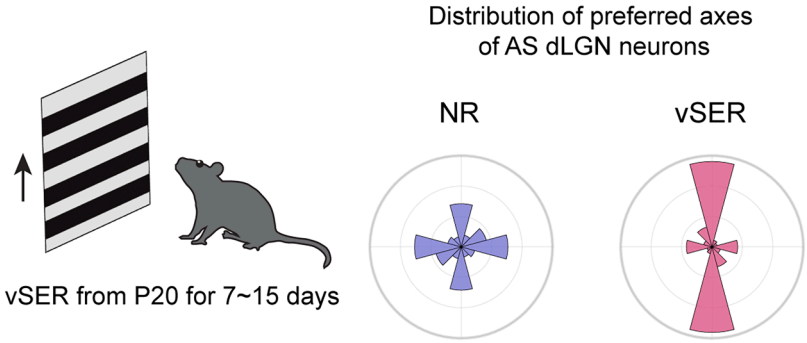
Since Hubel and Wiesel discovered ocular dominance (OD) plasticity and its critical period in the primary visual cortex (V1), experience-dependent binocular plasticity in the mammalian visual cortex has been intensively used as a model for understanding how extrinsic stimuli interact with intrinsic genetic programs to shape neural circuits.[2] Although Hubel and Wiesel initially claimed that no binocular plasticity was found in the primary visual thalamus (dLGN), extensive efforts have been made to re-examine this cortical form of plasticity in the dLGN. However, whether binocular plasticity exists in the dLGN still remains controversial. While OD plasticity and binocular matching of orientation preferences have been reported, others identified few functionally binocular neurons and very limited binocular plasticity in this brain area.[3–5] On the other hand, plastic interactions do exist between dLGN neurons and retinal ganglion cells via retinogeniculate inputs,[6] and the dLGN receives feedback inputs from V1, indicating plastic potential of dLGN neurons. Thus, the nature of experience-dependent plasticity in the dLGN and its distinction from cortical plasticity remain to be elucidated.

The work in this issue of *Neuron* by Sonoda et al.[1] reveals an unexpected form of experience-dependent plasticity in the dLGN. Instead of applying visual deprivation, the authors used a selective experience rearing (SER) paradigm in which mice were restricted to viewing horizontal gratings moving upward (vSER) for 7–15 days from P20 (Figure 1A), and then they examined changes on axis tuning of dLGN neurons via *in vivo* extracellular recording. By comparing distribution of axis preferences of axis-selective (AS) dLGN neurons between normal-reared (NR) and vSER mice, they found a drastic increase in the proportion of AS neurons preferring vertical axis — the selectively experienced feature (Figure 1A) — but saw no differences in the proportion of visually responsive neurons, their receptive field size and location, ON-OFF index, and axis selectivity of AS neurons. These results demonstrate that restricted exposure to a specific visual feature during the critical period causes marked shift of tuning preference of dLGN neuronal population to that feature.

How stable are these tuning changes? The authors showed that juvenile shift of axis preference is maintained into adulthood despite prolonged recovery of normal visual experience after the critical period. This stability of juvenile plastic changes in axis preference of dLGN neurons is highly analogous to the stability of juvenile plastic changes on binocularity occurring in V1 L2/3 neurons (Figure 1B). Conversely, although plastic changes in axis preference of dLGN neurons occur in adult mice, they are reversible after a recovery period. Interestingly, this instability of adult plastic changes in axis preference of dLGN neurons is also highly similar to the instability of adult plastic changes on binocularity in V1 L2/3[2] (Figure 1B). Thus, Sonoda et al. demonstrated SER-dependent plasticity in the dLGN, which "locks in" juvenile adaptation on statistics of experienced extrinsic stimuli.

The authors further provided mechanistic insights into this plasticity. They first asked whether corticothalamic feedback inputs are required for the axis preference shift. To do this, they acutely silenced excitatory neurons across all V1 layers during recording through excitatory (Gq) designer receptors exclusively activated by designer drugs (DREADD) introduced virally into V1 GABAergic neurons. Despite elimination of corticothalamic input activity, the increase in dLGN neurons preferring vertical axis persisted in vSER mice, indicating that SER-dependent plasticity is not due to changes in cortical feedback connections, at least during the recording session. However, the caveat remains that cortical feedback may play a role in dLGN neuronal populations making the preference shift, as the same group in 2016 reported that corticothalamic inputs from V1 L6 modulate the number of retinogeniculate inputs onto dLGN neurons during the critical period.

A



B

	dLGN plasticity	V1 plasticity (L2/3)
Selective visual experience	Drastic shift of tuning preference	Limited shift of tuning preference (about 10x less)
Visual deprivation	Few funtional binocular neurons and limited binocular plasticity	Remarkable binocular plasticity
Stability of plastic changes	Stable juvenile changes (developmental plasticity), unstable adult changes (homeostatic plasticity)	
Plasticity due to	Refinement of feedforward inputs	Changes on recurrent networks
Feedforward contribution to plasticity	Dependent on retinogeniculate input	Independent of L4 input
Local circuitry	No recurrent network	Recurrent networks
Nature of plasticity	Non-autonomous plasticity	Autonomous plasticity
Function of the brain area	Information relay	Multimodal integration
Experience-induced transcriptomic changes	Little change on cell-type composition	Marked changes on cell-type composition

C

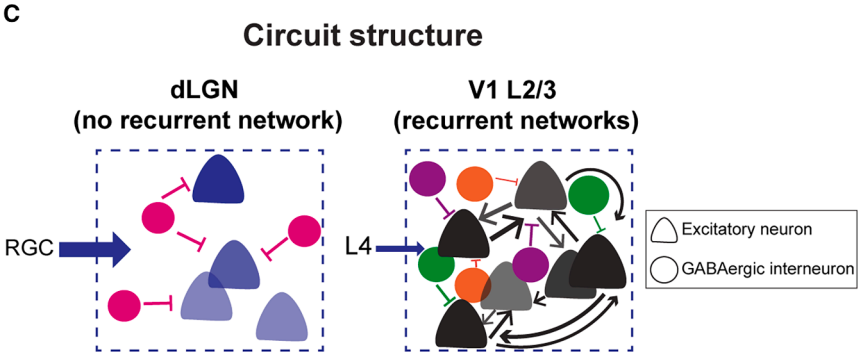


Figure 1. The nature of experience-dependent plasticity in the dLGN and its distinction from cortical plasticity

(A) Left: experience manipulation (vSER) in Sonoda et al. paper. Right: shift in axis preference of dLGN neurons in vSER mice.

(B) Comparisons on experience-dependent plasticity between dLGN and V1 L2/3.

(C) Circuit structure in dLGN and V1 L2/3. Arrows: synaptic connections between neurons.

The authors next asked whether refinement of retinogeniculate feedforward inputs is required for this dLGN plasticity. To test this, they utilized mutant mice with quadruple knockin (QKI) in the methyl-CpG-binding 2 (MeCP2) gene, which converts four important activity-dependent phosphorylation sites on MeCP2 into non-phosphorylatable alanines and disrupts retinogeniculate refinement during early postnatal development. In MeCP2 QKI mice, vSER failed to increase the proportion of dLGN neurons preferring vertical axis without affecting axis selectivity of these neurons. The authors concluded that feedforward input refinement, rather than changes on feedback inputs, is required for SER-dependent plasticity in the dLGN. This finding also indicates that MeCP2 phosphorylation is required for vSER to change retinogeniculate connectivity, which further leads to shift of axis preference of dLGN neurons.

In summary, by using selective visual experience instead of visual deprivation during the classical critical period, Sonoda et al. revealed SER-dependent, lasting preference shift in the dLGN through changes in feedforward inputs — a new form of dLGN plasticity. Their manipulation of experience relates to naturalistic sensory learning more closely, and their evaluation on neuronal feature selectivity relates to neuronal function more broadly, offering higher relevance to adaptive behaviors. An important follow-up question is whether this dLGN plasticity improves mouse perception to the selective experience. Further behavioral tests such as an axis/motion discrimination task could extend the authors' findings to behavioral outcomes. Overall, this work bridges knowledge gaps on experience-dependent plasticity between cortex and thalamus and enriches our understanding of how early-life experience shapes brain circuitry.

Interestingly, a parallel study examining the effect of SER on neuronal tuning in cortex by Bauer et al.[7] found that SER causes only modest drift of preferred orientations in V1 L2/3 neurons, with a median drift magnitude of less than 5° after 15 days of SER. This limited preference drift of V1 L2/3 neurons after prolonged selective visual experience is in sharp contrast to the remarkable shift of axis preference of dLGN neurons. Taking this distinction in SER-dependent plasticity together with differences in binocular plasticity between dLGN and V1 L2/3,[4] a more systematic understanding of thalamic versus cortical plasticity — and their underlying mechanisms — emerges (Figure 1B).

The hallmark of SER-dependent plasticity in the dLGN is that it depends

critically on refinement of retinogeniculate inputs, which are extrinsic structures of dLGN neurons and underscore a form of non-autonomous plasticity. By contrast, plasticity in V1 L2/3 is independent of L4 feedforward inputs but requires changes on recurrent networks, which are circuit structures intrinsic to V1 L2/3 neurons and underlie a form of autonomous plasticity[8,9] (Figure 1C). Existence of recurrent networks in V1 L2/3 can also explain smaller drift magnitude of neuronal orientation preference after SER and a larger proportion of functionally binocular neurons when comparing V1 L2/3 with the dLGN. The differences in circuit organization and circuit mechanisms underlying experience-dependent plasticity between dLGN and V1 L2/3 may reflect differences in specialized function between these two areas: the dLGN relays environmental information from retina to cortex, whereas V1 L2/3 integrates and processes information from multiple modalities to facilitate cognition.

What are the molecular mechanisms underlying plasticity in dLGN and V1 L2/3 during the critical period? Although Sonoda et al. did not dig deeply in this direction, the fact that QKI of MeCP2 that blocks its activity-dependent phosphorylation wiped out SER plasticity in the dLGN indicates that experience-dependent regulation on gene expression plays a pivotal role in dLGN plasticity. Intriguingly, Cheadle et al. found that visual experience upregulates the cytokine receptor Fn14 in dLGN neurons during the critical period, and *Fn14* knockout also disrupts experience-dependent refinement of retinogeniculate afferents,[6] raising the possibility that Fn14 is a downstream target of MeCP2. Notably, although visual experience changes expression level of many genes in dLGN neurons, no change on cell-type composition was reported.[6] This relatively small change in transcriptomic identity of dLGN cell types by experience is again in striking contrast to the vision-dependent specification of cell types in V1 L2/3.[10] Given the autonomous versus non-autonomous nature of cortical versus thalamic plasticity, more fundamental changes in cellular transcriptome might be required for V1 L2/3 to change its microcircuitry to adapt to early-life experience.[9]

In conclusion, Sonoda et al. demonstrated that the primary visual thalamus — dLGN — encodes lasting sensory imprints during early postnatal development.[1] Their work refreshes our understanding on thalamic versus cortical plasticity as non-autonomous versus autonomous plasticity, differing by circuit organization and transcriptomic responses to experience. Furthermore, it is plausible that higher-order visual thalamus — vLGN and LP — may exhibit other forms of experience-dependent plasticity with different circuit and molecular mechanisms, opening up new directions for future exploration.

ACKNOWLEDGMENTS

This manuscript is supported by the National Key R&D Program of China 2022YFA1105503; National Natural Science Foundation of China (NSFC) 32371019; Shenzhen Medical Research Fund B2402005; Shenzhen Key Laboratory of Neuropsychiatric Modulation; CAS Key Laboratory of Brain Connectome and Manipulation 2019DP173024; and Guangdong Provincial Key Laboratory of Brain Connectome and Behavior 2023B1212060055.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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