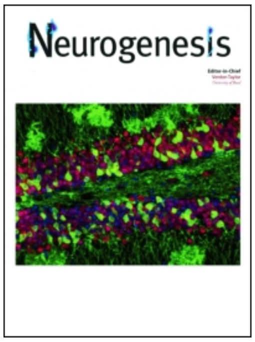

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COMMENTARY

The importance of constructive feedback: Implications of top-down regulation in the development of neural circuits

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ABSTRACT
Neural circuits in sensory pathways develop through a general strategy of overproduction of synapses followed by activity-driven pruning to fine-tune connectivity for optimal function. The early visual pathway, consisting of the retina → visual thalamus → primary visual cortex, has served for decades as a powerful model system for probing the mechanisms and logic of this process. In addition to these feedforward projections, the early visual pathway also includes a substantial feedback component in the form of corticothalamic projections from the deepest layer of primary visual cortex. The role of this feedback in visual processing has been studied extensively in mature animals, yet historically, its role in development has received comparatively little attention. Recent technological advances allowing for selective manipulation of neural activity in development led to the uncovering of a role for feedback in guiding the refinement of the forward projection from retina to visual thalamus. Here we discuss the implications of feedback exerting influence on the development of sensory pathways. We propose several possible advantages to constructing neural circuits with top-down regulation, and discuss the potential significance of this finding for certain neurologic disorders.

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The connection between retinal ganglion cells (RGCs) in the retina and relay neurons in the dorsolateral geniculate nucleus (dLGN, the visual thalamus) undergoes a pronounced refinement during development. In mice, this process involves multiple stages that span the first month of postnatal life.[1] Retinogeniculate connections are initially weak and profuse, but are then pruned or strengthened through these stages to produce the precise connectivity that determines a mature relay neuron's receptive field. During the final stage of this process, visually-driven activity guides this refinement, allowing the circuit to fine-tune with experience.[2] The observation that corticothalamic inputs innervate the dLGN and strengthen comparatively late in development[3,4] just before the experience-dependent remodeling of retinal inputs, led us to hypothesize that feedback may influence development of the forward pathway during this final stage. Using virally-delivered cre-activatable DREADDs[5] in a transgenic mouse line that expresses cre recombinase selectively in corticothalamic-projecting neurons, we manipulated feedback throughout this window and found that proper corticothalamic activity was required to establish the mature retinothalamic circuit.[6] Both increasing and decreasing feedback disrupted refinement specifically during the vision-dependent stage of retinogeniculate remodeling, indicating visually-driven cortical activity may be fed back to thalamus to modify feedforward connectivity.

The corticothalamic projection from layer 6 (L6) of primary visual cortex (V1) to dLGN forms over 4 times as many synapses onto thalamic relay neurons as the forward projection from RGCs.[7] Despite this remarkable fact, the precise function of this feedback in visual processing remains incompletely understood.[8] This is in part because the direct, glutamatergic inputs from L6 onto relay neurons are weak relative to inputs from RGCs,[9] engage a different composition of postsynaptic receptors,[10] and work in concert with disynaptic inhibitory pathways (also driven by L6) to dynamically modulate relay neuron activity patterns[11] (Fig. 1). Further complicating the picture, recent work in mice has shown the visual computations performed by dLGN relay neurons to be diverse[12,13] with some

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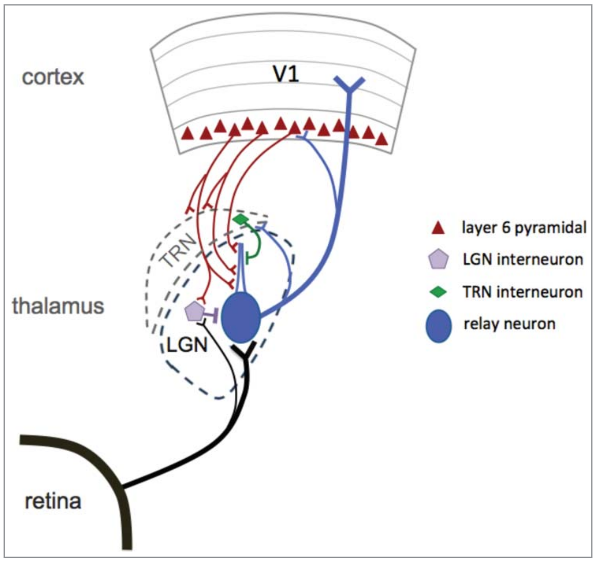

Figure 1. Schematic of the early visual pathway. Information flows from RGCs, the sole output cell type in the retina, to relay neurons in the dLGN to L4 of primary visual cortex. Feedback from L6 of cortex innervates the dLGN, forming numerous, but weak, inputs onto distal dendrites of relay neurons. Relay neurons are inhibited by local interneurons in the dLGN, which receive input from both RGCs and L6 feedback projections, as well as cells in the thalamic reticular nucleus (TRN), which receives input from relay neurons and L6 projections.

cells displaying classical center-surround receptive fields, others responding to stimuli with orientation- or direction-selectivity, and others signaling an absence of contrast in the visual field. This raises the possibility that the influence of cortical feedback on dLGN activity differs based on the relay neuron's receptive field type. Future work will be required to determine if distinct roles for corticothalamic feedback emerge when relay neurons are grouped by receptive field properties.

What are the implications of incorporating feedback into feedforward development? Are there potential advantages to constructing sensory circuits in this fashion, rather than in feedforward sequence? As others have suggested, building sensory circuits sequentially (feedforward model) would seem to afford the process more stability[14,15]; fine-tuning circuits in V1 before subcortical circuits fully mature presents the risk, for instance, that a microcircuit in cortex might refine to perform some computation, only to have thalamic input subsequently change and impair the function of that microcircuit. On the other hand, if thalamus receives visually-processed information from cortex while retinothalamic connectivity is malleable, this may confer unique opportunities for circuit optimization. For example, feedback could play a role in refining retinogeniculate connectivity to increase metabolic efficiency by training relay neurons to conserve spikes. dLGN relay neurons are known to filter incoming RGC action potentials to improve the efficiency of spike-coding.[16,17] If relay neurons receive information from their downstream targets regarding which spikes are driving cortical representations while retinogeniculate inputs are still plastic, then the weights and identities of retinal inputs could be fine-tuned to increase this efficiency. RGC receptive fields are typically mapped by averaging a cell's response to repeated presentations of the same stimulus, giving the impression of a high degree of reliability in a cell's response, but in reality, the brain pieces together a visual scene amidst a large amount of noise and uncertainty.[18] The filtering of signals from retina by thalamus may serve to prevent noise from propagating further along the visual pathway, and feedback from L6 cells in cortex (which receive their input from all layers of V1[19] and innervate dLGN in retinotopic register[20]) may help train relay neurons to discriminate signal from noise.

Another possibility is that incorporating feedback in the development of feedforward circuits contributes to feature learning in sensory pathways. The canonical model of visual processing in the early visual pathway describes a transformation of circular receptive fields in retina and dLGN into elongated receptive fields of a specific orientation in V1.[21,22] The implications of feedback influencing upstream synaptic refinement are particularly interesting when considering this heirarchical emergence of feature selectivity: a visual computation performed in V1 by a cell summing input from multiple thalamic relay neurons with distinct receptive fields could be optimized at the level of thalamus if output from that V1 cell is fed back to the dLGN and used to modify the retinal connectivity onto those relay neurons. (Lending credence to this hypothetical, 2 recent anatomic studies[23,24] suggest the structural basis of vision-dependent retinothalamic refinement may allow feedback to influence rewiring of a surprisingly large number of possible presynaptic partners).

The effectiveness of using downstream output to revise upstream connectivity is manifest in the recent breakthroughs with machine learning approaches using artificial neural networks (including, ironically, those of an architecture directly inspired by Hubel and Wiesel's description of information processing in the early visual pathway).[25,26] A key step in constructing a multilayer network to perform a classification task is application of the backpropagation algorithm[27] where the network is "trained" by iteratively adjusting feedforward synaptic weights according to the network's output in response to labeled training examples. The implementation of backpropagation in supervised learning with neural networks is distinct from how a biologic system might use feedback projections to optimize a sensory circuit (though a more biologically plausible variant of the algorithm was recently described)[28], but given its remarkable efficiency in training artificial networks, it is conceivable that the brain evolved to use feedback projections in development toward a similar goal.

The potential advantages of top-down regulation of circuit rewiring go hand in hand with added perils for developing neural circuits, which are worth considering in relation to the etiology of certain neurodevelopmental disorders. For example, previous work found that retinogeniculate development is disrupted specifically during the experience-dependent phase in a mouse model of Rett syndrome,[29] a brain disorder characterized by seemingly normal early development followed by stagnation and regression, leading to the loss of developmental milestones.[30] The general principle of feedback exerting influence on upstream circuit refinement may offer insight into such a disease progression. If earlier brain regions develop normally, but local defects arise during circuit consolidation in downstream areas, what begins as a limited disruption of a higher brain function could then propagate back to lower areas, eventually giving rise to much more widespread dysfunction. Similarly, as autism-spectrum disorders are increasingly thought to represent disorders of impaired synaptic wiring and plasticity[31,32] inquiry into their neurobiological basis might benefit from maintaining a global view of brain development, and considering the possibility that aberrant circuit refinement in higher brain areas could affect circuit wiring in upstream regions.

In a related manner, the heightened susceptibility of younger brains to the development of epilepsy[33] may be partially explained by feedback exerting influence in development. One of the chronic changes resulting from early-life seizures that can contribute to the eventual onset of epilepsy involves the reorganization of network connectivity and sprouting of new synapses.[34-36] If development at forward pathway connections can be altered by activity in downstream neural circuits, this may lead to an increased risk for a focal seizure in one brain area to affect synaptogenesis not just locally, but in upstream areas as well. To an extreme, this could create a positive feedback loop that lowers the threshold for seizure initiation. Furthermore, epilepsy that develops in children often presents with comorbid cognitive abnormalities later in life.[34] Thus, as with the potential cascading effect of misregulated plasticity in autism-spectrum disorders, the possibility of seizure-induced network changes spreading to earlier brain regions could be an important aspect of the pathophysiology underlying these associated cognitive deficits.

Finally, the idea that circuit development entails bidirectional interactions also has implications for stem cell therapies. One of the major challenges with implanting stem cells into the brain is promoting their incorporation into functional neural circuits. If cortical circuits are sculpted during development in collaboration with subcortical circuits, rather than in isolation as a feedforward model would entail, then another level of synaptic rewiring must be considered in the context of circuit reformation. If a cell in visual cortex normally has the ability to influence the development of afferent inputs to thalamus, then whether or not those synapses in thalamus retain any plasticity at the time when cells are implanted could influence the ability of those cells to integrate into normally functioning circuits.

Conclusion

Top-down connections are receiving increasingly more attention in the ongoing effort to understand how the brain processes sensory input.[37-40] In spite of this, the potential importance of feedback in the development of neural circuits is rarely considered. This basic principle bears relevance to work toward understanding disease progression, and may shed light on the logic of how neural circuits are constructed to process information. Particularly in light of recent progress with artificial neural networks in machine learning applications, key to which has been the fine-tuning of feedforward synaptic weights according to downstream output, the possibility that the brain uses feedback projections to optimize neural circuits during development is an attractive hypothesis. Recent evidence from the early visual pathway suggests this may indeed be the case, though future work will be required to test this hypothesis directly.

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References

[1] Hong, YK & Chen, C. Wiring and rewiring of the retinogeniculate synapse. Curr Opin Neurobiol 2011; 21:228–237.

[2] Hooks, BM & Chen, C. Distinct roles for spontaneous and visual activity in remodeling of the retinogeniculate synapse. Neuron 2006; 52:281–291.

[3] Jacobs, EC *et al.* Visualization of corticofugal projections during early cortical development in a tau-GFP-transgenic mouse. Eur J Neurosci 2007; 25:17–30.

[4] Jurgens, CWD, Bell, KA, McQuiston, AR & Guido, W. Optogenetic Stimulation of the Corticothalamic Pathway Affects Relay Cells and GABAergic Neurons Differently in the Mouse Visual Thalamus. PLoS One 2012; 7: e45717.

[5] Roth, BL. DREADDs for Neuroscientists. Neuron 2016; 89:683–694.

[6] Thompson, AD, Picard, N, Min, L, Fagiolini, M & Chen, C. Cortical Feedback Regulates Feedforward Retinogeniculate Refinement. Neuron 2016; 91:1021–1033.

[7] Montero, VM. A quantitative study of synaptic contacts on interneurons and relay cells of the cat lateral geniculate nucleus. Exp. Brain Res. 1991; 86:257–270.

[8] Denman, DJ & Contreras, D. Complex Effects on In Vivo Visual Responses by Specific Projections from Mouse Cortical Layer 6 to Dorsal Lateral Geniculate Nucleus. J. Neurosci. 2015; 35:9265–80.

[9] Turner, JP & Salt, TE. Characterization of sensory and corticothalamic excitatory inputs to rat thalamocortical neurones in vitro. J Physiol 1998; 510 (Pt 3) 829–843.

[10] Guillery, RW & Sherman, SM. Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. Neuron 2002; 33:163–175.

[11] Crandall, SR, Cruikshank, S.J., & Connors, BW. A Corticothalamic Switch: Controlling the Thalamus with Dynamic Synapses. Neuron 2015; 86:768–782.

[12] Piscopo, DM, El-Danaf, RN, Huberman, AD & Niell, CM. Diverse visual features encoded in mouse lateral geniculate nucleus. J. Neurosci. 2013; 33:4642–56.

[13] Suresh, V *et al.* Synaptic Contributions to Receptive Field Structure and Response Properties in the Rodent Lateral Geniculate Nucleus of the Thalamus. J. Neurosci. 2016; 36:10949–10963.

[14] Katz, LC & Shatz, CJ. Synaptic activity and the construction of cortical circuits. Science 1996; 274:1133–1138.

[15] Knudsen, EI. Sensitive periods in the development of the brain and behavior. J Cogn Neurosci 2004; 16:1412–1425.

[16] Sincich, LC, Adams, DL, Economides, JR & Horton, JC. Transmission of spike trains at the retinogeniculate synapse. J. Neurosci. 2007; 27:2683–2692.

[17] Sincich, LC, Horton, JC & Sharpee, T. Preserving information in neural transmission. J. Neurosci. 2009; 29:6207–6216.

[18] Meister, M & Berry, MJ. The neural code of the retina. Neuron 1999; 22:435–450.

[19] Vélez-Fort, M *et al.* The Stimulus Selectivity and Connectivity of Layer Six Principal Cells Reveals Cortical Microcircuits Underlying Visual Processing. Neuron 2014; 83:1431–1443.

[20] Murphy, PC & Sillito, AM. Functional morphology of the feedback pathway from area 17 of the cat visual cortex to the lateral geniculate nucleus. J. Neurosci. 1996; 16:1180–1192.

[21] Hubel, D & Wiesel, T. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J. Physiol. 1962; 160:106–154.

[22] Ferster, D & Miller, KD. Neural mechanisms of orientation selectivity in the visual cortex. Annu. Rev. Neurosci. 2000; 23:441–471.

[23] Hong, YK, Park, S, Litvina, EY, Morales, J, Sanes, JR, & Chen, C. Refinement of the retinogeniculate synapse by bouton clustering. Neuron 2014; 84:332–9.

[24] Morgan, JL, Berger, DR, Wetzel, AW & Lichtman, JW. The Fuzzy Logic of Network Connectivity in Mouse Visual Thalamus. Cell 2016; 165:192–206.

[25] Krizhevsky, A, Sutskever, I & Hinton, GE. ImageNet Classification with Deep Convolutional Neural Networks. Advances in Neural Information Processing Systems 2012; 25:1090–1098.

[26] LeCun, Y, Bengio, Y & Hinton, G. Deep learning. Nature 2015; 521:436–444.

[27] Rumelhart, DE, Hinton, GE & Williams, RJ. Learning representations by back-propagating errors. Nature 1986; 323:533–536.

[28] Lillicrap, TP, Cownden, D, Tweed, DB, & Akerman, CJ. Random synaptic feedback weights support error backpropagation for deep learning. Nat. Commun. 2016; 7:13276.

[29] Noutel, J, Hong, YK, Leu, B, Kang, E & Chen, C. Experience-dependent retinogeniculate synapse remodeling is abnormal in MeCP2-deficient mice. Neuron 2011; 70:35–42.

[30] Chahrour, M & Zoghbi, HY. The Story of Rett Syndrome: From Clinic to Neurobiology. Neuron 2007; 56:422–437.

[31] LeBlanc, JJ & Fagiolini, M. Autism: a 'critical period' disorder? Neural Plast 2011, 2011;921680.

[32] Yashiro, K *et al.* Ube3a is required for experience-dependent maturation of the neocortex. Nat Neurosci 2009; 12:777–783.
[33] Rakhade, SN & Jensen, FE. Epileptogenesis in the immature brain: emerging mechanisms. Nat. Rev. Neurol. 2009; 5:380–391.
[34] Holmes, GL, Gairsa, JL, Chevassus-Au-Louis, N & Ben-Ari, Y. Consequences of neonatal seizures in the rat: morphological and behavioral effects. Ann. Neurol. 1998; 44:845–857.
[35] Cross, DJ & Cavazos, JE. Synaptic reorganization in subiculum and CA3 after early-life status epilepticus in the kainic acid rat model. Epilepsy Res. 2007; 73:156–165.
[36] Holmes, GL. Effect of Seizures on the Developing Brain and Cognition. Semin. Pediatr. Neurol. 2016; 23:120–126.
[37] Gilbert, CD & Li, W. Top-down influences on visual processing. Nat. Rev. Neurosci. 2013; 14:350–363.
[38] Manita, S *et al.* A Top-Down Cortical Circuit for Accurate Sensory Perception. Neuron 2015; 86:1304–1316.
[39] Robinson, BL, Harper, NS, & McAlpine, D. Meta-adaptation in the auditory midbrain under cortical influence. Nat. Commun. 2016; 7:13442.
[40] Zhang, S *et al.* Selective attention. Long-range and local circuits for top-down modulation of visual cortex processing. Science 2014; 345:660–5.