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Dissecting the Dynamics of Corticothalamic Feedback

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The thalamus and neocortex are intimately interconnected via a reciprocal arrangement of feedforward and feedback projections. In this issue of *Neuron*, Crandall et al. (2015) provide key insight into the functional dynamics of feedback projections and reveal the cellular and circuit mechanisms that underlie a rate-dependent switch in the net influence, suppression versus excitation, that cortex can exert on thalamic relay cells.

Since the early days of in vivo neurophysiological recordings, sensory processing has been best understood in terms of feedforward hierarchical models. In these models, typified by Hubel and Wiesel's iconic work on the early visual system (Hubel and Wiesel, 1962), sensory processing is described as a unidirectional process that occurs in a series of discreet stages, with neuronal receptive fields becoming more selective due to feedforward lines of communication. Although the existence of hierarchical processing is undeniable, it is also clear that the neuronal circuits that comprise sensory systems are far more complex than indicated in feedforward models. Namely, when one looks at the organization of synaptic connectivity within a sensory system, in the thalamus and neocortex, it is clear that information is exchanged in both the feedforward and feedback directions. Indeed, each sensory area, both thalamic and cortical, receives excitatory synaptic input from higher-order areas. Despite the ubiquitous presence of these feedback projections, our understanding of the functional role(s) feedback serves during sensory processing is limited.

Anatomically, we know a great deal about how feedforward and feedback pathways are organized within sensory nuclei of the dorsal thalamus (Figure 1) (reviewed in Jones, 2006; Briggs and Usrey, 2011). With the exception of the olfactory system, sensory input from the periphery reaches the cortex via the dorsal thalamus. In the rodent somatosensory system, axons carrying information from the whiskers travel through the medial lemniscus (ML) to make synapses with neurons in the ventral posteromedial (VPM) nucleus of the thalamus, which in turn project to primary somatosensory cortex. A similar organization is found with visual system, where neurons in the lateral geniculate nucleus (LGN) supply primary visual cortex (V1) and neurons in the medial geniculate body (MGB) supply primary auditory cortex (A1). Importantly, neurons in each of these relay nuclei, the VPM, LGN, and MGB, also receive massive excitatory feedback from layer 6 of the cortical area they supply (S1, V1, and A1). This feedback is anatomically robust and accounts for approximately 50% of the synapses found on thalamic relay neurons, a percentage far greater than that supplied by feedforward projections.

Despite the anatomical prominence of corticothalamic feedback and the considerable amount of experimental effort that has been focused on it, a thorough understanding of the function of corticothalamic feedback remains elusive. This lack of understanding likely reflects the use of anesthetized animals for studying feedback, as anesthesia can significantly dampen sensory responses in corticothalamic neurons (reviewed in Briggs and Usrey, 2011). It may also reflect complex interactions involving the spatial specificity of feedback projections and the temporal structure of signals traveling in those projections (Granseth et al., 2002; Li et al., 2003; Briggs and Usrey, 2009; Olsen et al., 2002). Moreover, feedback has the opportunity to influence thalamic processing via monosynaptic excitation and disynaptic inhibition through connections with GABAergic neurons in the thalamic reticular nucleus (TRN) that also supply relay neurons. Evidence demonstrating the facilitative and suppressive effects of feedback comes from the bat auditory system, where Suga and colleagues found that cortical feedback amplified activity in thalamic neurons with receptive fields that matched those of active cortical neurons and suppressed activity in thalamic neurons with receptive fields that were a mismatch (reviewed in Suga and Ma, 2003). A similar type of effect has been found in the rodent barrel system where cortical feedback excites thalamic neurons that correspond to the whisker being stimulated and suppresses activity in thalamic neurons corresponding to surrounding whiskers (Temereanca and Simons, 2004; Li and Ebner, 2007). Likewise, neurons in the LGN are reported to be excited by cortical feedback when a visual stimulus is centered over their receptive fields and suppressed by feedback when the stimulus involves surrounding regions of space (reviewed in Cudeiro and Sillito, 2006). While these studies provide insight into the spatial organization of feedback pathways and the dual nature of feedback effects, facilitation versus suppression, an open and unresolved question is whether the dual nature of feedback is dynamic, being governed by temporal properties of the feedback neurons' activity.

In the current issue of *Neuron*, Crandall et al. (2015) provide critical insight into understanding the dynamic properties of corticothalamic feedback. Through a

series of elegant in vitro experiments, combining intracellular recordings of VPM and TRN neurons with optogenetic activation of corticothalamic axons, they identify a dynamic feature of corticothalamic circuitry that determines the net influence of feedback on thalamic processing. Namely, when cortical feedback was stimulated at a low rate (0.1 Hz), thalamic relay neurons in VPM displayed brief excitatory responses followed by longer-lasting suppression. In contrast, when cortical fibers were activated at a higher rate (10 Hz), feedback had a net excitatory influence that lasted until the next period of activation. Voltage-clamp recordings further revealed that the dynamic switch was the result of both facilitation of the EPSCs and depression of the IPSCs during high-frequency stimulation relative to low-frequency stimulation.

The facilitation of EPSCs during high-frequency stimulation of corticothalamic axons was expected. Indeed, previous studies have shown that cortical synapses onto thalamic relay neurons experience strong synaptic facilitation during high rates of stimulation (Granseth et al., 2002; Li et al., 2003; Sun and Beierlein, 2011). The presence of depressing IPSCs was surprising, however, as corticothalamic synapses onto TRN neurons also display rate-dependent facilitation (Jurgens et al., 2012). Crandall et al. (2015) investigated this paradoxical finding further and discovered that two properties of TRN inhibitory neurons contributed to the production of depressing IPSCs. First, TRN neurons, like thalamic relay neurons, fire action potentials in two distinct modes: tonic mode and burst mode. Burst mode is known to occur when thalamic neurons are sufficiently hyperpolarized to de-inactivate voltage-gated T-type Ca^{2+} channels, a state that allows subsequent suprathreshold depolarization to trigger a burst of action potentials. The slow dynamics of T-type Ca^{2+} channels, however, was found to reduce the ability of TRN neurons to follow high rates of cortical stimulation and resulted in a 40% reduction in the number of TRN action potentials generated by cortical stimulation. This mechanism alone, however, could not fully account for the 70% reduction in synaptic inhibition onto thalamic relay neurons. Interestingly, the remaining reduction in inhibition involved a second mechanism: synaptic depression of GABAergic transmission from TRN neurons onto VPM neurons.

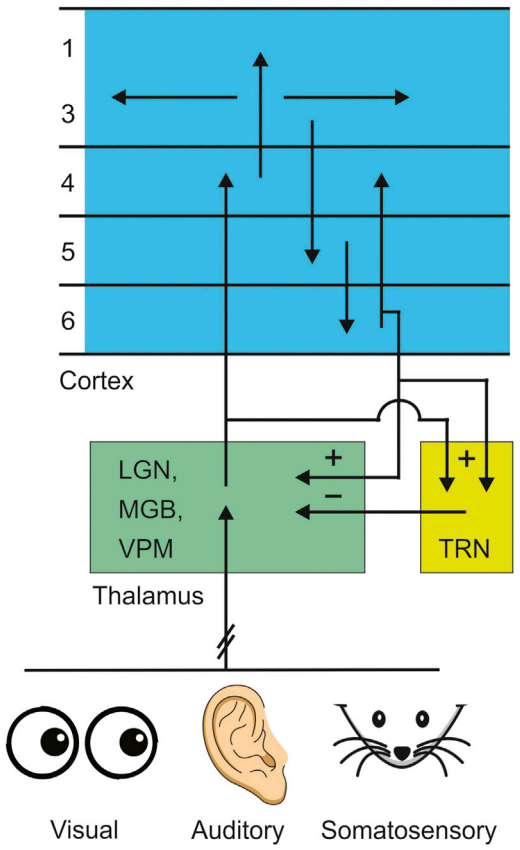

Figure 1. Corticothalamic Circuitry for the Visual, Auditory, and Somatosensory Systems

All three systems share a similar basic organization. Thalamocortical projections arise from relay neurons located in the LGN, MGB, and VPM that provide input to primary visual, auditory, and somatosensory cortex, respectively. Neurons in cortical layer 6, in turn, give rise to feedback projections to the thalamus. Corticothalamic feedback axons influence relay cell activity via monosynaptic and disynaptic connections. The monosynaptic pathway is excitatory and uses glutamatergic synapses, whereas the disynaptic pathway involves a collateral projection into the TRN that excites GABAergic neurons that, in turn, provide inhibitory input onto relay neurons.

The ability of corticothalamic feedback to switch between suppression and excitation may explain some of the inconsistencies in findings that have been reported in the literature, particularly under conditions of anesthesia where the influence of anesthesia on the firing rate of corticothalamic feedback neurons is known to be strong but is poorly understood. Along these lines, the excitatory versus inhibitory influence of corticothalamic feedback is predicted to depend on all of the factors that influence the firing rate of corticothalamic neurons. Stimulus strength is therefore predicted to influence cortical feedback, with suppression dominating when sensory stimulation is weak, and excitation dominating when sensory stimulation is strong. Likewise, attention is predicted to affect the influence of corticothalamic feedback, as attention directed toward a region of sensory space generally increases the activity levels of corresponding cortical neurons and, consequently, should shift the net influence of feedback toward greater excitation. In support of this view, fMRI and electrophysiological studies describe enhanced activity in the LGN with spatial attention (O'Connor et al., 2002; McAlonan et al., 2008). Looking forward, the influence of attention on thalamic activity is predicted to be strongest for cortical feedback originating from higher-order cortical areas that experience greater augmenting effects of attention on activity levels (e.g., the corticothalamic pathway from V4 to the pulvinar nucleus). Of course, the dynamics reported in the current studies may not hold for higher-order thalamic areas. Thus, additional experiments will need to be conducted to determine the generalizability of these findings to other thalamic regions.

Results from Crandall et al. (2015) may also provide important insights into how cortical feedback operates during sleep and awake quiescence, periods during which thalamocortical oscillations become prominent and sensory transmission between thalamus and cortex is disrupted. During these oscillations, the firing structures of both thalamic neurons and cortical neurons dramatically change. Thalamic relay neurons and TRN neurons become hyperpolarized, by mechanisms including withdrawal of cholinergic input,

and enter into burst mode, which may influence how corticothalamic input is modulated and filtered by thalamic circuits. Moreover, cortical neurons display slow wave oscillations (<1 Hz) that make the firing rates of cortical neurons bimodal, displaying long periods of low firing rates separated by briefer bouts of high firing rates. Thus, the rate-dependent dynamics revealed in Crandall et al. (2015) may play a role in maintaining thalamocortical oscillations.

In summary, Crandall et al. (2015) performed an elegant series of experiments to determine the cellular and circuit mechanisms that underlie a rate-dependent switch between suppression and excitation in the corticothalamic pathway of the rodent somatosensory system. Their findings provide a mechanistic understanding of how the cortex can dynamically influence its own input and reinforce the view that the thalamus and cortex are active and necessary partners in the processing of signals essential for sensory, motor, and cognitive functions. While past models of thalamocortical interactions based purely on feedforward circuits were able to provide important insight into the processing of sensory signals, a more complete understanding requires the formulation of new models that include the dynamic influence that corticothalamic feedback has on feedforward lines of communication.

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How Cumulative Error in Grid Cell Firing Is Literally Bounded by the Environment

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In this issue of *Neuron*, Hardcastle et al. (2015) show that the spatial firing patterns of grid cells accumulate error, drifting coherently, until reset by encounters with environmental boundaries. These results reveal important aspects of the neural dynamics of self-localization from self-motion and environmental information.

Estimating one's location relative to the environment is crucial for the survival of most mobile organisms, enabling planning and movement relating to important environmental locations beyond immediate perception, such as one's home, locations containing resources, friends, enemies, etc. An estimate of self-location can be made from environmental sensory information and can also be dynamically updated by integration of estimated self-motion, a process often referred to as "path integration" (PI, extending its original meaning of tracking displacement from a single starting point, as in classic experiments in spiders and ants). The two types of information, environmental and self-motion-related, make complementary contributions to self-localization. The cumulative nature of PI makes it accumulate error, which must be corrected by environmental information, while self-motion can be used to update self-location when appropriate environmental information is unavailable, unreliable, or too effortful to acquire. Ideally, both types of information should be combined according to their reliability, as seen in human navigation (Nardini et al., 2008) and in Kalman or particle filtering in robotics.

A canonical experimental demonstration of PI in mammals exploits an innate