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Cellular Specificity of Cortico-Thalamic Loops for Motor Planning

David P. Collins^{1,2} and Paul G. Anastasiades²

¹Sackler Institute of Graduate Biomedical Sciences, New York, New York 10010, and ²Center for Neural Science, New York University, New York, New York 10003

Review of K. Guo et al.

Ongoing communication between cortex and thalamus plays an important role in cognition, sensation, and motor function. The synaptic basis of cortico-thalamo-cortical interactions has been a field of intense study over many decades, often going hand-in-hand with studies of activity recorded *in vivo*. In the classical model of cortico-thalamo-cortical circuits, derived largely from studies of primary sensory cortices (e.g., S1, V1, A1), ascending input from sensory thalamus undergoes cortical processing, before being relayed back to thalamus via two distinct populations of deep-layer projection neurons (Guillery and Sherman, 2002). Layer (L)5 pyramidal tract (PT) neurons provide “driver” input to higher-order thalamic nuclei, which relay this information to the next region of the sensory hierarchy (e.g., S2, V2, A2) (Fig. 1A) and provide feedback to primary sensory cortices. In contrast, L6 cortico-thalamic (CT) cells provide “modulator” feedback to the primary sensory thalamic nucleus and target the thalamic reticular nucleus (TRN) to drive thalamic feedforward inhibition

(Fig. 1A). This architecture facilitates information flow up the hierarchy of sensory processing, with thalamus functioning as a relay between cortical regions (Guillery and Sherman, 2002) (Fig. 1A).

The organization of cortico-thalamo-cortical circuits in higher-order cortices has been proposed to diverge from the classical sensory model, with connections instead organized in reciprocal “loops” (Svoboda and Li, 2018). Studying the synaptic organization of these circuits has been challenging due to the inability to produce *ex vivo* slices with intact connectivity between higher-order cortices, TRN, and thalamus, a preparation that has greatly facilitated study of thalamo-cortical circuits in sensory regions (Agmon and Connors, 1991). A recent study by K. Guo et al. (2018) harnessed the power of optogenetics to overcome these anatomical constraints.

K. Guo et al. (2018) focused on interactions between ventromedial thalamus (VM), a higher-order thalamic nucleus that receives input from the basal ganglia and cerebellum, and anterolateral motor cortex (ALM), a region of frontal cortex involved in motor planning. Reciprocal connections between VM and ALM have recently been shown to play an important role in sustaining activity while mice plan to perform a movement in response to a tactile signal (Z. V. Guo et al., 2017). Therefore, understanding the organiza-

tion of this circuit is important to determining neural mechanisms of motor planning and is of broad interest to deciphering how higher-order cortico-thalamo-cortical loops support cognitive processing. Because detailed understanding of the circuit between VM and ALM requires knowledge of input-, layer-, and cell type-specific connectivity, K. Guo et al. (2018) used retrograde tracers to define projection neuron populations in individual layers: CT neurons in L6 (labeled via injection in VM), PT neurons in L5B (labeled via injection in the pons), and unlabeled cells in L2/3. They then used optogenetic stimulation of VM axons to measure synaptic responses at these three cell types and thus determine long-range input–output functions. They observed that VM input is strongest in L2/3, followed by L5 PT, with minimal input to L6 CT cells. These findings indicate that L5, not L6, plays a key role in monosynaptic loops between VM and ALM.

Previous work has shown that VM axons arborize in L1 of frontal cortex (Kuramoto et al., 2015), suggesting that VM input to L5 PT cells likely occurs at their apical dendrites, which ramify densely in that layer. To test this, the authors used a subcellular optogenetic mapping approach, termed sCRACM (Petreanu et al., 2009), which allows the dendritic location of VM synapses to be determined. By scanning a

Received Nov. 21, 2018; revised Jan. 28, 2019; accepted Feb. 4, 2019.

We thank members of the Carter laboratory for helpful discussions.

The authors declare no competing financial interests.

Correspondence should be addressed to Paul G. Anastasiades at pa68@nyu.edu.

<https://doi.org/10.1523/JNEUROSCI.2964-18.2019>

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Figure 1. *A*, Sensory information from the periphery is relayed via sensory thalamus to primary sensory cortex (A1, V1, S1). L6 CT cells provide feedback “modulator” input to sensory thalamus while also targeting TRN. L5 PT cells instead bypass TRN and provide strong “driver” input to higher-order sensory thalamus, which relays this signal to sensory regions higher up in the cortical hierarchy (A2, V2, S2). *B*, Work by K. Guo et al. (2018) reveals a distinct organization in higher-order motor regions, where VM receives input from both L5 PT and L6 CT neurons of ALM. Moreover, rather than relaying information between ALM and M1, the reciprocal loops involving ALM, M1, and VM are nonoverlapping, suggesting parallel loops linking VM and regions of motor cortex. *C*, Combining these two schemas, we propose that there may be a transition in the organization of cortico-thalamic signaling as we ascend the cortical hierarchy. Sensory input is relayed between cortical regions via direct intracortical pathways and via feedforward projections (black) to thalamus and subsequently relayed to higher cortical regions. In higher-order cortex, these circuits no longer function to relay information between regions, but instead form reciprocal loops to support high-level cognitive tasks, such as motor planning. In these schematics, feedback signals from thalamus to cortex have been omitted for clarity.

finely focused laser beam across the slice, in the presence of pharmacological agents to effectively restrict photoactivation to presynaptic boutons, they found that the apical dendrites of L5 PT cells do indeed receive significant VM input through L1. Interestingly, apical thalamic input to PT cells is observed across higher-order frontal regions (Collins et al., 2018) but is absent for higher-order thalamic input to

primary somatosensory cortex (Petreanu et al., 2009). Apical targeting therefore appears to be region-, cell type-, and input-specific (Petreanu et al., 2009; Suter and Shepherd, 2015; Anastasiades et al., 2018; Collins et al., 2018), suggesting a unique role in higher-order frontal cortices.

A consequence of apical targeting is that VM input is under the control of hyperpolarization-activated cyclic nucleo-

tide-gated (HCN) channels, which are highly enriched at apical dendrites of PT cells (Williams and Stuart, 2000). Extending previous work using glutamate uncaging (Sheets et al., 2011), K. Guo et al. (2018) measured VM inputs in current clamp, which allows HCN channels to influence the postsynaptic response (Sheets et al., 2011; Anastasiades et al., 2018). They first mapped the amplitude of EPSPs

across apical and basal dendrites of L5 PT cells, again using the sCRACM approach to provide subcellular specificity. Repeating these experiments in the presence of the HCN channel blocker ZD7288, they found selective enhancement in the amplitude of apical inputs, indicating that HCN channels normally limit the influence of VM input to PT cells.

This finding is especially interesting because of known interactions between neuromodulatory systems and HCN channels (Dembrow and Johnston, 2014). Cortical levels of neuromodulators, such as acetylcholine and norepinephrine, are elevated during periods of arousal or behavioral salience (Robbins, 1997; Hangya et al., 2015). Neuromodulators can reduce HCN channel activation, which produces pronounced shifts in the biophysical properties of PT dendrites, yielding larger postsynaptic potentials, with slower kinetics and resulting in enhanced temporal summation of synaptic inputs (Dembrow and Johnston, 2014). For example, previous studies showed that adrenergic signaling in motor cortex acts via HCN channels to increase firing of L5 PT cells in response to synaptic trains (Sheets et al., 2011). This phenomenon is observed in other cortical regions and may play a role in selectively enhancing cortical outputs in a state-dependent manner (Berger et al., 2001; Takahashi et al., 2016). In the context of thalamo-cortical loops between ALM and VM, increased PT activation is predicted to increase cortico-thalamic signaling and support ongoing communication between these regions.

For PT cells in ALM to function as part of a reciprocal loop (Fig. 1B) rather than a thalamic relay to another part of cortex (Fig. 1A), they would have to provide monosynaptic input to ALM-projecting cells in VM. To test this, K. Guo et al. (2018) selectively activated PT axons in thalamus using optogenetics. They showed that L5 of ALM does provide input to reciprocally connected thalamo-cortical neurons in VM. Extending this finding, they showed that PT projections from ALM and M1 are anatomically and synaptically segregated within VM. This suggests that VM does not function as a thalamic relay between ALM and M1, and indicates that VM instead contains two distinct reciprocal circuits: a medial ALM loop and a lateral M1 loop (Fig. 1B). The fact that these circuits are mediated by L5 PT cells, which provide “driver” input to VM, and largely avoid TRN, highlights a potential synaptic mechanism for sustain-

ing reverberant cortico-thalamo-cortical activity necessary for short-term memory during motor planning (Z.V. Guo et al., 2017).

Using conditional optogenetics to selectively drive L6 CT cells, K. Guo et al. (2018) next showed that ALM L6 provides strong input to TRN, indicating that this population functions as the main source of cortically evoked feedforward inhibition to VM (Fig. 1B). This connectivity is consistent with L6 connections to TRN providing feedforward inhibition across motor and sensory thalamus (Lam and Sherman, 2015). Cortical outputs mediated by L6 neurons therefore play a dual role in inhibiting and facilitating thalamic responses (Olsen et al., 2012; Crandall et al., 2015). TRN projections to thalamus are known to be topographically organized (Lam and Sherman, 2015). It will be interesting to determine whether populations within TRN selectively inhibit the medial and lateral subnuclei of VM identified by the authors.

The study by K. Guo et al. (2018) extends our understanding of cortico-thalamo-cortical circuits linking higher-order regions of motor cortex. The subcellular targeting of VM input to PT cells in ALM suggests an important role for modulatory systems in regulating these circuits through HCN channels. Interestingly, the presence of reciprocal loops between VM and ALM indicates distinct circuit architectures for thalamo-cortical processing across the cortical hierarchy. In first-order sensory thalamus, relay neurons are driven by input from external sensory organs and receive modulatory signals from L6 CT cells, whereas L5 PT cells function as relays to send cortical information to higher-order sensory thalamic nuclei. In contrast, K. Guo et al. (2018) reveal a cortico-thalamic circuit where both L5 and L6 inputs arise from the same region of cortex. This suggests a system where sensory information is relayed up the cortical hierarchy before ultimately reaching higher-order cortico-thalamo-cortical loops (Fig. 1C). The distinct organization of these higher-order loops is well suited to support ongoing integration during motor planning (Z. V. Guo et al., 2017). Moreover, the presence of anatomically and synaptically isolated loops within motor thalamus suggests the possibility of multiple systems capable of processing different aspects of motor related activity in parallel (although likely connected through interactions with cortical and subcortical systems). Finally, the exquisite specificity of connectivity in

both the thalamo-cortical and cortico-thalamic direction is only revealed when taking into account neuronal identity. As our understanding of neuronal diversity expands, cell type-specific studies, such as that by K. Guo et al. (2018), will be necessary to reveal the complex interactions within and between brain regions.

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