

# Thalamocortical Circuit Motifs: A General Framework

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The role of the thalamus in cortical sensory transmission is well known, but its broader role in cognition is less appreciated. Recent studies have shown thalamic engagement in dynamic regulation of cortical activity in attention, executive control, and perceptual decision-making, but the circuit mechanisms underlying such functionality are unknown. Because the thalamus is composed of excitatory neurons that are devoid of local recurrent excitatory connectivity, delineating long-range, input-output connectivity patterns of single thalamic neurons is critical for building functional models. We discuss this need in relation to existing organizational schemes such as core versus matrix and first-order versus higher-order relay nuclei. We propose that a new classification is needed based on thalamocortical motifs, where structure naturally informs function. Overall, our synthesis puts understanding thalamic organization at the forefront of existing research in systems and computational neuroscience, with both basic and translational applications.

In the context of mammalian evolution, the expansion of the cortex has been associated with the rise of higher-order cognitive functions (Buckner and Krienen, 2013; Krubitzer and Prescott, 2018). In fact, human cortical expansion is hypothesized to be the core driver of our ability to reason (Mansouri et al., 2017), conceive abstract thoughts, generate language (Hage and Nieder, 2016), and build elaborate social structures (Bicks et al., 2015; Jost et al., 2018). The focus on cortical function in neuroscience and its quest for intelligence has inspired the construction of artificial neural networks that can rival human abilities of visual recognition (Yamins et al., 2014), playing video games (Silver et al., 2017), and spatial navigation (Banino et al., 2018).

In this review, we propose that the quest for the neural basis of cognition requires a better understanding of the role of the thalamus in cortical function, especially because thalamic evolutionary expansion parallels that of the cortex itself and is intimately involved in communication between cortical areas (Halassa and Kastner, 2017; Rikhye et al., 2018b; Sherman, 2016). The thalamus is a collection of nuclei primarily composed of excitatory neurons that project to the cortex but lack local excitatory recurrent connections, a hallmark of cortical circuitry. In other words, all of the known excitatory inputs to these thalamic neurons emanate from extrathalamic sources, whereas the vast majority of such inputs to cortical neurons are quite local in origin (Binzegger et al., 2009; Braintenberg and Schütz, 1998). Therefore, the computations performed by a thalamic neuron will be dependent on its long-range excitatory inputs (Rikhye et al., 2018b) as well as local inhibitory recurrence through the thalamic reticular nucleus (Lee et al., 2014; Pinault and Deschênes, 1998). The effect of the ensuing thalamic output on cortical computations is dependent on the connectivity patterns thalamic neurons make in the cortex.

A major impediment to understanding the thalamus and its role in cortical function is the fact that our knowledge of input-

output connectivity schemes across the thalamus is limited. Thus, what is needed is a complete classification of these functionally relevant connectivity patterns, which we refer to as “thalamocortical motifs.” Our definition of a motif is the input-output functional architecture of a single thalamic neuron, where its input patterns are informative of which computations it performs and output patterns are informative of its impact on cortical computations. Therefore, it includes the set of driving inputs to a single thalamic neuron along with the precise cortical connectivity pattern of that same neuron. Of course, additional knowledge of the capacity of the input and output connections for plasticity, along with the precise learning rules, is an important determinant of the types of computations performed, but we will only briefly mention this important topic here.

An important point we would like to communicate throughout this review is that identifying the variety of thalamocortical motifs represents a basic classification strategy that is an essential early process in understanding any complex system, and indeed, such a classification strategy has proven quite fruitful in CNS research more generally. For instance, early advances in retinal research have involved classification of component cell types—photoreceptors, ganglion cells, etc.—followed by subclassification of these cells, such as rods and cones and different ganglion cell types. This type of early work paved the way for complete connectomics of the retina’s inner plexiform layer (Helmstaedter et al., 2013), which has played important roles in constraining models of retinal function, such as those involving the computation of visual motion (Borst and Helmstaedter, 2015). Similarly, and given the increasing interest in the role of thalamocortical interactions in cognitive function, we believe it is important to recognize that a proper classification of motifs underlying these interactions is lacking and that this is vitally needed. We argue that current attempts of classification, and there have been many, are inadequate. We will review



recent developments in thalamocortical research that highlight limitations of these existing classification schemes and discuss the sorts of data required to establish a comprehensive one. More specifically, we will argue that the diversity of thalamic functions will clarify how an organizational scheme based on input-output connectivity data at the single-cell level would provide a thalamocortical classification system that is far more comprehensive and functionally meaningful than currently existing ones. Last, we will discuss how such basic understanding will propel future efforts in biomedical sciences, including clinical applications, as well as development of brain-inspired artificial neural networks with expanded cognitive capacity.

### Existing Thalamocortical Classification Systems

#### Broad Classification: Thalamic Nuclei

Perhaps the oldest classification scheme for the thalamus is the use of histological criteria to divide the structure into a number of distinct nuclei. These nuclei can be segregated into an anterior group (anteromedial, anterolateral, anterodorsal, and laterodorsal nuclei); a medial division composed of the midline group (paratenial, paraventricular, and centromedian), an intralaminar group (centrolateral, centromedial, and parafascicular), and the mediodorsal nucleus; a lateral division containing the ventroanterior/ventrolateral group, the ventrobasal complex (the ventral posteromedial and ventral posterolateral nuclei), and ventromedial nucleus; and a posterior group containing the posteromedial nucleus, the lateroposterior nucleus, the pulvinar, and the medial and lateral geniculate nuclei. Abutting these nuclei laterally is a shell of inhibitory neurons, collectively known as the thalamic reticular nucleus, which is derived from the ventral thalamus (Jones, 2007). Although these nuclear divisions broadly inform function, the idea that a single thalamic nucleus performs a single function is far from accurate. Instead, it is clear from studying a limited subset of thalamic nuclei that heterogeneity of circuit form is the rule rather than the exception (Rikhye et al., 2018b). This is a major thrust for our proposal of a new classification system.

#### Classification Based Solely on Thalamocortical Output

**Core and Matrix.** Jones (2001) has suggested a major thalamic classification scheme that divides thalamocortical projections into what he calls “core” and “matrix.” Core neurons project in a spatially dense and topographically restricted manner and innervate middle cortical layers, whereas matrix neurons project in a spatially sparse and topographically diffuse manner, innervating superficial cortical layers and largely layer 1 (Figure 1A). Also, core neurons innervate only the cortex (with branches to the thalamic reticular nucleus en route to the cortex), whereas matrix neurons also innervate the basal ganglia; the quantitative breakdown of individual matrix neurons preferentially innervating the cortex or basal ganglia, dually innervating both structures, or forming a population that continuously represents both features remains unclear (Kuramoto et al., 2015; Nakamura et al., 2015; Ohno et al., 2012; Unzai et al., 2017). This classification refers to individual thalamocortical cells because thalamic nuclei are composed of different proportions of core and matrix neurons. The lateral geniculate nucleus is a nucleus that contains both types (see below). However, some nuclei are chiefly core, such

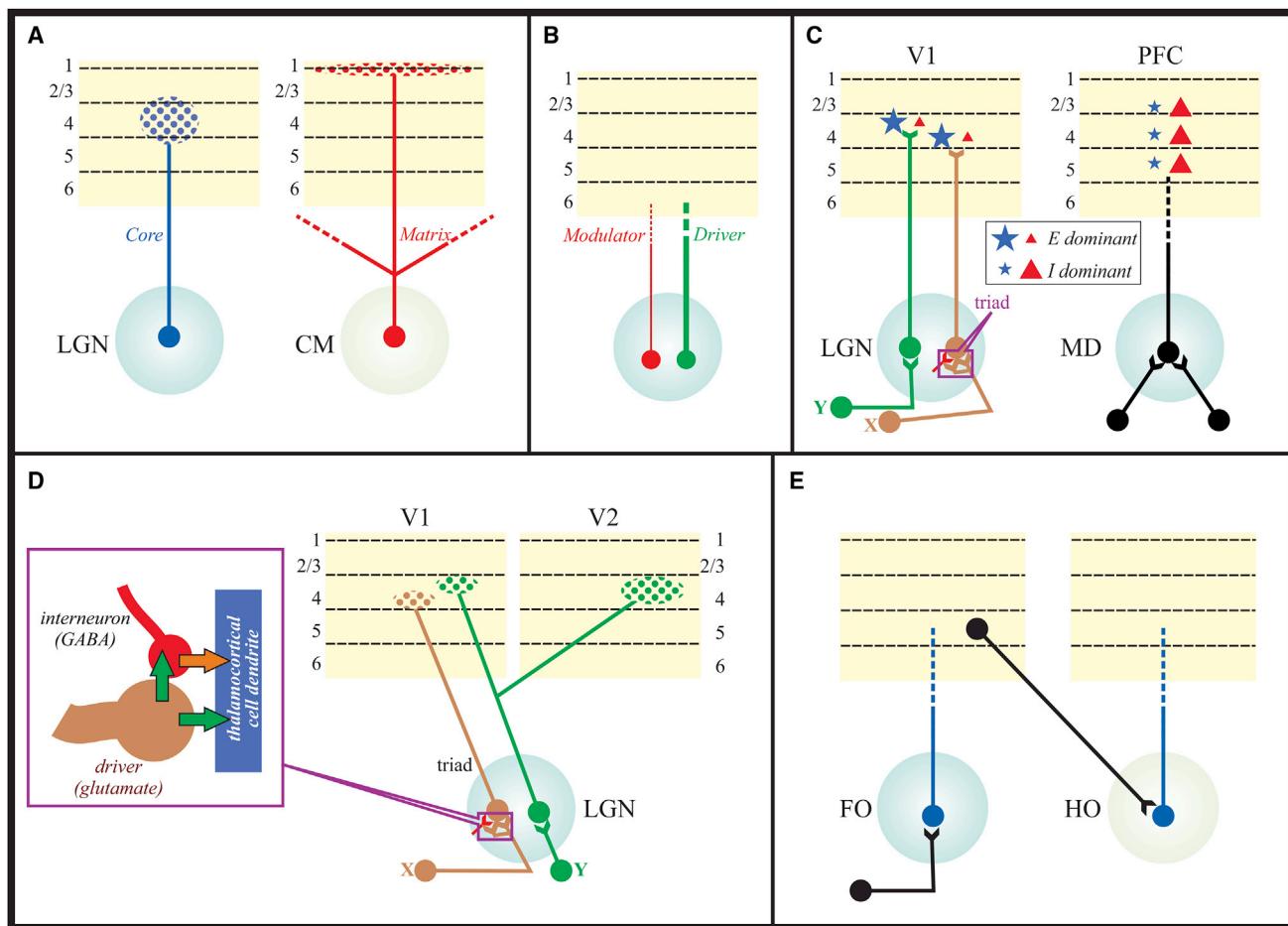
as ventral posterior medial, and others matrix, such as centromedian.

More recent systematic single-cell fills have challenged the core/matrix dichotomy by showing a substantially richer variety of thalamocortical output types (Clascá et al., 2012; Kuramoto et al., 2017). For example, in frontal thalamic structures, the same neurons can branch to exhibit spatially diffuse projections that target middle layers or spatially dense projections that target superficial and deep layers simultaneously. To complicate matters even more, an individual thalamic neuron may, via a branching axon, have one or more core-like projections targeting one area and a matrix-like projection targeting another (Clascá et al., 2012). Therefore, it is clear that the idea of core and matrix either captures only a limited subset of thalamocortical output types or represents ends of a single continuum with considerable variability. This, compounded with the complexity added when factoring in the types of cortical neurons these thalamic outputs target, suggests that there may be a wide range of functional outputs the thalamus imparts on cortical circuitry.

**Drivers and Modulators.** Sherman and Guillery (1998, 2013) noted that glutamatergic pathways, which include thalamocortical projections, are not homogeneous but, rather, can be classified into two types, which they referred to as drivers and modulators. They further proposed that drivers carry the main information to their targets, whereas modulators perform many of the same operations as the classical modulators (e.g., acetylcholine [ACh], noradrenaline [NA], 5-hydroxytryptamine [5-HT], etc.). For example, retinal input to geniculate thalamocortical cells has driver properties, and the layer 6 input from the visual cortex has modulator properties, and both are glutamatergic. There is evidence that thalamocortical projections contain both types, although the documented examples are too few to draw more general conclusions (Figure 1B). For details of the patterns described so far, see Lee and Sherman (2008) and Viaene et al. (2011a, 2011b, 2011c).

**Excitatory versus Inhibitory Cortical Targets.** Of equal significance is the functional effect a thalamocortical projection has on its cortical target, which will necessarily depend on the strength and timing of connectivity to the various cell types within that particular cortical region. For example, although projections from primary sensory thalamic regions contact both excitatory and inhibitory cortical neurons, the inhibitory component is largely accounted for by connections onto parvalbumin-positive interneurons (Tuncdemir et al., 2016). This can be contrasted to thalamic projections from higher-order sensory nuclei, such as the posterior medial nucleus, which also targets vasoactive intestinal peptide-positive interneurons (Williams and Holtmaat, 2018), known to specialize in disinhibitory control (Pietal., 2013). In addition, purely functional evidence derived from mediodorsal thalamic projections onto the prefrontal cortex suggests that these projections are far more efficient at driving cortical inhibition compared with the inhibitory effect of a first-order sensory thalamic input on its cortical targets (Schmitt et al., 2017; Figure 1C).

**Single versus Multiple Cortical Targets.** Some thalamic cells target a single cortical area (e.g., geniculate X cells in the cat; Figure 1D), whereas others send axons that branch to innervate multiple areas. This is seen for both core projections (e.g., geniculate Y cells; Figure 1D) and matrix projections (Figure 1A).



**Figure 1. Examples of Various Classification Attempts that Include Partial Descriptions of Thalamocortical Motifs**

(A) Core and matrix (output characteristics). The geniculocortical projection, an example of a core system, mainly targets middle cortical layers in a highly topographical manner (left), whereas the projection from the centromedian nucleus, an example of a matrix system, diffusely targets upper cortical layers, chiefly layer 1 (right), and typically innervates multiple cortical areas.

(B) Drivers and modulators (output characteristics). Thalamocortical afferents can be either driver or modulator.

(C) Lateral geniculate nucleus versus mediodorsal (input and output characteristics). In addition to the input differences shown in (D), lateral geniculate nucleus X and Y cells receive input from very few retinal axons, often only one, and their outputs chiefly innervate excitatory cells in V1 (left), whereas some mediodorsal neurons, which receive significant convergent driver input, predominantly activate inhibitory cells in the prefrontal cortex (PFC, right).

(D) X and Y streams through the cat's lateral geniculate nucleus (both input and output characterization). On the input side, retinal Y axons form simple synapses onto dendritic shafts, whereas retinal X axons form triadic synaptic complexes (inset). On the output side, X axons innervate only V1, chiefly in the lower half of layer 4, whereas Y axons innervate the upper half of layer 4 and branch to innervate V2 as well.

(E) First-order (FO) and higher-order (HO) (predominantly input characteristics) thalamocortical circuits. Driver input to FO cell derives from a subcortical source (i.e., retina to lateral geniculate nucleus), whereas HO thalamocortical cells receive driver input from layer 5 of the cortex (e.g., pulvinar from layer 5 of V1).

### Classification Based Solely on Input

**First- and Higher-Order Thalamic Nuclei.** Perhaps the best-studied thalamic structure is the lateral geniculate nucleus, which represents the main station for visual information traveling from the retina to the primary visual cortex (Sherman, 2017; Sherman and Guillery, 2013, 2014). Although structural and functional features of the lateral geniculate have been useful for interpreting data from other thalamic structures interposed between subcortical sensory inputs and primary sensory cortical areas (Lee, 2013; Reichova and Sherman, 2004), the utility for understanding thalamic function more broadly may be limited. The key limitation stems from the fact that lateral geniculate neurons are driven by retinal inputs, with cortical input derived only from layer 6 playing

only a modulatory role (Briggs and Usrey, 2011; Sherman and Guillery, 1998, 2013).

In contrast, many other thalamic nuclei contain neurons that are primarily driven by layer 5 cortical inputs, potentially with varying degrees of convergence (Groh et al., 2014; Reichova and Sherman, 2004; Rovó et al., 2012; Sherman, 2016; Sherman and Guillery, 2013). Higher-order relays appear to serve as a station in *trans-thalamic* corticocortical communication as opposed to direct corticocortical pathways; often cortical areas are connected by both direct and transthalamic pathways organized in parallel (for a review, see Sherman, 2012; Sherman and Guillery, 2011) (Figure 1D). This has provided one useful classification of thalamic nuclei: first-order nuclei receive their driving input

from a subcortical source, such as the retina, whereas higher-order relays are driven by input from layer 5 of the cortex.

One problem with this classification scheme is that, although first-order thalamic nuclei seem to be completely first order, meaning that all driving input emanates from subcortical sites, higher-order nuclei may often contain first-order elements. For instance, the pulvinar and mediodorsal nucleus are both innervated by the superior colliculus, a subcortical source, and if this collicular input contains driver afferents (Beltramo and Scanziani, 2019; Kelly et al., 2003), then these higher-order nuclei also contain first-order circuitry. Another problem is that this classification does not account for a key distinguishing feature across distinct thalamic circuits: convergence. Limited convergence of driver inputs, such as retinogeniculate synapses, is well known, but in such examples, the driver inputs share basic receptive field properties, meaning that transformation of information passed on to the cortex is limited. However, there is evidence of layer 5 cortical input convergence from different cortical areas onto single thalamic neurons (Groh et al., 2014; Rovó et al., 2012), and this suggests that significant transformation of information is possible. In addition, evidence of cortical input convergence onto single thalamic neurons can be inferred from functional studies involving prefrontal inputs onto the mediodorsal nucleus, where thalamic neurons represent conjunctions of cortical signals (Rikhye et al., 2018a; Figure 1C). This type of encoding is reminiscent of activity observed in the non-human primate pulvinar, where thalamic neurons reflect a transformation of cortical motion signals that are directional into a non-directional signal of confidence (Komura et al., 2013), which may be explained by corticothalamic convergence (Jaramillo et al., 2019). The degree of input convergence (both in terms of magnitude and type) coupled with distinct types of learning rules may endow thalamic circuits with truly distinct computational functions, which we think is critical to consider in a comprehensive classification scheme.

**Triadic versus Non-triadic Circuitry.** Triadic circuitry, which involves three synapses (see inset to Figure 1D), is ubiquitous throughout the thalamus (reviewed in Sherman and Guillory, 2013). Such circuitry involves the driver input. In a triad, the driver input forms two synapses, one onto the dendrite of a thalamocortical cell and the other onto a terminal from a GABAergic interneuron, and the interneuron terminal forms a synapse onto the same thalamocortical cell dendrite. Thus, the three synapses are (1) driver input onto a thalamocortical cell dendrite, (2) driver input onto an interneuronal terminal, and (3) a synapse from the same interneuronal terminal onto the same thalamocortical cell dendrite. Note that the interneuronal terminal is both presynaptic and postsynaptic; it also derives from an interneuronal dendrite rather than from the axon (Sherman, 2004).

However, many driver inputs do not enter into triadic arrangements. Instead, they form simple, conventional synapses onto thalamocortical cell dendrites. An example of these two types of driver input is seen in retinal X and Y innervation of the cat's lateral geniculate nucleus (LGN) (Figure 1D): X axons innervate via triads whereas Y axons do not (Hamos et al., 1987; Wilson et al., 1984). Although the function of the triad remains unknown (but see Sherman, 2004), it seems likely that the presence or

absence thereof is a significant classificatory parameter for defining thalamocortical motifs.

### Classification of Parallel Thalamocortical Streams

Parallel processing of streams to classify thalamocortical pathways may be regarded as the ultimate form of identifying thalamocortical motifs because it seems likely that most or all such defined motifs will be seen as operating independently and in parallel with respect to one another. Unfortunately, this classification approach has been used successfully only with respect to the lateral geniculate nucleus, mainly in carnivores and primates.

In the cat, for instance, independent and parallel retino-geniculo-cortical streams known as W, X, and Y have been identified (Sherman, 1985; Stone, 1983). These start with distinct classes of retinal ganglion cell, each of which innervates a distinct class of geniculate cell for projection to the visual cortex. A comprehensive description of these pathways is beyond the scope of this account, but details can be found in Sherman (1985) and Stone (1983). Differences are seen both on the inputs to geniculate cells as well as their cortical outputs, but this is best seen in the X and Y pathways involving the presence or absence of triads, as noted above.

The outputs of cat geniculate X and Y cells also differ (Humphrey et al., 1985a, 1985b; Figure 1E). Both chiefly innervate layer 4 of V1 (also known as area 17 or the primary visual cortex) and, therefore, would be considered core projections (see above). However, Y axons terminate in the upper half of layer 4, whereas X axons terminate in the lower half. Also, X axons branch less and innervate a single patch of layer 4, whereas Y axons branch to innervate several patches, and some even innervate V2 (also known as area 18 or the secondary visual cortex) as well. As a result, each geniculate Y axon produces more synapses and covers more territory on average than each X axon.

W cells in the retina and the lateral geniculate nucleus pose a classificatory problem because they are probably a heterogeneous group that includes multiple classes. Thus, the classification of this group is incomplete. Nonetheless, with this proviso in mind, it is clear that W cells have yet a projection pattern to cortex different from X and Y cells. W cells do not innervate layer 4 but, rather, chiefly innervate layers 2/3 (Boyd and Matsubara, 1996; Kawano, 1998). Some extend axon arbors into layer 1, and these would be seen as matrix projections (see above). However, there is no innervation by the lateral geniculate nucleus of the basal ganglia, a matrix feature. These discrepancies further reinforce the notion that the core/matrix dichotomy does not adequately describe the diversity observed even in a fairly well-characterized structure such as the lateral geniculate.

Data from the monkey regarding differences among parallel retino-geniculo-cortical streams are less well documented than those in the cat, but the available data indicate a similar arrangement. In the monkey, these are called K (for koniocellular), M (for magnocellular), and P (for parvocellular), and these seem homologous to the pathways in the cat: K is homologous with W, M with Y, and P with X (Casagrande and Xu, 2004). Like the differences in cortical projection patterns in the cat, M and P chiefly target layer 4, with the M pathway terminating dorsal to P and producing larger terminal arbors, and the K

pathway seems to involve multiple classes that mainly innervate layers 2/3 with some innervation of layer 1 but no innervation of the basal ganglia (Casagrande and Xu, 2004; Ding and Casagrande, 1997).

It is thus clear that these parallel retino-geniculo-cortical streams represent distinct thalamocortical motifs. A problem is that such parallel processing has not yet been documented more generally beyond the lateral geniculate. Such further documentation is, in fact, a main point of this manuscript.

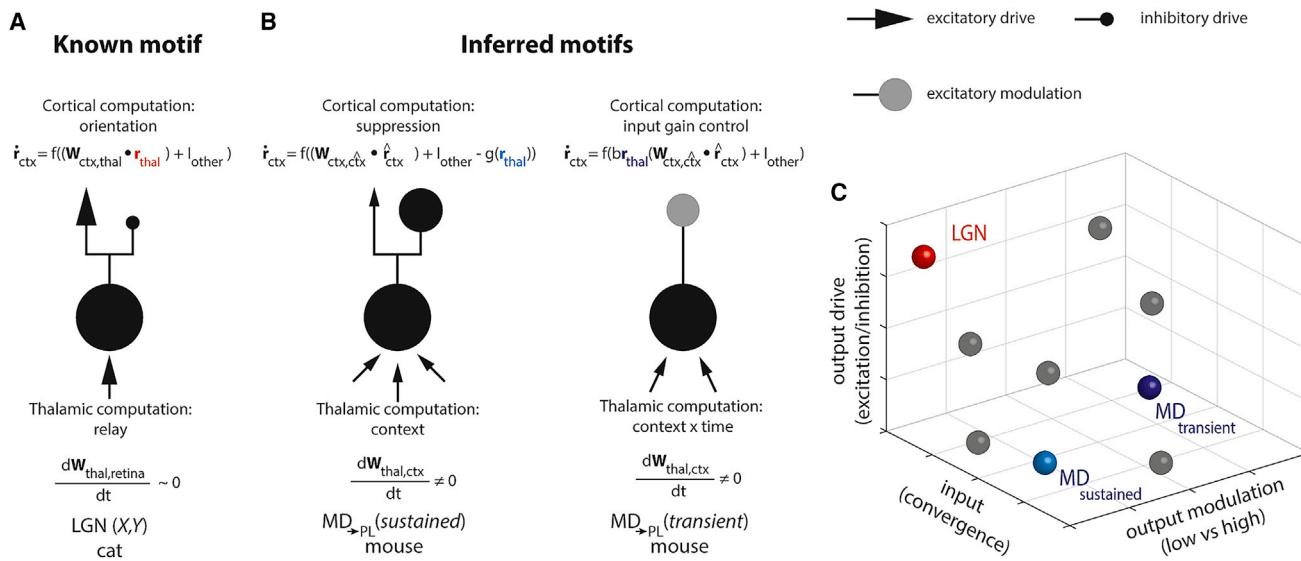
### Toward a Comprehensive Classification of Thalamocortical Circuit Motifs

The structural diversity of thalamocortical projections observed within and across thalamic nuclei indicates that the thalamus can influence cortical representations and dynamics in a multitude of ways. Importantly, different thalamocortical outputs from within a single nucleus can give rise to distinct computational functions partly through differences in which layers and cell types a thalamic terminal innervates in the cortical recipient region. We suggest that comprehensive mapping of the different types of thalamocortical output types is of critical importance. Methods of achieving this are experiencing rapid technical growth and include high-resolution single-cell terminal mapping (Lichtman et al., 2008). Although traditional methods have relied on sparse labeling and complete reconstruction of single-cell terminal fields, recent developments in fluorescent (Chung et al., 2013; Gradinaru et al., 2007) and genetic bar-coding technologies (Kebschull and Zador, 2018) may allow for deriving similar insights based on densely labeled samples, which would provide substantially higher throughput. Utilizing these insights to build functional models would also require the incorporation of ultrastructural data, which would provide a proxy for synaptic strength based on terminal size, number of vesicles, and mitochondria (Cserép et al., 2018; Harris and Weinberg, 2012). Furthermore, correlating such ultrastructural data for thalamocortical pathways identified as driver or modulator (Viaene et al., 2011a, 2011b, 2011c) might permit identification of such functional classes in connectomics data. Separately, determining which cortical neurons are innervated by a thalamocortical projection would benefit from the development of anterograde transsynaptic tracing (Zingg et al., 2017). Ultimately, a combination of all these structural tools and physiological recordings will be necessary to directly test the inferred functional models.

Comprehensive mapping of thalamocortical output types will only constitute half the battle; the other half will require determining what the inputs are, including the type, strength, and degree of convergence individual thalamic neurons receive (Figures 1A–1D). Such an endeavor would benefit from monosynaptic transsynaptic retrograde labeling originating from single thalamic neurons, which currently requires the use of pseudorabies viruses (Ghanem and Conzelmann, 2016). Alternatively, if bar-coding methods were to be developed in which both the pre- and postsynaptic neurons are identifiable, then such mapping could be performed in a high-throughput manner. Similar to output mapping, input mapping would require co-registration with physiological studies to provide a blueprint for subsequent functional studies.

Although we can only speculate as to what this endeavor would ultimately yield, it is almost inevitable that several putative thalamocortical motifs would be identified (Figures 2A and 2B). One key idea we emphasize is that these motifs are informative of computational function. For example, the fact that retinal terminals form excitatory driving inputs that exhibit little convergence onto individual geniculate neurons renders geniculate receptive fields very similar to those of retinal ganglion cells (Hubel and Wiesel, 1961; Usrey et al., 1999). Receptive fields of thalamo-recipient visual cortical neurons are built from the appropriately wired geniculate inputs, giving rise to orientation- and direction-selective neural responses (Finn et al., 2007; Hubel and Wiesel, 1961; Lien and Scanziani, 2013, 2018; Usrey et al., 2000). Combining these known input-output properties, this geniculate motif intuitively supports the idea that the thalamic neurons included operate as relays because minimal alteration of the retinal inputs occur (Figure 2A). In contrast, inferred input-output connectivity patterns of a subset of neurons within the mediodorsal nucleus indicate that their interaction with the prefrontal cortex is not well explained by a similar relay design (Figure 2B). More specifically, these mediodorsal neurons may receive highly convergent prefrontal inputs, and by adjusting the strength of these inputs, each neuron may generate a distinct conjunctive representation. Our experimental data have shown that these conjunctive representations can be understood as ones encoding a task context. In a sense, we hypothesize that these thalamic neurons may implement a competitive Hebbian learning algorithm that allows them to capture cortical input statistics (principal components) (Diamantaras and Kung, 1996; White, 1992). Therefore, and solely based on their conjunctive neural responses, these thalamic neurons violate the notion of a relay. Based on other experimental findings, we also suggest that their functional effect on the prefrontal cortex deviates from that of the geniculate nucleus on the primary visual cortex. More specifically, some neurons appear to efficiently drive cortical inhibition (Figure 2B, left), likely through stronger and/or more plentiful contacts onto inhibitory interneurons compared with excitatory ones. Other mediodorsal neurons appear to exert a modulatory effect on prefrontal neurons, enhancing their local functional connectivity ((Schmitt et al., 2017; Figure 2B, left)). Mechanistically, this modulatory effect may be exerted through a neuromodulatory signal from thalamic terminals (Casas-Torremocha et al., 2019; Viaene et al., 2011b) or disinhibitory circuit motifs (Williams and Holtmaat, 2018), as shown in other thalamic structures.

Directly testing these inferred motifs and ultimately defining them will hopefully lead to a new “classification space” where the axes are structural attributes that most explain the functional variance across thalamic circuits. In Figure 2C, we utilize attributes we have discussed throughout this review (although we do not know whether these will ultimately be the most meaningful) to illustrate how the geniculate and mediodorsal circuits discussed would be plotted within such a space. Other thalamic circuits would fall into different locations within this space, making clustering in this feature space a natural way to group circuits based on similarities in their input-output computations. Our guess is that these clusters (which would be informative of common computations across



**Figure 2. Toward a Classification System Based on Thalamocortical Motifs**

(A and B) Individual and idealized single thalamic neurons are shown to illustrate the notion of the motif being a single-cell attribute (A). Also shown is an example of a well-characterized thalamocortical motif involving the retino-geniculo-cortical pathway, with the set of computations required for retinal signal transmission. X and Y geniculate neurons of the cat receive retinal inputs with minimal convergence and, therefore, show similar responses to those of the retina. An important feature of this system is that the retinogeniculate connections are relatively stable in adult animals, rendering geniculate neurons stably tuned to visual features. On the output side, because geniculate neurons provide predominantly driving excitatory inputs to the visual cortex, cortical responses can be largely explained as weighted sums of the thalamic output. Shown in (B) are two examples of inferred motifs within the mediiodorsal thalamus of the mouse. These connections are derived from statistical dependencies between the mediiodorsal neurons and prefrontal ones, which are recorded in a context-switching task (Rikhye et al., 2018a). These statistical dependencies have also been tested through pathway-specific optogenetic manipulations. Mediiodorsal neural types can be segregated based on inputs, which are explained by the degree of their cortical input convergence. Specifically, a subset of neurons encodes a set of task-relevant prefrontal cue-selective signals over a broad temporal scale (left) and another encoding the same type of task-relevant variable but on a shorter timescale (right). Given that these response profiles shift on a session-by-session basis depending on how the context is experimentally configured, a reasonable interpretation is that the corticothalamic connections are highly plastic. These same mediiodorsal types also segregate based on output, with high-input-convergence neurons exhibiting predominantly suppressive effects on prefrontal cortical activity and low-input-convergence neurons exhibiting predominantly modulatory excitatory effects. By modulation, we do not necessarily mean that the effect is implemented through a neuromodulator but, rather, that it controls the gain of effective recurrent connections in the prefrontal cortex (see equations within the figure).

(C) A putative classification space for thalamocortical motifs, with the relevant geniculate and mediiodorsal types plotted within. The number and distribution of points within this space are currently unknown, but we expect that their pattern will inform function and comparisons across species. The embedded equations describe the input-output transformations of the thalamocortical motifs. Lower boldface symbols denote vectors, and upper boldface symbols denote matrices.  $r_{ctx}$ , cortical output;  $f$ , cortical non-linearity;  $\hat{r}_{ctx}$ , recurrent drive;  $r_{thal}$ , thalamic input;  $g$ , non-linearity over thalamic input for the middle motif;  $b$ , scaling parameter for the thalamic term in the last motif. The key idea for this formalism is that the thalamic input shows up as very different terms in the cortical computation performed. This is what is precisely meant by relay versus non-relay functions of the thalamus.

thalamocortical motifs) would not necessarily respect traditional nuclear boundaries.

Achieving a proper classification of thalamocortical motifs, including a hierarchical subclassification analogous to the classification of retinal ganglion cells, is of critical importance for at least two reasons. First, such a classification is a prerequisite for significantly improving our understanding of thalamocortical functioning. Second, it is also a prerequisite for establishing homologs needed for generating an appreciation of thalamocortical functioning applicable to mammals as a whole.

#### Classification as a Prerequisite to Better Understanding Thalamocortical Functioning

The structural diversity of thalamocortical projections observed within and across thalamic nuclei indicates that the thalamus can influence cortical representations and dynamics in a multitude of ways. Importantly, different thalamocortical outputs from within a single nucleus can give rise to distinct computational functions partly through differences in which layers and cell types a thalamic terminal innervates in the cortical recipient

region(s). Current models of thalamocortical functioning tend to be biased by a few examples, such as the geniculocortical pathways, but we now know that thalamocortical circuitry contains considerable variability and that geniculocortical pathways represent a limited set of thalamocortical motifs. However, in addition to the diversity of thalamocortical projections is the potential diversity in inputs to thalamocortical neurons, including the type, strength, and degree of convergence these individual neurons receive. An open question is how many distinct types of computational functions are supported by the diversity of thalamocortical motifs, which includes an analysis of both inputs to and outputs of thalamocortical neurons. We submit that, until this answer is realized, we will lack an important insight into thalamocortical functioning.

Given the growing evidence of thalamic dysfunction across a variety of neurological (Schiff, 2008) and psychiatric (Clinton and Meador-Woodruff, 2004; Krol et al., 2018; Scheibel, 1997; Schmitt and Halassa, 2017) disorders, we predict that the result of identifying functional thalamocortical motifs will have a

significant effect on public health. For example, the recognition that the lateral geniculate nucleus can be a locus for attentional control across mice (Wimmer et al., 2015), non-human primates (Briggs et al., 2013; McAlonan et al., 2006), and humans calls for further studies regarding the dysfunction of sensory thalamic motifs in disorders with an attentional component. Which motifs are related to attentional demands, and how are these affected in disorders related to attention? As another example, there is evidence of cognitive defects associated with pathology in higher-order thalamic relays (Chauveau et al., 2005; Means et al., 1974; Rafal and Posner, 1987), but again, which specific motifs are involved?

Furthermore, thalamocortical research may benefit the growing synergy between neuroscience and artificial intelligence. The fact that multiple studies have shown different roles of thalamic circuits in cortical learning and dynamic switching of computational states (Rikhye et al., 2018a; Saalmann and Kastner, 2015) is of great relevance for the development of artificial intelligence architectures that can rapidly learn and flexibly switch (Masse et al., 2018). Proper classification is a prerequisite for understanding which motifs may be involved in these behaviors and how they operate, and therefore, this would enhance the potential of the synergy noted above.

We recognize that achieving such a classification is a daunting task and may seem unattainable at present. However, we are experiencing an amazing period of new technology applicable to neuroscience questions such as those raised here. Tools for identifying unique neuron classes, for defining detailed connectivity at electron microscopic resolution in larger and larger volumes, for exploring functional circuitry via new imaging and recording techniques, and for transsynaptic neuroanatomical tracing are already available and can be expected to increase in quality and quantity. Although it may be the case that a complete classification of thalamocortical motifs is beyond our capabilities now and for the foreseeable future, we feel nonetheless that emphasizing the issue is important.

#### **Classification as a Prerequisite for Establishing Homologies with Other Mammalian Species**

What has not yet been stated explicitly here is that the sort of classification we describe will almost certainly depend heavily on the mouse as the model species. This is because most of the technical advances applicable to mammals and alluded to above have been pioneered in the mouse, and many of these are applicable only to this species. The challenge with the mouse as a model for neuroscience is that those of us working with this species hope to address questions that are relevant to all mammals and avoid those that apply only to mice or rodents. This is not an easy or straightforward approach.

Studies of parallel processing in the visual system across mammalian species serve as good examples for this point (see above). In the cat, W, X, and Y pathways have been documented, and these appear to be homologous, respectively, to the K, P, and M pathways in the monkey. As noted above, this has served as a partial classification of thalamocortical motifs. More to the point here, the distant evolutionary relationship between cats and monkeys suggests that these motifs are general mammalian features, and study of identified homologous thalamocortical motifs in any species can provide insights applicable to all. The

mouse has now become a major model to study visual pathways, but in doing so, how do we determine the relevance of any findings to mammals more generally? An important first step would be to identify motifs in the mouse pathways, especially geniculocortical ones, that are candidates for homology to those of the cat and monkey. We cannot hope to establish geniculocortical homologies across species until we first determine how many classes exist in each species. Of course, the number of geniculocortical motifs may differ across species because, for instance, the process of evolution may produce extra motifs found in the monkey compared with those in the mouse. Nonetheless, a classification of geniculocortical motifs in the mouse should be seen as a first step in determining which, if any, are candidates for being homologous to those in the cat or monkey.

#### **Conclusions**

As we have documented above, there have been numerous attempts to classify thalamocortical motifs, but each is demonstrably quite limited. These attempts demonstrate the understood value in providing such a classification. However, this understanding has generally been implied subtly or not at all, and we feel it is important to clarify rather explicitly the importance of a thorough classification of thalamocortical motifs as a prerequisite to a more complete understanding of thalamocortical functioning in health and disease. Even though the means to achieve such a complete classification are not yet available, we nonetheless argue that identifying the issue, as we have attempted to do here, is a useful step in the process.

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#### **DECLARATION OF INTERESTS**

The authors declare no competing interests.

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