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Rodent somatosensory thalamocortical circuitry: neurons, synapses, and connectivity

Christian O'Reilly[1,2,3], Elisabetta Iavarone[3], Jane Yi[4] & Sean L. Hill[3,5,6]

[1] Azrieli Centre for Autism Research, Montreal Neurological Institute, McGill University, Montreal, Canada

[2] Ronin Institute, Montclair, New Jersey, USA

[3] Blue Brain Project, École Polytechnique Fédérale de Lausanne, Geneva, Switzerland

[4] Brain Mind Institute, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

[5] Department of Psychiatry, University of Toronto, Toronto, Canada

[6] Centre for Addiction and Mental Health, Toronto, Canada

Contact author information:

Christian O'Reilly, Ph.D.

McGill University

3775 Rue University, Room C18

Duff Medical Building

Montréal, Québec, H3A 2B4

christian.oreilly@mcgill.ca

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Highlights:

- We review the circuitry of the somatosensory thalamocortical system in rodents
- We provide an overview of the thalamocortical interdependencies from a modeling perspective
- It provides an accessible yet comprehensive reference on thalamic microcircuitry
- It covers the properties of neurons, synapses, network connectivity, and neuroanatomy
- We identify gaps in current knowledge in order to guide future research

Abstract

As our understanding of the thalamocortical system deepens, the questions we face become more complex. Their investigation requires the adoption of novel experimental approaches complemented with increasingly sophisticated computational modeling. In this review, we take stock of current data and knowledge about the circuitry of the somatosensory thalamocortical loop in

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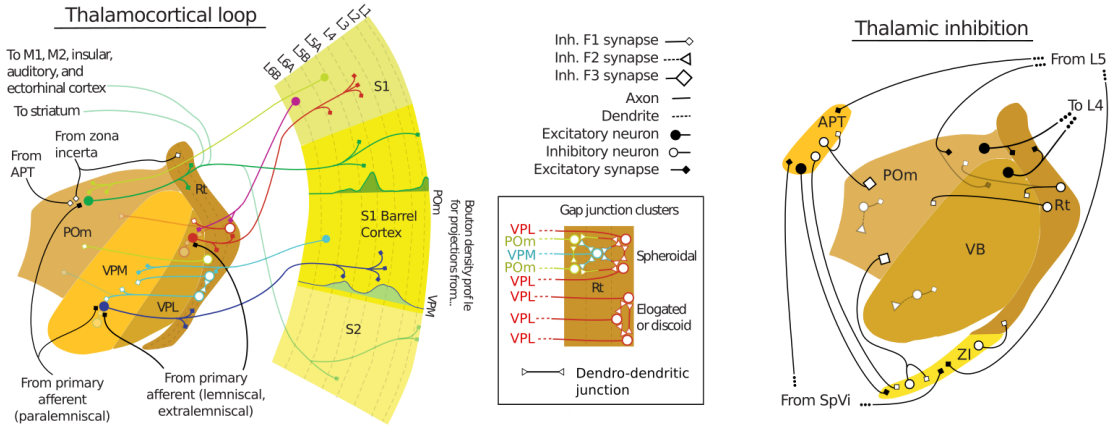
rodents, discussing common principles across modalities and species whenever appropriate. We review the different levels of organization, including the cells, synapses, neuroanatomy, and network connectivity. We provide a complete overview of this system that should be accessible for newcomers to this field while nevertheless being comprehensive enough to serve as a reference for seasoned neuroscientists and computational modelers studying the thalamocortical system. We further highlight key gaps in data and knowledge that constitute pressing targets for future experimental work. Filling these gaps would provide invaluable information for systematically unveiling how this system supports behavioral and cognitive processes.

Graphical abstract



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1. Introduction

The thalamocortical (TC) loop is known to play a central role in cerebral rhythmogenesis (Buzsaki, 2006; Fogerson and Huguenard, 2016; Steriade, 2006, 2000). As such, it supports many functions, such as sleep and wakefulness (McCormick and Bal, 1997; Steriade et al., 1993, 1991; Timofeev et al., 2012), and is involved in many diseases associated with dysfunction of rhythmic activity (Schulman et al., 2011), such as epilepsy (Brodovskaya and Kapur, 2019; Halász, 2013; Nowack and Theodoridis, 1991; Timofeev et al., 2012), schizophrenia and bipolar disorder (Anticevic et al., 2014b, 2014a; Baran et al., 2019; Ferri et al., 2018; Klingner et al., 2014; Murray and Anticevic, 2017; Skåtun et al., 2018; Woodward et al., 2012), and autism (Iidaka et al., 2019; Linke et al., 2018; Nair et al., 2013; Woodward et al., 2017).

Further, the thalamus plays an important role in many cognitive processes. Initially considered to be a simple relay station passing along information between the cortex and the peripheral nervous system, the thalamus is increasingly understood as an intricate looped system working in tight interaction with cortical networks. Such interactions were proposed early (Miller, 1996) based on spreading depression experiments (Aquino-Cias et al., 1966; Bureš et al., 1965). Since then, optogenetic experiments demonstrated how continuous thalamic input is necessary for sustaining cortical activity (Reinhold et al., 2015) and how it supports behavioral tasks by enhancing functional cortical connectivity (Schmitt et al., 2017). In turn, cortical inputs

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shape thalamic activity through an extensive network of corticothalamic (CT) projections, outnumbering their thalamocortical (TC) counterpart by an order of magnitude (Deschênes et al., 1998; Sherman and Koch, 1986). Through these projections, the cortex can, for example, sharpen the thalamic receptive fields to selectively enhance TC transmission of sensory information (Briggs and Usrey, 2008). Further, by modulating the level of hyperpolarization in TC cells, CT afferents can switch the mode of operation of these neurons between event detection (burst firing) and perception (tonic firing) (Ahissar and Oram, 2015). They can similarly leverage thalamic reticular cells to control sensory selection (Ahrens et al., 2015; Wimmer et al., 2015).

The thalamus has also been shown to preprocess raw peripheral inputs by encoding abstract functions. For example, this was demonstrated in the lateral geniculate nucleus (LGN) for center-surround inhibition, direction and orientation selectivity, and evaluating level of contrast in a visual scene (Piscopo et al., 2013). Similarly, cells from higher-order thalamic nuclei (HO) have been shown to encode stimulus-reward relationships by modulating their activity according to the detection of rewarded stimulus, the expected delay before reward, and the value of a reward (Komura et al., 2001). More generally, the thalamus has been proposed to play a central role in shaping mental representation (Wolff and Vann, 2019). This dual role as encoding mental representation and filtering input stimuli is supported by the convergence of ascending and descending afferents on thalamic targets. It uniquely positions this structure for integrating bottom-up and top-down information streams and therefore for binding cognitive predictions with

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sensory input, as proposed by the predictive-coding theory (Groh et al., 2014). All these properties of the thalamus makes it a key component in a large number of cognitive domains (Saalmann and Kastner, 2015) such as learning (Bradfield et al., 2013), memory (Funahashi, 2013; Jankowski et al., 2013), language (Klostermann, 2013), attention (Kinomura et al., 1996), motor control (Prevosto and Sommer, 2013), and multisensory processing (Cappe et al., 2009).

In the last decade, large-scale *in silico* simulations have been developed with an ever-increasing level of biophysical details which allow us to better understand such complex systems. Simulation neuroscience has also proven to be invaluable for guiding or corroborating experimental investigations. Recent studies in this area have demonstrated how small volumes of brain tissue can be simulated using morphologically and biophysically detailed neuron models (Markram et al., 2015). Less detailed frameworks have also been used to perform large-scale simulations at the microscopic scale (i.e., the scale of the neuron) (Ananthanarayanan et al., 2009; Hill and Tononi, 2005; Izhikevich and Edelman, 2008; Schumann et al., 2017). Alternatively, other approaches have focused on the mesoscopic scale (i.e., the scale of a cortical column) using, for example, the neural field approach (Sanz Leon et al., 2013). These simulation frameworks provide platforms to integrate available knowledge and push forward our understanding of cross-scale, cross-species, and cross-modalities mechanisms underlying cognition and behavior.

As opposed to the cortical microcircuitry which has been modeled in

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fine detail, the TC circuitry has received much less attention. As we better appreciate the interdependencies between thalamic and cortical networks, the details of these interactions increase in significance. The rising awareness of the crucial role played by the TC loop in cerebral rhythmogenesis, in diseases associated with TC dysrhythmia, and in various cognitive processes motivates the comprehensive synthesis of current knowledge on thalamic microcircuitry proposed herein. In the following sections, we describe the TC system related to somatosensation, review the biophysics of its neurons and their synapses, the neuroanatomy of the related nuclei, and the connectivity within this system and with its external afferents. We conclude by highlighting knowledge gaps that need to be addressed to allow computational neuroscientists to build accurate predictive models. This review focuses on the rodent somatosensory system but we also mention data from other species or thalamic regions whenever available and relevant.

2. Overview of the somatosensory TC loop

The thalamus is divided into two structures, the dorsal thalamus (also referred to simply as the thalamus) and the ventral thalamus (also referred to as subthalamus or prethalamus) (Puelles et al., 2012). In the somatosensory system, the ventrobasal complex of the dorsal thalamus (VB) is comprised of two first-order nuclei (FO) responsible for relaying somatosensory signals: the ventral posteromedial nucleus (VPM) for the face and neck area and the ventral posterolateral nucleus (VPL) for the rest of the body. These nuclei receive their peripheral inputs through various pathways (i.e., the lemniscal,

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extralemniscal, and paralemniscal pathways which are reviewed in section 6.1). Other thalamic nuclei such as the nucleus submedius and the ventromedial nucleus also receive somatic input, probably respectively for nociception and sensorimotor integration (Ebner and Kaas, 2015), but will not be discussed here because of their secondary role with respect to somatosensation.

The rodent VB is mainly composed of excitatory TC cells that target the primary somatosensory cortex (S1). It primarily innervates the layers 4 (L4), but also to some extent, L2-3 and L5b-6 (Clasca et al., 2012; Meyer et al., 2010; see also Figure 1). Additionally, it sends collaterals to the inhibitory reticular nucleus of the ventral thalamus (Rt). Although TC signals are amplified and further processed within a rather complex cortical microcircuitry (Markram et al., 2015), they are also fed back directly to the thalamus through pathways involving only one cortical synapse (Briggs and Usrey, 2007).

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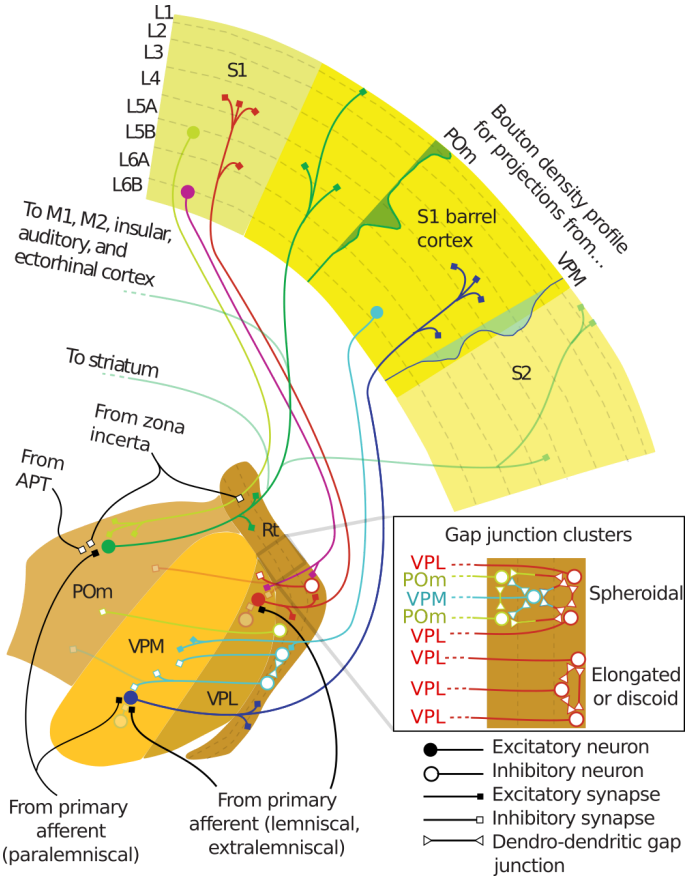

Figure 1. Schema displaying the key features and primary pathways for the somatosensory TC loop in rodents. Bouton density profiles for VPM and POm projections are taken from (Meyer et al., 2010)**.**

In general, cortical L5 and L6 pyramidal cells close the TC loop by projecting to their initial FO (i.e., VPM or VPL) as well as the associated HO, namely, for the somatosensory system, the medial sectors of the posterior nucleus (POm) (Ohno et al., 2012). These projections also send collaterals to Rt, which in turn generates inhibitory postsynaptic potentials (IPSP) in the same nuclei (i.e., VPL, VPM, POm). We should not oversimplify the effect of this parallel inhibitory pathway since the interplay of monosynaptic CT excitation and disynaptic cortico-reticulo-thalamic inhibition results in complex

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time-frequency properties. For example, at low frequency, the net effect of CT projections is briefly excitatory before becoming dominated by inhibition. However, at high frequency, it remains excitatory because of short-term facilitation of the CT synapses and short-term depression of Rt synapses (Crandall et al., 2015; reviewed in section 5.2).

On top of the afferents already discussed, POm also receives inhibition from extrareticular sources including the zona incerta (ZI) and the anterior pretectal nucleus (APT) (Bartho et al., 2002; Groh et al., 2014; reviewed in section 6.3) and excitation from the paralemniscal pathway (Pierret et al., 2000; reviewed in Section 6.1).

In our schematic summary of the key features of the somatosensory TC system in rodents (Figure 1), we separated the Rt into three tiers according to their projection targets (Lee et al., 2014; Pinault et al., 1995a). The specificity of tier targets by TC collaterals is yet unknown (Lee et al., 2014). About 90% of TC-Rt connections are expected to form open-loop connections (reviewed in section 5.4), probably to provide lateral inhibition. There is some disagreement on the presence of interneurons in VB, with proportions reported being between 0% and 4% (reviewed in section 4.3). Clusters of gap junctions in the Rt (reviewed in section 5.3) are shown as per Lee et al. (2014).

POm projections from the anterior part of the nucleus are preferentially targeting L5, whereas those from the posterior part target preferentially L1 with sparser and wider axonal arborization (Ohno et al., 2012). FO and HO TC projections tend to innervate complementary cortical lamina (Clasca et al.,

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2012; Meyer et al., 2010). Similar to TC cells in VB, projections from POm do not send intra-nucleus collaterals but send collaterals to Rt on their way to the cortex (Ohno et al., 2012). Most of them also send collaterals to the striatum – particularly for cells from the posterior part of POm – and also form arborization in other cortical regions, including secondary somatosensory (S2), primary and secondary motor, insular, auditory, and ectorhinal cortex (Ohno et al., 2012). Individual POm neurons send axons simultaneously to both S1 and S2 in a minority of cases (Ohno et al., 2012; Spreafico et al., 1987).

3 Thalamic neurons: their types and properties

A deep understanding of the inner workings of the TC loop is only possible with a thorough knowledge of the properties of its neurons, i.e., their morphologies, their electrophysiological behavior, their ion channels, and their synapses. Furthermore, establishing cell types across these different dimensions is fundamental for dissecting and reproducing this system *in silico*, an identification often facilitated by knowing the different protein markers expressed by these cells. These different aspects are reviewed in this section for the neurons of the VB (TC cells and interneurons) and the Rt (Rt cells). In rodents, FO contains relatively few interneurons, except for the LGN. Thus, most observations were made on LGN interneurons, knowledge on VB interneurons being much more scarce.

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3.1 Morphological properties

3.1.1 Somata and dendrites

Early Golgi impregnation studies show that TC cells in the VPL have two to seven primary dendrites and predominantly fusiform somata in the coronal or horizontal planes, depending on their location in the VPL (McAllister and Wells, 1981). The discoid appearance of these neurons (e.g., see Figure 2) follows the laminar organization of the VPL consisting in concentric circles centered around the VPM and running parallel to the Rt (McAllister and Wells, 1981).

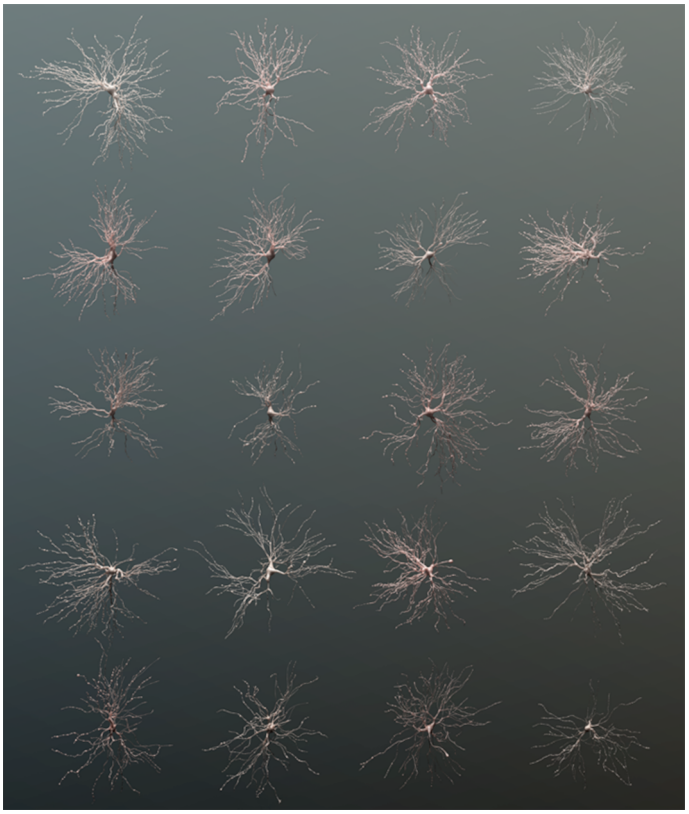

Figure 2. Example of somato-dendritic morphologies of VB TC cells.

By visual inspection, three variations of VB TC cells morphologies have been proposed depending on whether their dendrites radiate in all directions

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(radiate) or along the rostrocaudal direction with (biconcave-radiate) or without (biconcave) a prominent group of dendrites radiating medially (McAllister and Wells, 1981). The majority of VPL neurons are biconcave, while VPM neurons have more radiate dendritic fields, with larger and rounder somata (McAllister and Wells, 1981). However, other authors reported no substantial evidence of subclasses of VB TC cells according to their dendritic morphologies (Harris, 1986; Iavarone et al., 2019).

Similarly to what has been observed by McAllister and Wells (1981) in VB, dorsal LGN (dLGN) TC neurons of the mouse can be classified into three classes using quantitative assessment of their dendrites orientation: X-like (biconical, 22 %), Y-like (symmetrical, 49 %), or W-like (hemispheric, 29 %). All three types have large round somata and multipolar dendritic arbors, but the X-like type has significantly shorter dendrites and comparatively smaller somata (Krahe et al., 2011). They also have different spatial distribution within the dLGN: the majority of X-like cells are located near the borders with other nuclei (intergeniculate leaflet, ventral LGN), W-like cells are more often situated at the outer borders of the dLGN, and Y-like cells are more evenly distributed but with a larger prevalence within a central band running parallel to the optic tract. Similar classes have been described in the rat dLGN (Ling et al., 2012) with ~13% of bipolar (biconical) cells aligned approximately parallel to the optic tract, ~55% of radial (symmetrical) cells, and ~32% of basket cells (similar to W-like type). Rats bipolar cells are located preferentially on the borders of the nucleus, similar to biconcave TC cells in the VB.

Based on morphological features, membrane properties, response to

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stimuli, and differential immunofluorescence, mouse interneurons can be separated into two classes referred to as small and large soma types (9.3±1.3μm vs 11.7±6.5μm [mean±sd], measured along their longest axis) (Leist et al., 2016). Interneuron somata are either spindle-shaped with primary dendrites branching from opposite poles or tripolar with three primary dendrites (Leist et al., 2016). They are about 5 times smaller than their TC counterparts, with mouse dLGN TC cells having an area of 1530±170μm^2 (X-like; mean±se), 2040±460μm^2 (W-like), and 1710±200μm^2 (Y-like) (Krahe et al., 2011), which correspond to 45-50μm diameters for round somata. However, irrespective of their relatively small soma, mouse thalamic interneurons spread dendrites that arborize within broad areas of the dLGN (Morgan and Lichtman, 2020).

Dendrites in thalamic interneurons of rats produce varicose branches that end in beaded formations (Williams et al., 1996). Electron microscopy revealed synaptic vesicles in dendritic terminals which are thus said to be “axoniform” (Ralston, 1971). Inhibitory influences from both axonal and dendritic origins have also been shown pharmacologically (Cox and Sherman, 2000; Crandall and Cox, 2013). Dendritic terminals, also known as F2 terminals, contain more pleomorphic and sparsely distributed vesicles when compared with regular axonic (F1) terminals which have flattened and densely packed vesicles (Hamos et al., 1985). In a nearly complete electron microscopy reconstruction, three thick dendrites were present as an initial bifurcation from the soma. The dendrites later progressed into thinner and circuitous neurites that were interlinked with swellings as previously

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described. These smaller dendrites ranged from short, spike-like projections to longer (>50µm) branched trees (Morgan and Lichtman, 2020).

Rt cells have oblong or discoid shapes and their dendrites are mostly parallel to the lateral border of the nucleus (i.e., along the plane formed by this sheet-like nucleus). Although the Rt can be divided along its thickness into functionally different tiers (e.g., see Rt projections in Figure 1), most Rt dendrites cross these borders, allowing for information integration across different streams (Pinault, 2004). Existence of subtypes of Rt cells based on their morphology is debated (Pinault, 2004). Three types of Rt morphologies have been proposed based on the shape of their soma and the orientation of their dendritic fields : small fusiform (f-type), large fusiform (F-type), and round (R-type) (Spreafico et al., 1991, 1988). However, part of this variability may be due merely to constraints imposed on the dendritic field by the borders of the Rt (Pinault and Deschênes, 1998a). Further, some other authors report no subclass of Rt morphologies (Lubke, 1993; Ohara and Havton, 1996). Nevertheless, this classification seems to correlate with location along the anteroposterior axis (Vantomme et al., 2019) and with differences in electrical and chemical connectivity (Deleuze and Huguenard, 2006).

3.1.2 Axons

Depending on their cortical projections, TC cells can be separated into a core type, an intralaminar type, and a matrix type with either focal or multi-areal projections (Clasca et al., 2012). FO contains only core type cells (Clasca et al., 2012; Pape et al., 1994). These neurons tend to project mostly in L4 and to a limited region of primary sensory areas, sending coloraterals to Rt

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(Jones, 2007) but not within their own nucleus (Harris, 1987; Lee et al., 2010; Sawyer et al., 1994). In VB, these axons emerge from a prominent hillock and traverse the nucleus in a highly topographical manner, following an anterior-lateral direction, although neurons located more laterally in the nucleus sometimes follow a more unpredictable trajectory (Harris, 1987). Some arbors innervating the Rt have extensive branches contacting multiple Rt neurons, while others have a more limited extent (Harris, 1987).

POm, as a HO nucleus, contains matrix type cells, with more focal projections on its lateral part and more multriareal projections on its medial side (Clasca et al., 2012).

Reconstructed interneuron axons were shown to ramify locally within the LGN, with a small caliber, frequent *en passant* varicosities (Zhu and Lo, 1999a), and F1 terminals (Hamos et al., 1985). It resembled the thinner and circuitous dendrites that are located distally from the interneuron soma and possessed a relatively small arbor with only 5 terminal neurites (Morgan and Lichtman, 2020). The small size of the interneuron axon is in agreement with previous light microscopy reconstructions (Zhu and Lo, 1999a) and indicates a limited functionality for these axons, as compared to these interneuron dendrites. The relative contributions of interneuron axons and dendrites is further explained in sections 5.2.4 and 5.2.5.

In a series of experiments using juxtacellular recordings in rats (Pinault, 2004; Pinault et al., 1995b, 1995a; Pinault and Deschênes, 1998a), Rt axons were reported to project in a topographically precise manner (i.e., somatotopic for cells projecting to POm and VB), generally to single nuclei — with a few

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exceptions of cells projecting to corresponding FO and HO — and without making local collaterals within Rt. Most Rt axons branch locally in the thalamus and contact mainly distal dendrites of TC cells (Guillery and Harting, 2003; Pinault and Deschênes, 1998a).

3.2 Electrophysiological properties

3.2.1 Burst and tonic firing in TC and Rt cells

Rt and TC cells from different thalamic nuclei and species can fire tonic trains of action potentials and bursts (Jahnsen and Llinas, 1984). The former consists of a low-frequency sequence of sodium spikes and is most common at depolarized membrane potential during alert states *in vivo* (Jones, 2002). The latter is a calcium-mediated low-threshold spike superimposed with high-frequency discharges of sodium spikes. Bursting in TC and Rt cells is elicited from hyperpolarized membrane potentials and contributes to the oscillations recorded in EEG during slow-wave sleep, like slow waves (< 1Hz) (Steriade et al., 1993) and sleep spindles (7-14Hz) (Steriade et al., 1987). These two firing modes are associated with different states of neuronal responsiveness, e.g., TC neurons respond only to low-frequency stimuli (<15Hz) when bursting, but can relay inputs at frequencies as high as 100Hz in tonic mode (McCormick and Feeser, 1990). The possibility for external inputs to switch TC and Rt cells between these two states is a fundamental characteristic of the thalamus. It can be leveraged to control functional properties across the whole TC loop, as shown for example by the suppression of cortical paired-pulse facilitation after switching TC cells from bursting to tonic mode using an optogenetic depolarization (Whitmire et al.,

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2017).

Even though TC and Rt cells share a similar bursting capability, the presence of small-conductance Ca^{2+}-activated SK-type K^+ currents endows Rt cells with a natural tendency to generate repetitive bursts following a single stimulation (Cueni et al., 2008). Further, Rt cells are more prone to generate oscillations, as demonstrated in cats by the spontaneous generation of sleep spindles in deafferented Rt (Steriade et al., 1987) but not in TC cells deafferented from the Rt nucleus (Steriade et al., 1985). Also, compared to TC cells, Rt cells have a more heterogeneous bursting behavior and can be subdivided into different firing types according to their bursting propensity, such as non-bursting, bursting, or atypically bursting (Clemente-Perez et al., 2017; Lee et al., 2007; see Figure 3). The bursting characteristics can also be separated in terms of PV and Sst cell markers in the Rt: PV+ neurons have more sodium spikes within their calcium burst and increased a tendency to rebound, whereas Sst+ neurons have weak bursts and sometimes do not burst at all (Clemente-Perez et al., 2017) (protein markers are further discussed in section 3.3.2).

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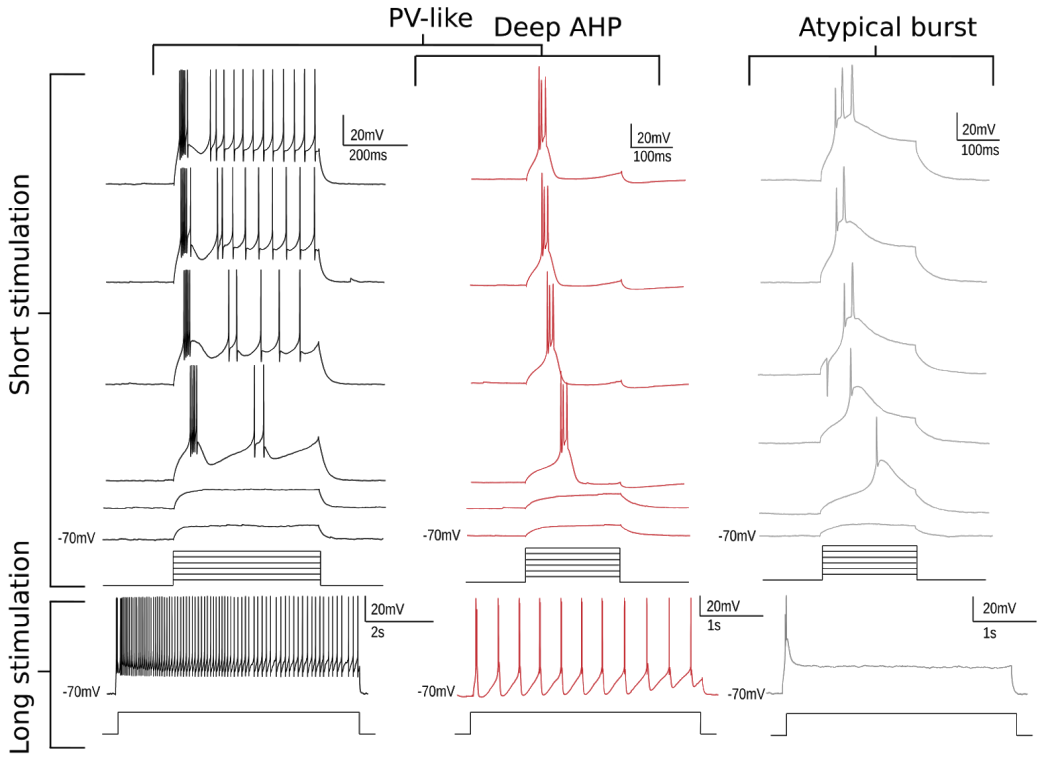

Figure 3. Examples of PV-like burst, atypical burst, and non-bursting Rt neurons. Left three columns in p14-18 rats, right column in p14-18 mice (Yi et al., *in prep*).

Although characterized by an homogeneous bursting behavior across cells and nuclei (Bartlett and Smith, 1999), TC neurons display a more diverse repertoire of tonic firing responses. For example, VB TC cells of cats exhibit accelerating, accommodating, intermittent and accommodating, and burst-suppressed firing (Iavarone et al., 2019; Turner et al., 1997) as well as delayed firing (Huguenard and Prince, 1991). Spike-frequency adaptation during tonic firing was also shown in the visual thalamus for cats (Smith et al., 2001) and, to a lesser degree, for rats (Iavarone et al., 2019; Williams et al., 1996). Similarly, about 50% of the neurons in the medial geniculate body

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(MGB) display noticeable adaptation (Bartlett and Smith, 1999). Such paired-pulse adaptation is responsible for the reported phase advance in the response of TC cell to slow sinusoidal current injections (Smith et al., 2001) and was associated with improved encoding of the spatiotemporal context of stimuli (Liu et al., 2017). Tonic firing also exhibits a particularly variable range of responses in HO TC cells (Li et al., 2003).

These different firing modes (tonic and burst) and levels of paired-pulse adaptation have been demonstrated to be reproducible in experimentally constrained biophysical TC cell models (Iavarone et al., 2019, see Figure 4).

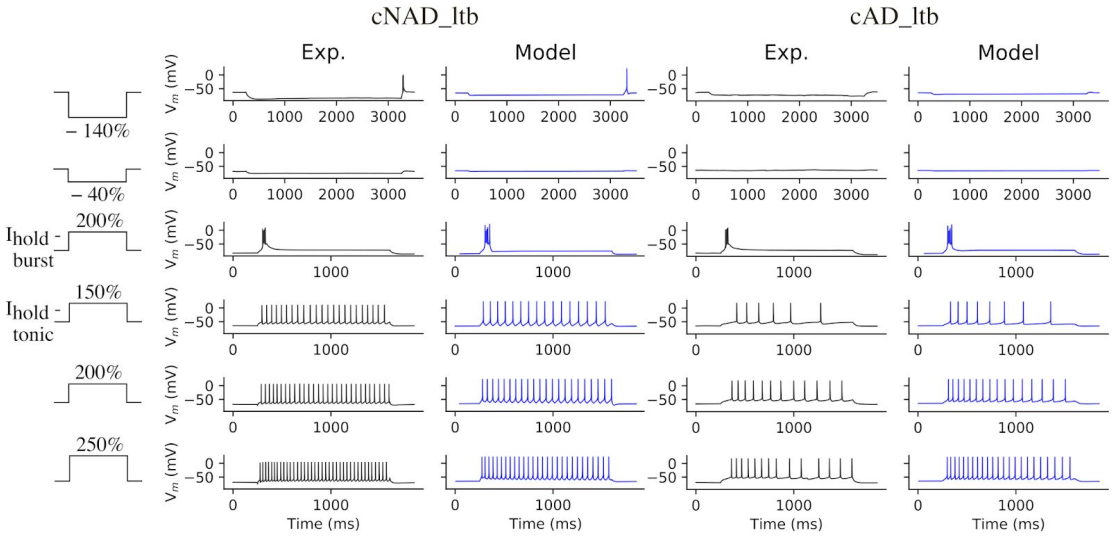

Figure 4. Exemplary models and experiments of continuous adapting (cAD) and continuous non-adapting (cNAD) low threshold burst (ltb) TC neurons of the VB . Exp: experiment. Adapted from Iavarone et al. (2019) with permission.

3.2.2 Depolarizing sag

A depolarizing “sag” in response to hyperpolarizing current injection has been

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observed in TC cells of different nuclei and species, such as in the ventral division of the MGB (vMGB) (Bartlett and Smith, 1999), in the dLGN neurons of rats and mice (Krahe et al., 2011; Williams et al., 1996), and in a fraction of the rat VB neurons (Pinault, 2003). This sag has been associated with HCN4 channels, an isoform present in various dorsal thalamic nuclei including VB, but absent from the Rt (Zobeiri et al., 2019).

3.2.3 NMDA spikes

Synaptic input limited to single TC dendrites were shown to be sufficient to trigger NMDA spikes/plateaux in LGN TC cells of rats and mice (Augustinaite et al., 2014). Due to the electrotonic compactness of TC cells, even NMDA spikes generated on distal dendrites can reach the soma, providing a powerful control mechanism for CT cells targeting these sites. These spikes can trigger bursting in quiescent hyperpolarized TC cells or can inhibit subsequent bursting by preventing T-channels de-inactivation in cells that were recently bursting (Augustinaite et al., 2014). When TC cells are in tonic mode, NMDA spikes tend not to cause action potentials but to increase the rate of successful transmission of incoming action potentials, potentially providing an efficient mechanism for cortical control of incoming stimuli by facilitating TC cell spiking. In L5 pyramidal cells, NMDA spikes have been reported to cause long-lasting depolarization in dendritic trees and constitute a cellular mechanism for the temporal binding of information and synaptic modification (Antic et al., 2010). It is unclear if they serve a similar role in the thalamus.

3.2.4 Interneurons

In interneurons, a depolarizing square current pulse evokes a train of action

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potentials, which sometimes exhibit a slight oscillatory bursting (Leist et al., 2016). An intrinsic subthreshold oscillation of the membrane potential at approximately 8Hz has also been previously described (Williams et al., 1996). Rat interneurons have a slightly higher resting membrane potential compared to TC cells (interneurons: -52mV; TC: -63mV) (Williams et al., 1996). In mice, resting membrane potentials are slightly different for small versus large soma interneuron types (small: -62.4mV; large: -64.8mV). Also, small, but not large, interneurons exhibited rebound bursting after a hyperpolarizing pulse and had a pronounced voltage sag, which is indicative of a higher I_h density (Leist et al., 2016).

All FO interneurons and 80% HO interneurons develop from the embryonic tectum, with the remaining 20% deriving from the forebrain (Jager et al., 2019, 2016). This common origin is indicative of similarities in FO interneurons, regardless of sensory modalities. This homogeneity in origins echoes to the consistency observed for TC morphologies and electrical properties across modalities. However, thalamic interneurons and Rt cells have a different origin, and hence, may show significant functional differences (Jager et al., 2016).

3.3 Molecular properties

3.3.1 Ion channels

Firing modes of TC and Rt neurons critically depend on the subtypes of ion channels they express. The low-threshold (T-type) calcium current (I_T) is one of the most studied ionic currents in the thalamus and depends on the $Ca_V3.1$ isoforms in TC neurons (Talley et al., 1999) and the $Ca_V3.2$ (30%) and $Ca_V3.3$

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(70%) isoforms in Rt cells (Astori et al., 2011). In Rt cells, calcium imaging indicates that I_T density increases from proximal to distal dendrites, reaching a peak at around 100 μm from the soma (Crandall et al., 2010). In TC neurons, the $Ca_V3.1$ channels are distributed in somata and dendrites, with early electrophysiological studies suggesting a higher density in stem dendrites compared to the soma (Williams and Stuart, 2000) and subsequent studies demonstrating their presence in intermediate and distal dendrites (Errington et al., 2010). Because TC cells are electrotonically compact in the somatofugal direction, $Ca_V3.1$ channels generate “global spikes” by triggering low-threshold bursts simultaneously across the whole dendritic tree (Connelly et al., 2015). The presence of $Ca_V3.1$ channels on distal dendritic sites has been suggested to support the amplification of CT inputs targeting these sites (Errington et al., 2010), while knocking down their corresponding gene in mice has been associated with disturbances of delta waves and sleep (Astori and Lüthi, 2013).

Hyperpolarization-activated cationic current (I_H) also contributes to burst firing in TC and Rt neurons. This current depends on HCN ion channels, which all four known isoforms are expressed in varying degrees across the thalamus of the rat. In particular, the neuropil of VB shows moderate to intense immunoreactivity for HCN1, HCN2, and HCN4 (Notomi and Shigemoto, 2004), with significantly increasing levels during development (i.e., approximately a 6-fold increase between P3 and P106) (Kanyshkova et al., 2009). The Rt contains HCN4-immunoreactive cell bodies and its neuropil is highly (HCN2) to moderately (HCN3, HCN4) immunoreactive for HCN

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isoforms (Notomi and Shigemoto, 2004). In mice, HCN2 and HCN4 are the major types expressed in VB and Rt (Abbas et al., 2006; Leist et al., 2016), with Rt cells being about 10 times more immunoreactive for HCN2 but equally immunoreactive for HCN4 when compared to TC cells (Abbas et al., 2006). Differential comportamental distribution of HCN2 channels in TC versus Rt cells is also likely to be associated with significant differences in I_H properties in these two cell types. Further, given that I_H kinetics varies across HCN isoforms, changes in their relative proportions may be linked with functional differences (Santoro et al., 2000).

In rats, L-type high-voltage activated Ca^{2+} currents have also been recorded in dLGN TC cells, interneurons, and Rt neurons. Highest densities were found at the base of TC dendrites, in more central somatic regions for Rt cells, and uniformly distributed across the soma for interneurons (Budde et al., 1998). These currents are likely to work in close interaction with T-channels to control the homeostasis of calcium concentration and bursting activity (Budde et al., 1998; Zhang et al., 2002).

Calcium influx in TC and Rt neurons contributes to the activation of Ca^{2+}-activated potassium currents of the SK (small conductance) and BK (big conductance) types. In rats, the SK2 ($K_{Ca}2.2$) type dominates in Rt and TC cells (Gymnopoulos et al., 2014) and it is responsible for repetitive bursting in Rt cells (Astori et al., 2013; Cueni et al., 2008). In the dLGN TC neurons of rats, the activation of BK channels was shown to decrease the number of action potentials per burst and increase the adaptation during tonic firing (Ehling et al., 2013). Specific antibodies against BK channels intensely stains

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all dorsal thalamic nuclei as well as the Rt in mice (Sausbier et al., 2006).

In mice VB, TC neurons were also found to have m-type potassium currents (K_V7.2 and K_V7.3 subunits) which helps hyperpolarizing their membrane and deinactivating I_T (Cerina et al., 2015) as well as A-type K+ currents (I_A; K_V4.1-K4.3 subunits) which act as a functional antagonist of I_T and determine the kinetics and amplitude of the low-threshold spike during burst firing (Kanyshkova et al., 2011).

Like LGN TC cells, interneurons have been shown to have I_T and I_A currents. However, the ranges of steady-state activation and inactivation of these two currents are highly overlapping (Pape et al., 1994). Thus, the I_A current causes a net membrane current counteracting the I_T-driven regenerative low-threshold Ca^{2+} response and results in a different firing pattern than the low-threshold burst displayed by TC and Rt cells (Pape et al., 1994).

Background K^+ channels (such as two-pore-domain, K_2p) TASK and TREK play a critical role in switching between activity states in TC neurons. These channels are also extensively modulated by neurotransmitters, such as muscarinic acetylcholine receptors (Bista et al., 2015).

A persistent sodium current is also active in soma and dendrites of TC neurons from rats dLGN, both during tonic and burst firing (Parri and Crunelli, 1998).

3.3.2 Protein markers

Molecular markers such as calcium-binding proteins (CBPs) and neuropeptides can be identified with conventional histological procedures and

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have been instrumental in differentiating cell types. In general, excitatory neurons express only a limited number of common markers and this is true for TC neurons as well. For example, some calcium-binding proteins, such as calretinin (CR), have been detected only in HO (Lu et al., 2009). In rats, parvalbumin (PV) has been shown to be virtually absent from the dorsal thalamus, while calbindin (CB) was absent from VB TC cells but was expressed in about two-thirds of POm TC cells (Rubio-Garrido et al., 2007). A differential distribution of parvalbumin (PV) and calbindin (CB) also distinguishes FO and HO auditory mouse nuclei, with PV densely and CB weakly expressed in vMGB neuropil (FO) and an inverted pattern in the auditory HO. The identity of the cells contributing to this PV immunoreactivity is however unclear since it can be associated with PV+ fibers coming from different origins, including Rt axons, ascending auditory fibers, and descending projections from the auditory cortex (Cruikshank et al., 2001).

PV labels different afferents in the VB as well: projections from Rt neurons are GABA+ and PV+, dendritic terminals from local inhibitory interneurons are GABA+ and PV-, and ascending terminals are GABA- and PV+ (De Biasi et al., 1994). Faintly labeled CB+ cells were found in the caudal part of the VPL, while the VPM is almost devoid of CB+ cells. PV+ and CR+ fibers can also be found in the VPL (Arai et al., 1994).

Immunoreactivity for CBPs is more complicated in dLGN (Arai et al., 1994), with CR labeling numerous fibers but few cell bodies (Winsky et al., 1992). In some studies (Meuth et al., 2006; Okoyama and Moriizumi, 2001), PV was suggested to be a marker of TC neurons at least in the magnocellular

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part of the vLGN. However, other studies found TC cells to be PV- (Lintas et al., 2013; Luth et al., 1993). Confounders may partially explain these conflicting results: 1) TC cells seem to be PV+ in monkeys (Jones and Hendry, 1989; Rausell and Jones, 1991) but not in rodents (Lintas et al., 2013; Luth et al., 1993); dorsal thalamus nuclei can show PV immunoreactivity due to incoming fibers without expressing it locally in TC cells (Cruikshank et al., 2001; Luth et al., 1993); and 3) PV mRNA but not PV proteins may be found in rat TC cells (Sieg et al., 1998).

Similarly to other inhibitory neurons in the brain, different types of CBPs and neuropeptides are expressed in Rt cells.This property could prove useful for parcellating this nucleus which is already known to be heterogeneous in terms of topographic maps and thalamic and cortical connections (section 4.4; Mitrofanis and Guillery, 1993). In rats, PV is present in all sectors, while CR and CB are mostly expressed in the ventromedial corner of the rostral portion of Rt (Arai et al., 1994; Winsky et al., 1992). In mice, somatostatin (Sst) and PV can be found across the entire anterior-posterior axis of the Rt, with a different distribution of Sst+ neurons in the medial-lateral extent of the somatosensory sector (Clemente-Perez et al., 2017). Differences in the expression of these two proteins allows segregating two functionally distinct subpopulations of Rt neurons (Ahrens et al., 2015; Clemente-Perez et al., 2017). By acting through the Sst-5 receptors of Rt cells, Sst can inhibit the GABA release and the oscillatory activity of these cells (Clemente-Perez et al., 2017; Leresche et al., 2000; Sun et al., 2002). Similarly, the neuropeptide cholecystokinin (CCK) has been shown to affect

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the firing behavior of Rt neurons and the oscillatory state of the thalamic network by suppressing a K^+ conductance (Cox et al., 1997). Neuropeptide-Y (NPY) and its receptors are also present in Rt neurons, allowing these cells to auto-regulate Rt activity by releasing NPY in a recurrent manner (Sun et al., 2003).

4 Neuroanatomy and cell composition

4.1 Parcellation

A 3D volume parcellation of the brain is required in various applications, such as for atlasing cell types (Erö et al., 2018) and their connections (Fürth et al., 2018), for modeling the brain at the cellular resolution (Markram, 2006), or for comparing brain characteristics (e.g., volume of regions) between conditions (e.g., age, gender, diseases). Two dimensional stereotaxic atlases have been made available to allow precise positioning in context of experimental surgical manipulations in mice (Paxinos and Franklin, 2013) and rats (Paxinos and Watson, 2014). Although these resources can be used to generate volumetric atlases (Majka et al., 2012), the process of stacking annotated 2D slices creates severe artifacts due to partial misalignment of slightly distorted slices. As an alternative, the Allen Mouse Brain Connectivity Atlas provides a finely parcellated atlas of over 800 brain structures specified within their Common Coordinate Framework (CCF) and based on a population average of over 1,200 mice (Oh et al., 2014). For the rat, the Waxholm Space Atlas of the Sprague Dawley Rat Brain has been built from ex-vivo magnetic resonance imaging (MRI) and diffusion tensor imaging and provides a reconstruction free

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from slicing artifacts (Papp et al., 2014). However, due to the lower resolution of MRI compared to optical microscopy, this atlas currently[1] contains only a gross parcellation of the brain with 118 major anatomical structures and no thalamic subregions.

Initiatives like the CCF have proven to be highly useful, but a finer parcellation is still needed to support the development of increasingly detailed models. For example, quantitative resources for somatotopy are still direly needed. Such data have often been collected (e.g., for the barrels) (Meyer et al., 2013; see section 4.4) but have not necessarily been standardized and released as a shared resource. For the thalamus, aside from these functional maps (e.g., somatotopy, tonotopy, and retinotopy), better quantitative data on the division of the Rt (e.g., head, tail, and tiers) (Clemente-Perez et al., 2017; Lam and Sherman, 2011; Pinault and Deschênes, 1998a) would be invaluable for mapping connectivity. Similarly, most somatosensory thalamic nuclei could be subdivided in smaller subregions than what is typically available in atlases, i.e., PO can be divided into four sub-nuclei (Sumser et al., 2017), VPM can be divided in dorsomedial (VPMdm), ventrolateral (VPMvl), and parvocellular parts (VPMpc) (Haidarliu et al., 2008), and the VPL can be split in caudal (VPLc), middle (VPLm), and rostral (VPLr) regions (Francis et al., 2008).

4.2 Stereological studies

Cell distributions in the whole brain have been recently made available,

[1] As of May 26th 2020, using the version stored on the NeuroImaging Tools & Resources Collaboratory website (https://www.nitrc.org).

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mostly for mice due to the development of genetically modified strains. For example, an atlas reporting the position in space of every cell of a mouse brain has been created using CUBIC-X expansion microscopy and tissue clearing (Murakami et al., 2018). This resource is currently limited since the propidium iodide fluorescent agent used for labeling cannot distinguish glial cells from neurons, but the same technique can be combined with immunostaining or transgenic mouse lines to provide a more precise identification of cell types. Other resources mapping individual cell types (Erö et al., 2018) or counting cells expressing different CBPs (i.e., PV, Sst, and vasoactive intestinal polypeptide) (Kim et al., 2017) across the mouse brain have also recently been made available. These new resources are a welcomed addition to stereological studies of the thalamus since the latter provide relatively scarce and very inconsistent information. Reported cell densities in the rodent thalamus (Diaz et al., 1999; Lifshitz et al., 2007; Luczynska et al., 2003; Meyer et al., 2013; Mooney and Miller, 2010, 2007; Parent and Descarries, 2008; Ramos et al., 1995; Ross et al., 1995) span over two orders of magnitude and show a clear and sizable between-laboratory effect (see Figure 5), plainly illustrating the low reliability of these estimates, a result similar to what has been observed all across the mouse brain (Keller et al., 2018).

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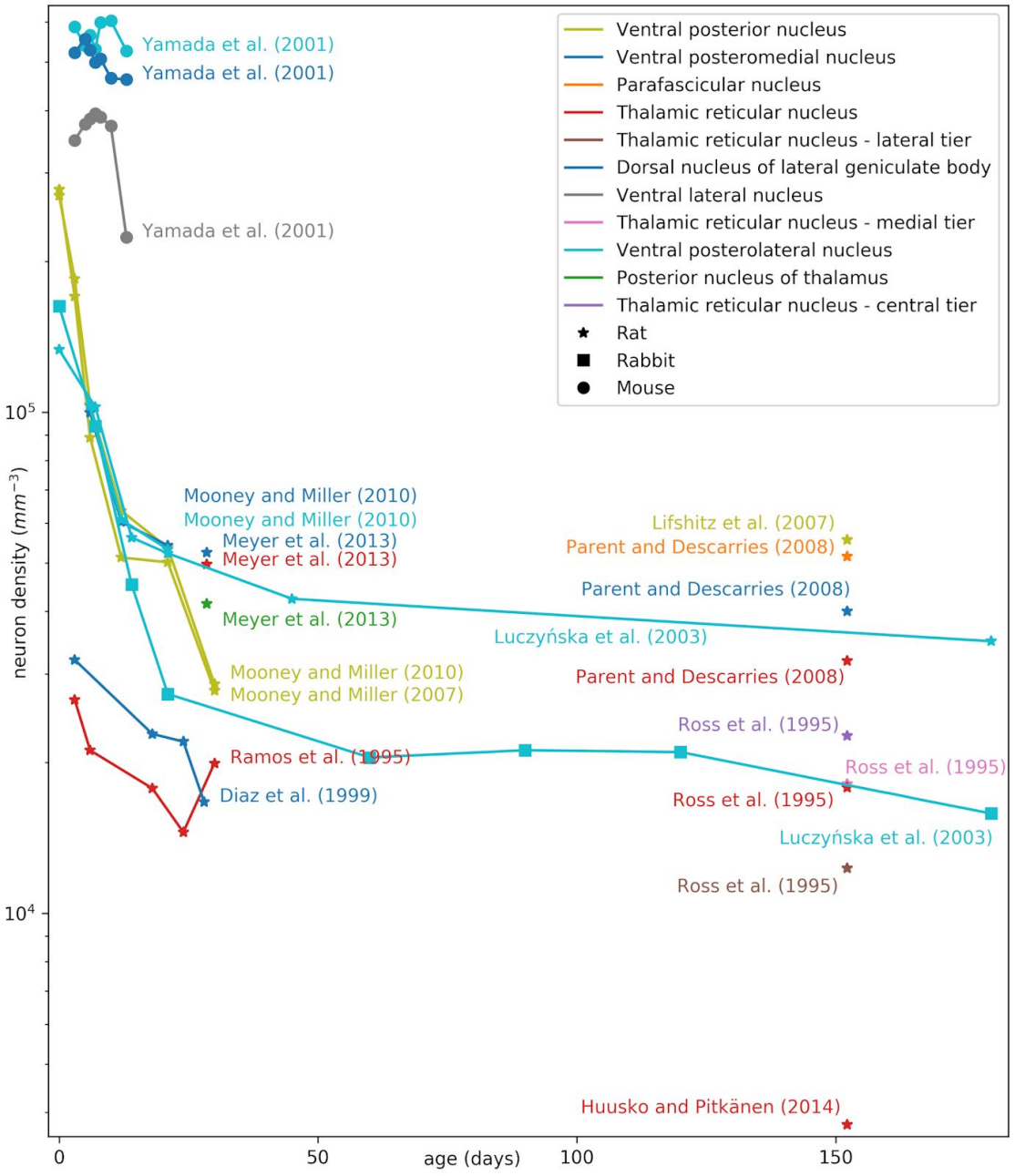

Figure 5. Cell densities for different thalamic nuclei, in different rodent species, and at different ages. Data pooled from a systematically annotated corpus of literature on the rodent thalamus (O'Reilly et al., 2018, 2017).

4.3 Presence of interneurons

In rodent FO, the presence of interneurons differs significantly across

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modalities. In the visual system, the dLGN is composed of a sizable proportion of interneurons, although the exact numbers vary greatly between studies (see Table 1).

Table 1. Percentages of interneurons in dLGN.

Percentage	Method	Species	Reference
5.8%	GABA-immunopositive interneurons counted with optical fractionator	mice	(Evangelio et al., 2018)
8%	Golgi staining and two-dimensional counting	mice	(Werner et al., 1984)
15–20%	GABA immunostaining and thionin two-dimensional counting	various species	(Arcelli et al., 1997)
20-25%	unlabeled cells after massive injection of HRP into areas 17 and 18	cats	(LeVay and Ferster, 1979)

In contrast, interneurons are very sparsely distributed in non-visual FO. Early studies were even suggesting their absence from VB (de Biasi et al., 1986; McAllister and Wells, 1981; Ottersen and Storm-Mathisen, 1984), but more recent investigations reported proportions around 0.4-1.0% (Arcelli et al., 1997; Harris and Hendrickson, 1987). A recent study reported significantly higher proportions (4.2% in VPM; 3.7% in VPL) using light microscopy immunocytochemistry with a GABA immunogold marker in 6–12 months old Wistar rats (Cavdar et al., 2014). Low proportion of interneurons in VB is particular to rodents, this proportion being around 20-30% in cats and primates (Arcelli et al., 1997; Penny et al., 1983; Spreafico et al., 1983).

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This low prevalence is not sufficient to disregard any significant role since interneurons have been shown to serve important functions in regions with similarly low proportion, like in the striatum (Koós and Tepper, 1999). Further, interneuron connectivity has been ascribed some peculiar functional features such as triadic circuitry (section 5.2.5; Sherman, 2004) and presynaptic dendrites (Cox and Beatty, 2017). Moreover, computational experiments suggest that they may serve essential roles such as transitioning between brain states (Bhattacharya et al., 2016).

4.4 Functional organization

The cellular composition and the neuronal projections have a very organized topology across the different types of thalamic nucleus (i.e., Rt, FO, and HO) and across the sensory modalities. For the somatosensory system, it is most clearly evidenced in VPM by the presence of whisker barreloids, the thalamic counterpart of cortical barrels (Hoogland et al., 1987; Sugitani et al., 1990; Van Der Loos, 1976). Cellular density has been shown to vary substantially across barreloids, increasing by about 50% when going from E1 to A4 barreloids (Figure 6; Meyer et al., 2013). This regional specificity demonstrates not only the importance of modeling differences between septal and barreloid regions but also across barreloids. In general, the whole VB has a somatotopic arrangement (Emmers, 1965; Saporta and Kruger, 1977; Waite, 1973), with a primary somatotopic map containing unilateral representations and a secondary with bilateral projections (Emmers, 1965).

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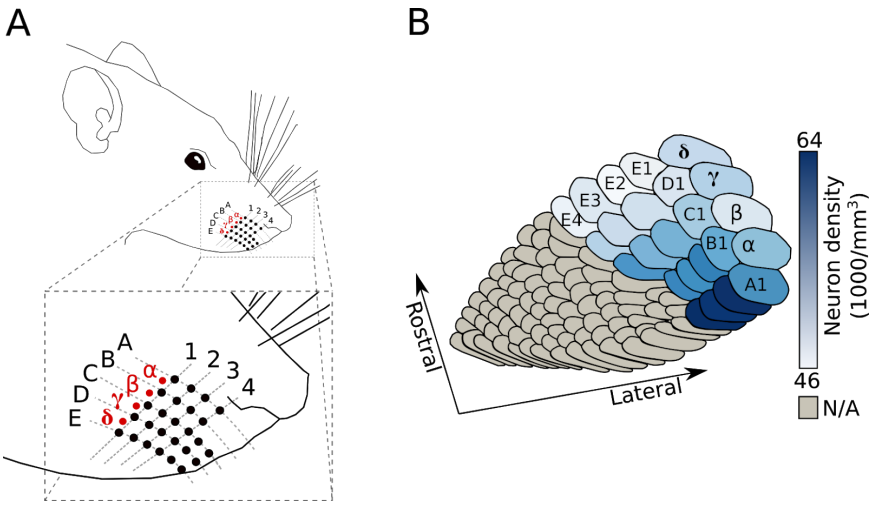

Figure 6. Topological relationship between whiskers and barreloid in the rodent VPM. A) The snout of the rat with macrovibrissae arcs (A-E) and rows (1-4) in black and straddlers in red. B) Barreloids in the VPM, as represented by Haidarliu and Ahissar (2001) (reproduced with permission), with cellular densities per barreloid taken from Meyer et al. (2013). In grey, next to macrovibrissae rows are aggregates of neurons associated with microvibrissae, for which no density estimates are available.

POm has also been shown to be somatotopic (Fabri and Burton, 1991; Nothias et al., 1988; Ohno et al., 2012), with cortical driver projections from L5b innervating four distinctly oriented somatotopic maps in different subdivisions of this nucleus (Sumser et al., 2017). Early investigations have shown a clearer arrangement in VB than in Rt and POm (Hoogland et al., 1987), but a more recent study reported VB and POm somatotopic maps to be equally well defined (Alloway et al., 2003), suggesting that the precision of such spatial mapping might be conserved along the pathways from FO to HO.

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For the auditory system, the MGB can be divided into ventral/lemniscal (vMGB) and dorsal/extralemniscal (dMGB) parts. Whereas tonotopic organization has been shown in the former, it is absent in the latter (Bartlett and Smith, 1999). More precisely, four, possibly five, distinct tonotopic maps have been identified in the vMGB, with projections to different subregions of the auditory and the insular cortex. See Tsukano et al. (2017) for a review.

For the visual system, the dLGN has long been known to be retinotopic (Reese, 1988; Reese and Jeffery, 1983; Roth et al., 2016). The dLGN is further structured, with regions specific for ipsilateral versus contralateral inputs and different TC cells types in different subregions. Kerschensteiner and Guido (2017) recently reviewed the organizational principles within this nucleus.

Regarding the Rt, it has also been shown to have a topographic organization along its plane (sectors) and across its thickness (tiers) (Figure 7A; Crabtree, 1999; Crabtree, Collingridge, and Isaac, 1998; Jones, 1975; Lam and Sherman, 2005; Pinault, 2004; Shosaku, Kayama, and Sumitomo, 1984). The posterior part of this nucleus is separated in a dorsal region responding to visual stimuli in a retinotopic way (Hale et al., 1982) and a ventral region responding to auditory stimuli. A somatotopic representation of the different whisker receptive fields and the other body parts is found anterior to the visual and auditory sectors (Figure 7B; Shosaku et al., 1984). The most ventral part of Rt is associated with taste (Hayama et al., 1994) and the region immediately dorsal to it is related to the visceral activity (Kimura et al., 2012; Stehberg et al., 2001). Limbic and motor systems are connected to sectors of

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the most rostral portion of the nuclei, with the motor sector also containing a somatotopic map (Cicirata et al., 1990; Gonzalo-Ruiz and Lieberman, 1995a, 1995b; Lozsadi, 1995, 1994).

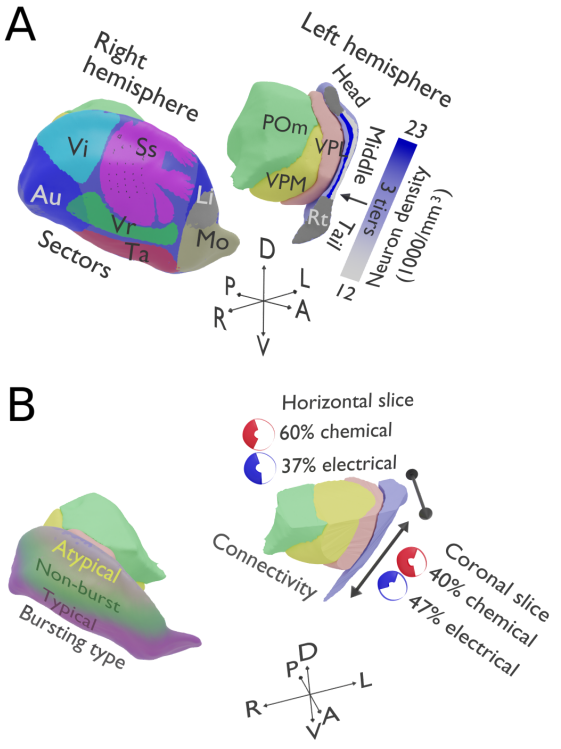

Figure 7. Schematic representation of sources of topological variability within Rt, overlaid on the volumes of somatosensory thalamic regions, as parcellated by the Allen Mouse Brain Atlas. Thalamic regions are shown from the front side of the brain. Axis system: dorsal (D), ventral (V), right (R), left (L), anterior (A), and posterior (P). A) Right hemisphere (left side): Schematic representation of the topological organization of the Rt in the sectors most often described in the literature: somatosensory (Ss), visual (Vi), auditory (Au), visceral (Vr), taste (Ta), Limbic (Li), and motor (Mo). Somatotopy in the Ss sector is represented

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as proposed by Shosaku et al. (1984) (reused with permission). Although not represented here because of the lack of sufficiently precise descriptions, a similar topological organization can be observed across different modalities. Left hemisphere (right side): cut view of the somatosensory thalamus, including POm, VPM, VPL, and Rt. Rt is shown separated in head, tail, and tiers in the middle part. Cell densities (for adult rats) (Ross et al., 1995) in the different tiers are color-coded to highlight the heterogeneity of the cell composition across this nucleus. No cell density has been reported for the head and tail sections specifically. Connectivity, dendritic fields, and gap junctions networks have also been shown to depend on tiers (not represented here). B) Right hemisphere (left side): Schematic representation of the electrophysiological behavior of Rt cells varying along the dorsoventral axis (Lee et al., 2007). Left hemisphere (right side): Percentage of coupled cells depends on the plane in which the connectivity is probed, with more electrical connectivity along the dorsoventral direction in coronal slices and more chemical connectivity along the anteroposterior direction in horizontal slices (numbers for P12-15 rats from Deleuze and Huguenard (2006)).

Further, the connectivity between the Rt and different thalamic nuclei supports its division in three tiers along its thickness (e.g., see Figure 1 for tiers specificity of VPL, VPM, and POm projections) (Clemente-Perez et al., 2017; Lee et al., 2014; Pinault, 2004; Pinault et al., 1995a). Differences in cell bursting behavior along the dorsoventral axis of the nuclei (non-bursting,

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bursting, or atypical bursting) has also been reported (Lee et al., 2007) and suggest regional variation in this nucleus not only in terms of cell densities but also in terms of cellular electrophysiological behavior (Figure 7B).

5 Microconnectivity

Studying the connectivity patterns and the properties of synaptic connections is necessary for understanding and modeling the dynamics of TC interactions. These aspects are reviewed here for the microconnectivity within the TC system and in the next section for external afferents.

5.1 Connectivity patterns

As a rule, FO TC cells do not send collaterals within the dorsal thalamus. Some rare cases of lateral connections have been reported in young animals, but these connections are thought to be pruned during maturation (Lee et al., 2010). TC cells from cat LGN have been shown to send intranuclear collaterals that form synapses onto intralaminar interneurons[2] (Cox et al., 2003) and potentially even to other TC cells (Soltesz and Crunelli, 1992). However, the presence of such collateral has not been supported experimentally for other nuclei or for rodent species (Harris, 1987; Sawyer et al., 1994).

TC cells target directly extrathalamic (e.g., cortical) areas, sending collaterals to the Rt on their way to the cortex. The Rt project back inhibitory input onto FO (and other) nuclei, creating either 1) a disynaptic inhibitory

[2] As opposed to cats, nocturnal rodents do not show clear lamination in the LGN (Monavarfeshani et al., 2017).

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feedback loop, 2) a disynaptic center-surround type of local lateral inhibition or 3) a disynaptic lateral inhibition between nuclei of the dorsal thalamus (Guillery and Harting, 2003; Kimura et al., 2007).

The literature suggests a certain number of basic rules related to microconnectivity in the thalamus:

1. TC cells do not project within their nucleus.
2. TC cells do not project directly to other nuclei of the dorsal thalamus.
3. Rt cells do not have other external targets than the dorsal thalamus.
4. Thalamic interneurons project only within their nucleus.

From a theoretical point of view, these four rules eliminate a good number of possible connection patterns and leave 18 possible disynaptic or trisynaptic pathways for a TC cell to provide feedback to itself (intra-nucleus, closed-loop), to a neighboring TC cell (intra-nucleus, open-loop), or to a TC cell of another nucleus (inter-nucleus). Each of these combinations (i.e., intra vs. inter-nucleus, closed vs. open-loop, disynaptic versus trisynaptic) can have an inhibitory or excitatory impact, considering disinhibition as providing an overall excitatory impact (Figure 8).

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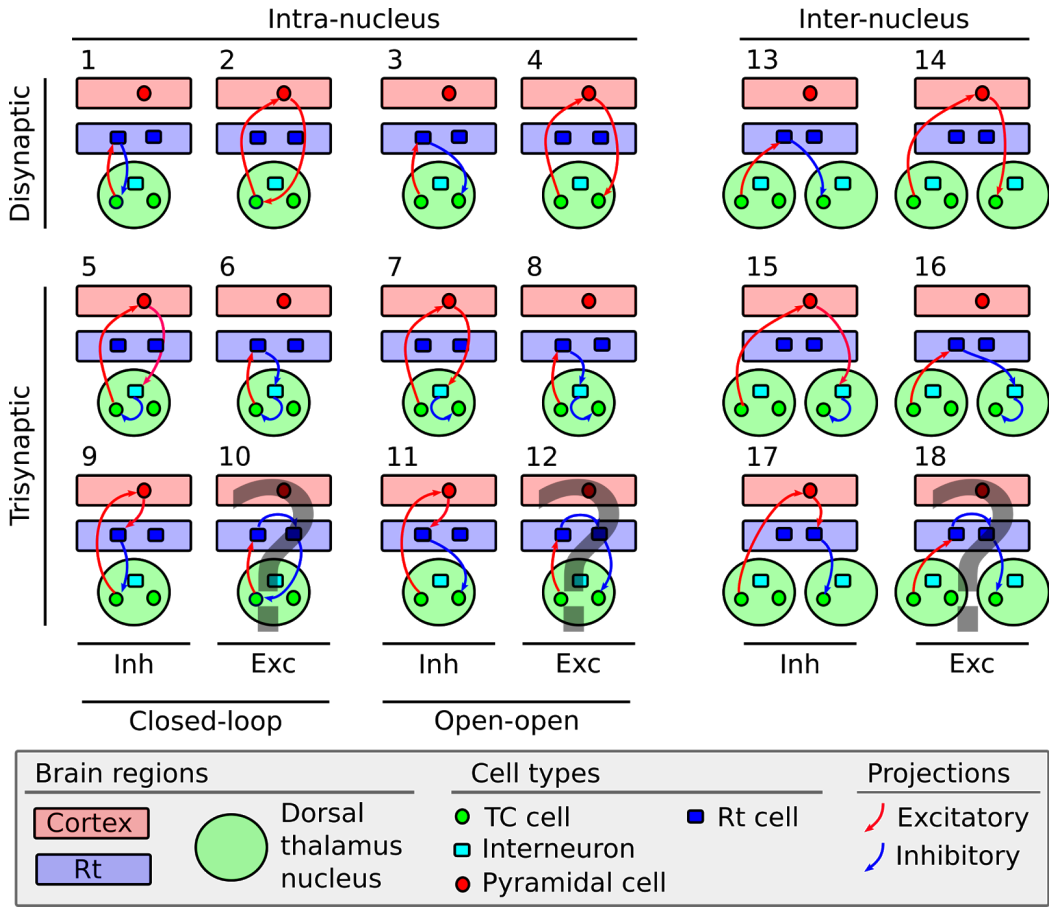

Figure 8. All possible connectivity patterns from one TC cell to itself or to another TC cell in at most three synapses according to the four rules previously listed. Grey interrogation marks have been superimposed over patterns involving Rt-Rt chemical connections since evidence about their existence in adult rodents is equivocal (section 5.2.2). Rt-Rt connections through electrical synapses (section 5.4) are not represented in this figure. Inh: Inhibition; Exc: Excitation or disinhibition.

Information about the relative proportion of these different connection patterns is key for understanding and modeling the TC system. Even when they constitute an emergent property of a modeling approach (e.g., deriving

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connections from appositions of realistic morphologies as in Hill et al. (2012)), these proportions are required for model validation. Relatively few studies report such figures, except for patterns 1 (closed thalamo-reticular loop) and 3 (open thalamo-reticular loop) for which proportions have been reported both structurally and functionally (see Table 2; Gentet and Ulrich, 2003; Lee et al., 2010; Lo and Sherman, 1994; Pinault and Deschênes, 1998; Shosaku, 1986). Such proportions need to be assessed both structurally and functionally since these two types of connectivity are linked through an intricate relationship. Many factors are involved in how structural connections support functional interactions, such as the strength of the synaptic connections, cellular electrophysiological properties, or time-frequency patterns of incoming activity. For example, at low frequency, the combination of patterns 2 and 9 produces a very short excitation (pattern 2) followed by inhibition (pattern 9). However, at high frequency, this combination produces only excitation because of short-term facilitation in the corticothalamic synapses and short-term depression in the reticulo-thalamic pathway (Crandall et al., 2015).

5.2 Chemical synapses

5.2.1 Rt-TC synapses

The strength of reticular inhibitory connections to VB in paired recordings is very variable (inhibitory postsynaptic current (IPSC) amplitude range: 18.5-514.0 pA; latency: 1.5-3.1 ms) and depends on various factors such as the proportion of postsynaptic failures, the amplitude of unitary IPSCs, and the density of axonal swellings. It is qualified as either weak (conductance: 0.46±0.14 nS; range 0.35-0.61 nS) or strong (conductance: 4.5±4.6 nS;

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range: 1.85–12.7 nS) (Cox et al., 1997). Each synaptic contact generates a unimodal (mean amplitude 12.2 ± 1.3 pA) or a bimodal (mean 13.2 ± 6.3 pA and 24.2 ± 16.8 pA) distribution of miniature IPSC (mIPSC) amplitudes (Cox et al., 1997).

VB responses from reticular inhibition can last up to hundreds of milliseconds and typically display an early Cl^--mediated $GABA_A$ component and a late K^+- mediated $GABA_B$ component of about 20% the amplitude of the $GABA_A$ component (Huguenard and Prince, 1994). Compared to other cells, the $GABA_A$ reversal potential in TC cells is very negative, suggesting the existence of a mechanism extruding Cl^- (Huguenard and Prince, 1994).

When compared with $GABA_A$-mediated mIPSCs recorded in dLGN TC cells, mIPSCs in VB TC cells have faster kinetics (VB: 1.4 ± 0.2 ms, dLGN 1.7 ± 0.5 ms rise times; VB: 18.6 ± 3.6 pA/ms, dLGN: 14.8 ± 5.2 pA/ms decay slopes) and narrower half-widths (VB: 8.19 ± 1.46, dLGN: 11.6 ± 3.5 ms), but similar amplitudes (VB: 25.9 ± 0.89 pA, dLGN: 29.4 ± 0.8 pA) (Yang et al., 2017). The slower rise time and longer half-widths of mIPSC are characteristics of dendritic release from dLGN interneurons and may be due to differences in the subunit composition of their $GABA_A$ receptors. This suggests that the reported differences between mIPSCs in VB and dLGN TC cells may be attributed to a larger contribution from interneurons in the dLGN (Yang et al., 2017).

5.2.2 TC-Rt synapses

The Rt receives excitatory inputs from TC and CT axons, with the latter accounting for ~60% of the total excitatory terminals (Liu and Jones, 1999), in

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line with previous reports showing much denser CT than TC projections (Deschênes et al., 1998; Sherman and Koch, 1986). These two types of input can be distinguished by their short-term dynamics: L6 CT synapses onto Rt neurons are facilitating, while TC axons are depressing (Astori and Lüthi, 2013; Gentet and Ulrich, 2003; Golshani et al., 2001).

TC-Rt synapses in VB generate strong excitatory postsynaptic potentials (EPSP; amplitudes [mean±SEM]: 7.4 ± 1.5 mV, range 0.7-27 mV), few synaptic failures, and low variability of the kinetic properties and synaptic latencies (rise time: 0.63 ± 0.03 ms; decay time: 15.12 ± 0.91 ms) (Gentet and Ulrich, 2003). Similar EPSP amplitudes (0.5-2.0 mV in Rt neurons held between –70 and –80 mV) and short-term depression were found in dLGN TC neurons of ferrets (Kim and McCormick, 1998).

Depending on the baseline potential, AMPA contributes between 68.1 ± 4.9 % and 71.4 ± 4.1 % of the total EPSP in the VB TC-Rt synapses of juvenile (P14-20) rats (Gentet and Ulrich, 2003). This contribution changes during development, with NMDA/AMPA ratio decreasing from 0.42 at P14 to 0.27 at P21-28 in mice (Astori and Lüthi, 2013). Although this indicates synaptic maturation, NMDA receptors in Rt neurons continue to express GluN2B instead of seeing it substituted by GluN2A as it is usually the case during development (Astori and Lüthi, 2013).

VB TC-Rt synapses may also contain a rare type of NMDA receptor subunit not requiring depolarisation to remove the Mg^{2+} block since only a low proportion of NMDA receptors are blocked at resting membrane potentials lower than −70 mV (Gentet and Ulrich, 2003).

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5.2.3 Rt intrinsic connections

Recurrent inhibition in Rt is controversial. Some studies in rats report relatively frequent recurrent connections: 40% to 60% at P12-15 (Deleuze and Huguenard, 2006); 62% (N=47) at P10-12 (Lam et al., 2006). However, other studies found these connections to be rare (2.8% incidence of inhibitory connections (N=180) in P4-P8 mice (Parker et al., 2009)) or absent (in P12-P21 rats (Landisman et al., 2002; Long et al., 2004)). Recent optogenetic experiments in mice suggest that these connections are pruned within the first two weeks after birth (Hou et al., 2016). However, other investigators, also using optogenetic stimulation, found weak but present Rt-Rt connections in 2-4 months old mice (Makinson et al., 2017). Reciprocal inhibitory connections in Rt have been hypothesized to help desynchronize Rt activity in context of sleep and epilepsy (Huntsman et al., 1999). GABAergic terminals in Rt account for about 10 % of all connections to the Rt (Guillery and Harting, 2003) but it is currently unclear what proportion of these terminals come from external afferents (e.g., ZI, basal forebrain, globus pallidus, pretectum; see section 6.3) or from recurrent Rt connections.

5.2.4 Interneurons synapses

Electron microscopy studies have shown that interneuron dendrites together with incoming retinal ganglion axons form a triadic synapse onto TC dendrites (Hamos et al., 1985; Morgan and Lichtman, 2020; section 5.2.5). F2 terminals of these interneurons have been shown to be associated with two types (A and B) of feedforward inhibitory responses depending on their type of receptors. Although every F2 terminal has AMPA and NMDA receptors, only

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those exhibiting the type B response also contain type 5 metabotropic glutamate receptors (mGluR5) which cause longer-lasting feedforward inhibition. Both types of response were observed in the same postsynaptic cells, and these cells were morphologically different from those not displaying any response typical of F2 terminals (Crandall and Cox, 2013).

The amplitude and duration of IPSCs caused by interneuron spikes depend on the contribution of sodium and calcium conductances. In presence of TTX, sodium spikes of axonal and dendritic origin cause rapid $GABA_A$ IPSCs (10% to 90% rise time: 1.2ms) whereas dendritic calcium spikes generate slow IPSCs (10% to 90% rise time > 20ms) at the interneurons-TC synapse (Acuna-Goycolea et al., 2008). These differences indicate that these interneurons may rely on a variety of inhibitory signaling mechanisms.

There is some anatomical evidence from electron microscopy that Rt to local interneuron synapses exist (Morgan and Lichtman, 2020). Further, LGN interneurons in rats have been shown to receive IPSPs when the Rt is extracellularly stimulated. These IPSPs are mediated only by bicuculline-sensitive $GABA_A$ receptors expressed by the interneurons (Zhu and Lo, 1999b).

5.2.5 Glomeruli, triadic synapses, and local connectivity motifs

Triadic synapses insulated by sheaths of astrocytic processes form glomerulus-like arrangements in the thalamus (Sherman, 2004; Spacek and Lieberman, 1974). These triadic synapses allow ascending glutamatergic driving inputs to trigger fast feedforward inhibition onto proximal TC dendrites by directly releasing GABA from interneurons dendrites (i.e., dendro-dendritic

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contacts; Figure 9.A). Compared to non-triadic configurations, these synapses provide faster (~1 ms delay) and more reliable feedforward inhibition (Blitz and Regehr, 2005).

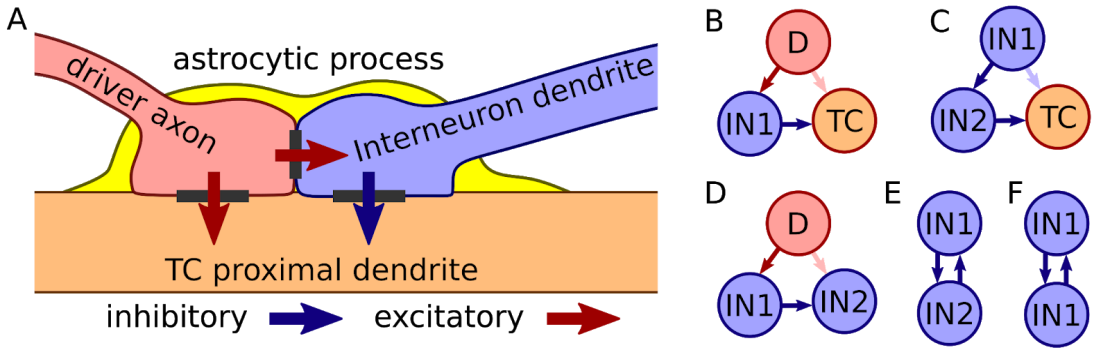

Figure 9. Schematic representation of triadic synapses and local connectivity motifs. A) A triadic synapse ensheathed in an astrocytic process. B-F) Examples of various connectivity motifs involving interneurons that have been observed (Morgan and Lichtman, 2020). Paler arrows indicate optional connections, i.e., meaning that both the motifs with and without such a connection exist. Most of the connections from interneurons are dendro-dendritic. D: Driver afferent; IN1, IN2: Two different interneurons; TC: Thalamocortical relay cell.

Because they involve interneurons, triadic synapses have been studied mostly in the LGN, where they have been shown to modulate driving inputs by controlling their gain (Heiberg et al., 2016; Sherman, 2004) and by inducing a response lag (Vigeland et al., 2013). They also sharpen the temporal precision of incoming information by generating short windows of excitatory input on TC cells, i.e., an initial monosynaptic excitation followed 1ms later by

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disynaptic feedforward inhibition mediated by interneurons (Babadi et al., 2010; Butts et al., 2011; Casti et al., 2008).

As opposed to modulatory L6 afferents that target distal TC dendrites with small non-glomerular synapses (Guillery and Sherman, 2002), L5 afferents can drive thalamic activity through glomerular synapses formed on proximal dendrites of HO TC cells (Hoogland et al., 1991; Rouiller and Welker, 1991). These glomerular arrangements further enable L5 afferents to trigger a feed-forward inhibition of TC cells through incerto-thalamic terminals (Bartho et al., 2002).

Interestingly, one LGN thalamic interneuron is seen to create diverse types of connectivity motifs, such as those illustrated in Figure 9.B-F as well as various other chain variants of these motifs not shown (Morgan and Lichtman, 2020). This implies that the interneurons hold very complex computing power and are responsible for many aspects of shaping incoming sensory stimuli. Computational simulations of such circuitry could serve as a helpful tool to parse out these sophisticated microcircuitries.

5.3 Electrical synapses

Gap junction (GJ) protein connexin36 is known to be highly expressed in Rt (Liu and Jones, 2003). Both connexin36 and connexin45 are also expressed in VB TC cells, where they play a role in the early development of chemical synapses and gradually disappear during the first postnatal week (Lee et al., 2010; Zolnik and Connors, 2016). GJ protein Pannexin1 has also been reported in the thalamus (Cone et al., 2013), particularly in Rt cells (Ray et al., 2005; Zappala et al., 2006), but it may not be contributing to electrical

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coupling (Huang et al., 2007; Lee et al., 2010).

Rt GJs create a strong electrical coupling between Rt cells (Blethyn et al., 2008; Landisman et al., 2002; Long et al., 2004) and support the reticular rhythmogenesis by synchronizing neuronal activity (Long et al., 2004), similar to what was observed in GJ-connected cortical inhibitory neurons (Deans et al., 2001). Although both chemical and electrical synapses may be involved in different functions such as the synchronization of cell assemblies in the Rt of young rodents (Deleuze and Huguenard, 2006), the coupling remaining in adult rodents is mostly due to electrical synapses (Hou et al., 2016; Makinson et al., 2017).

Different types of GJs-connected cell clusters (~15% elongated, ~45% discoid, and ~40% spherical) may support functionally distinct networks in Rt (Lee et al., 2014). Elongated and discoid clusters tend to be constrained within single Rt tiers, spreading up to 30% of the thickness of the nucleus. Accordingly, these types of clusters were reported to project to a single target (i.e., either POm or VB). That contrasts with spherical clusters that span up to 60%-70% of Rt thickness, covering multiple tiers which project to both POm and VB (see Figure 1). The relationship between these types of clusters and the morphological subtypes of Rt cells (see section 3.1.1) is currently unclear and should be elucidated in order to establish whether the shape of these clusters is an emerging property of the cellular composition or if a distinct mechanism is responsible.

Neurons with inter-somatic distance up to 300 μm were shown to be

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coupled through GJ using dye-coupling imaging (Lee et al., 2014). By contrast, paired recordings show connections only for neurons separated by inter-somatic distances up to 40 µm (Long et al., 2004). However, in this technique, the sampling volume increases rapidly with inter-somatic distances, quickly reducing probabilities of successfully finding connected pairs. Clusters of GJ connected Rt cells obtained with dye-coupling were found to include many, but not all cells with short inter-somatic distances, suggesting selective connectivity within the space spanned by these clusters (Lee et al., 2014).

Rt neurons were found to be connected through gap junctions with 8 +/- 2.5 (range: 1-24; N=9) neighbors when using dye-coupling. However, these figures are likely to be underestimated due to limited diffusion of dye through gap junctions, as indicated by lower coupling prevalence at short inter-somatic distances when compared with paired recordings. Using photostimulation, between 17% and 47% of Rt neurons were reported to be locally connected through GJs (Deleuze and Huguenard, 2006; Lam et al., 2006).

By introducing electrical coupling, GJs allow the low-frequency subthreshold activity to move across Rt cell networks (Bennett, 1966; Connors and Long, 2004). Membrane passive properties result in low-pass filtering of this activity, with stronger high-frequency attenuation early in development due to a nearly four times higher membrane time constant at P1 (72 ± 4 ms) compared to P14 (19 ± 1 ms) in mice (Parker et al., 2009).

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Coupling coefficient of 0.12 +/- 0.08 (N=313) and synaptic conductance of 0.80 +/- 0.63 nS (N=313) have been reported for Rt GJs (Haas et al., 2011). However, long-term depression (LTD) can modulate the strength of this coupling. Two mechanisms can trigger such LTD: 1) simultaneous bursting in coupled neurons (Haas et al., 2011) and 2) activation of metabotropic glutamate receptors from cortical input (Landisman and Connors, 2005). These two sources of plasticity act through distinct mechanisms, allowing intrinsic Rt activity and cortical afferents to independently fine-tune GJ strength (Sevetson et al., 2017). This LTD is sufficient to influence spike synchronization in coupled Rt cells (Landisman and Connors, 2005) and it modulates GJ coupling independently in both directions (Haas et al., 2011; Sevetson and Haas, 2015), providing a flexible mechanism for regulating the spread of rhythmic activity.

5.4 Closed and open-loops

The proportion of connections forming open or closed loops is a fundamental characteristic of the TC microconnectivity (Halassa and Acsády, 2016). The degree of convergence (closed-loop; feed-back inhibition) or divergence (open-loop; lateral inhibition) of information propagation in the system depends on the relative proportion of these patterns. Since most of the thalamus has a topological structure, the degree of divergence or convergence is likely impacting on the sharpness of stimuli (e.g., the resolution of touch stimuli localization) and on selective attention.

This topic has been more often studied in the thalamo-reticular loop

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than in the TC loop, probably because of the challenge it poses to track long-distance projections between the thalamus and the cortex. The thalamo-reticular network comprise a mix of open and closed-loop connections (Deschênes et al., 1998; Desilets-Roy et al., 2002; Halassa and Acsády, 2016; Lam and Sherman, 2005; Pinault and Deschênes, 1998b; Rouiller and Welker, 2000), with a dominance of 80%-90% of open-loop connections (see Table 2). However, the number of closed-loop connections may be underestimated due to severed connections in sliced preparations. The thalamus probably needs to fine-tune this degree of divergence to generate TC rhythms (e.g., sleep spindles) that do not degenerate in uncontrolled oscillations (e.g., epileptic activity). A proper degree of divergence is required for populations of cells to be recruited and initiate population rhythmic activity (waxing), to limit their spatial spread, and to timely desynchronize cell assemblies (waning) (Pita-Almenar et al., 2014).

Table 2. Prevalence of open versus closed thalamo-reticular loops.

Prevalence of open-loop	Sample size	Animals	Region	Type of experiment	reference
84%	86	Adult rats	AD(1), AV(1), LD/LP(5), MD(1), Po(1), VL(8), VB(5)	Anatomical	Pinault and Deschênes (1998)
93%	14	Juvenile (P14–20) rats	VB	Physiological	Gentet and Ulrich (2003)
79%	34	Rats	VB	Physiological	Shosaku

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					(1986)
83%	36	Adult cats	LGN	Physiological	Lo and Sherman (1994)

At the level of the TC loop, small (<1 um) and giant (2-10 um) CT axon terminals are involved in different functional networks. Small terminals provide cortical feedback and are more likely to form closed-loop, whereas giant terminals are passing along feed-forward signals through cortico-thalamo-cortical routes (Rouiller and Welker, 2000). Because of their focal and topologically accurate projection patterns, core TC cells from FO are likely to participate in a higher proportion of closed-loop circuits. By opposition, the greater spread of matrix TC projections from HO is likely to support a larger proportion of open-loop circuit associated with feed-forward cortico-thalamo-cortical communication and a lower proportion of closed-loop connections providing feedback to CT cells (Clasca et al., 2012).

6 Afferents

The specifics of thalamic afferents need to be carefully considered for both experimental and modeling work in the TC system since they are closely related with behavioral differences in subpopulation of thalamic cells. By considering the direction of the flow of neural information, we can categorize thalamic afferents as being either ascending (from sensory inputs to percepts) or descending (from mental representation to motor actuators). To some extent, the patterns of afferent pathways can be generalized across modalities by considering FO/HO and driver/modulatory properties of the nuclei and the

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afferents. However, because there are also many details that are specific to every sensory modality, our review of thalamic afferents is limited to the somatosensory system.

6.1 Ascending projections for the somatosensory system

The major afferent pathways for the rodent somatosensory system are depicted in Figure 10. The VPL and VPM receive input from sensory cells through two main pathways: the lemniscal and the extralemniscal. For the region of the head, the lemniscal pathway goes through the trigeminal ganglion and synapse in the principal nucleus of the trigeminal complex (Pr5). Then it crosses contra-laterally and passes through the trigeminal lemniscus to reach the VPMdm (Pierret et al., 2000; Veinante et al., 2000). For the rest of the body, first-order neurons have their somata in the dorsal ganglion root and project along the dorsal column to the brainstem where they synapse to cells in the gracile (lower body) or the cuneate (upper body) nuclei. Axons of these second-order neurons cross contra-laterally and climb up through the medial lemniscus, which projects to VPL, most heavily to its rostral portion. This pathway is also named the dorsal column-medial lemniscus pathway. It is the main pathway for fine touch, vibration, two-point discrimination, and proprioception. It is fast, precise, and phylogenetically recent (Ebner and Kaas, 2015).

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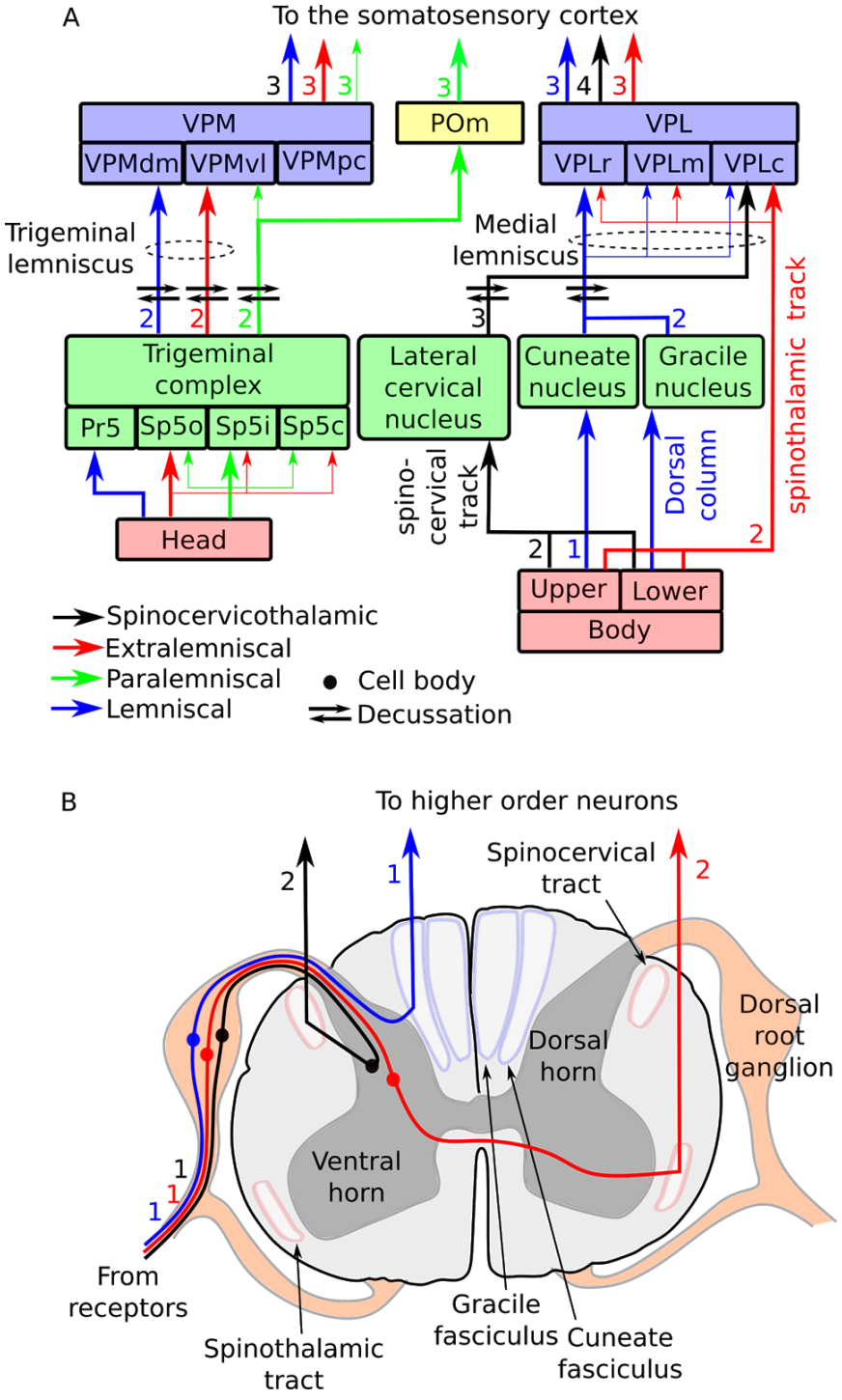

Figure 10. Major ascending pathways for the somatosensory system of the rodent. A) High-level representation of the neural paths from the periphery up to the somatosensory cortex. B) Detailed view of the pathways at the spinal level. The numbers indicate the order of the

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neurons involved at each step of the pathways.

The extralemniscal pathway is also called neospinothalamic or spinothalamic (Yu et al., 2006) and is part of the anterolateral or ventrolateral system. It is associated with nociception (pain) and dull sensations, such as crude touch and temperature sensation. It reaches the spine through the dorsal ganglion root, crosses to the contralateral side, and climbs up through the ventral and lateral spinothalamic fasciculi to project to VPL, most heavily to its caudal portion. Similarly, for the head, the analog pathway passes through the trigeminal ganglion, then the spinal trigeminal complex (Sp5), most importantly through the interpolar division (see Veinante et al. (2000) for characterization of these projection separately for the oral (Sp5o), interpolar (Sp5i) and caudal (Sp5c) divisions). Then, it reaches the VPMvl (Pierret et al., 2000; Veinante et al., 2000) through the contralateral anterior division of the trigeminal lemniscus. Although terminals from the Sp5 (spinothalamic) and Pr5 (lemniscal) have been reported to be indistinguishable within VPM, they have been found to target distal and proximal dendrites, respectively (Williams et al., 1994).

A third pathway, the spinocervicothalamic (also named only spinocervical) pathway, is much less often discussed and generally only in the context of nociception. Contrary to the other trisynaptic pathways, it has four synapses. Cells from the dorsal root ganglion form synapses onto neurons of the spinal dorsal horn. Then, spinal neurons project to the ipsilateral lateral cervical nucleus. Cervical projections cross contralaterally and project through

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the medial lemniscus to the most caudal part of VPL (Giesler et al., 1988).

Another important ascending somatosensory pathway, the paralemniscal pathway, projects to Sp5, and more particularly to the Sp5i. It involves Sp5i large soma cells with thick and fast conducting axons, as opposed to the spinothalamic projections from Sp5i, which project thin and slow conducting axons from smaller cells (Pierret et al., 2000; Veinante et al., 2000). It reaches the PO directly and also targets the non-barreloid VPMvl region (Williams et al., 1994). It is associated with nociception (Frangeul et al., 2014) and contains poorly segregated information. For example, as opposed to the lemniscal pathway, for which specific input has strong single-whisker dominance (Gauriau and Bernard, 2004; Pierret et al., 2000), this pathway contains multi-whisker information (Williams et al., 1994). As opposed to lemniscal input to VPM which are only of a driver type, the paralemniscal pathway projects to PO with a mix of driver (29%) and modulatory (71%) inputs (Mo et al., 2017). Feedforward inhibition from ZI inhibits this driving input to PO. Surprisingly, electrophysiological characterization has shown that disynaptic trigeminal-incertal-PO inhibitory input arrives earlier to PO than the monosynaptic trigeminal-PO excitatory input. These temporal properties explain the relatively low responsiveness of PO when it is only activated from this ascending driver input (Lavallée et al., 2005). However, PO cells are highly responsive when a paralemniscal input is shortly preceded by descending inputs (further discussed below; Groh et al., 2014).

Some other pathways associated with the somatosensory system, particularly for nociception, reach other parts of the thalamus, e.g., the

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pathway reaching the centromedian parafascicular nuclei of the thalamus from the anterior spinothalamic tract. We do not review these pathways here.

In summary, the pattern of ascending afferents is complex, with different pathways supporting different functions such as touch, proprioception, and nociception. The thalamic regions that these pathways target partially overlap, but are nevertheless characterized by modality and afference dominance (i.e., afferents are not perfectly segregated, nor are they homogeneously mixed within somatosensory thalamic nuclei). These different afferents evolved in steps, newer systems being built on top but in interaction with older systems. Most ascending afferents have large terminals with round vesicles, which partly distinguish them from Rt or CT afferents, but not between themselves. Further, some ascending afferents (e.g., lemniscal) exhibit a mixture of driver and modulatory properties, which complicates their segregation from cortical afferents based on synaptic physiology. However, VGluT1/VGluT2 immunohistochemistry can be used to distinguish brainstem and spinal cord inputs (VGluT2 positive) from cortical ones (VGluT1 positive) (Graziano et al., 2008).

6.2 Descending projections for the somatosensory system

Three distinct CT projections have been described, depending on their laminar origin: L5, L6a, or L6b (Hoerder-Suabedissen et al., 2018). To restrain the scope of this review, we focus on S1 projections, although other areas such as S2 and the motor cortex also project to the somatosensory thalamus (Rouiller et al., 1991). To facilitate the comparisons across these pathways,

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Table 3 provides a summary of some of their key properties.

Table 3. Summary table for the properties of the descending afferents to the somatosensory thalamus.

	L5	**L6a**	**L6b**
Rt collaterals	No	Yes	No
Type	Driver for PO; Modulator for VB, except maybe on its fringes	Modulator	Modulator
Target VPL	Sparse collaterals with small varicosities; some large L5 varicosities in dorsal, medial, and ventral fringes of VB and in VPMvl	Yes	It occasionally has a few collaterals
Target VPM		Yes	No direct collaterals; Sometimes dendrites travels back from PO
Target PO	Dense collaterals with small and large varicosities	Yes	Yes
Subcellular target	Proximal dendrites	Distal dendrites; colocalized with ascending input	

As a population, L5 projections target more densely HO (e.g., POm) than FO (e.g., VPM) (Hoerder-Suabedissen et al., 2018). L5 cells often project only to HO (Bourassa et al., 1995; Reichova and Sherman, 2004; Veinante et al., 2000). The size of POm varicosities from L5 projections vary in a wide range, with some being relatively small (similar to those from L6) but also with a significant proportion being much larger (3-8 um) (Bourassa et al., 1995;

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Hoerder-Suabedissen et al., 2018). Only small L5 varicosities have been reported in FO (Hoogland et al., 1991), except for some large L5 terminals found in the dorsal, medial, and ventral fringes of VB as well as in VPMvl (Liao et al., 2010). L5 cells project to the thalamus but not to the Rt (Bourassa et al., 1995; Bourassa and Deschenes, 1995). They do so through collaterals, their final target being regions of the brainstem (e.g., superior colliculus) and the spinal cord (Bourassa et al., 1995; Deschênes et al., 1994). Similarly to TC projections, synapses from L5 afferents have a fast conduction time (Miller, 1996) suggesting a feed-forward role (Rouiller and Welker, 2000).

Through its L5 afferents to the ZI (Mitrofanis and Mikuletic, 1999), the cortex can lift the powerful incertal feedforward inhibition of paralemniscal inputs to PO (e.g., passive whisker deflection) when they are co-occurring with top-down stimulation (e.g., active whisking) (Lavallée et al., 2005). Two mechanisms are available to the cortex for this: 1) by triggering auto-inhibition of ZI through its network of re-entering GABAergic collaterals (Bartho et al., 2002; Power and Mitrofanis, 1999) or 2) by cortical activation of the APT projections to ZI (section 6.3; Giber et al., 2008).

As opposed to the driver afferents from L5 that targets proximal TC dendrites, L6 afferents are modulator and target distal TC dendrites. In the PO of rats and mice, L6 afferents synapses have been shown to be colocalized with driving spinal trigeminal inputs, both afferents forming terminals close (<5um) to one another (Groh et al., 2014). This proximity allows PO to integrate ascending and descending streams, as supported by a supralinear gain for spiking probability when ascending input arrives within a time window

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spanning tens of milliseconds after the arrival of cortical activity.

Afferents from L6a project to both FO and HO with a similar density (Hoerder-Suabedissen et al., 2018) and provide feed-forward inhibition through their collaterals to Rt (Bourassa et al., 1995; Bourassa and Deschenes, 1995; Lam and Sherman, 2010). They project only to sensory-specific nuclei (Bourassa et al., 1995; Deschênes et al., 1998) and those from barrel columns project only to corresponding barreloids (Deschênes et al., 1998).

Some L6b cells have been shown to arborize in POm without any collaterals to either VB or Rt. A genetically labeled subset of CT axons from this layer of the somatosensory cortex has also been reported to arborize at the edge of POm, with some branches traveling back to VPM. As opposed to cells from L6a, they do not send collaterals to Rt and, in some cases, send collaterals to VPL, but not to VPM (Hoerder-Suabedissen et al., 2018). These may correspond to a small proportion of CT cells in the lower part of L6 that have been reported to arborize only in POm (Bourassa et al., 1995). Deep L6 projections have more frequently multinuclear innervation patterns. For example, they can target associative and/or intralaminar thalamic nuclei associated with given modalities. They also participate in the formation of rods or barreloids in specific nuclei (Deschênes et al., 1998). However, since L6a/L6b have not been clearly distinguished in earlier studies, it is difficult to unambiguously associate observations about lower/upper L6 with L6a/L6b. Further, the distinction observed within L6a and L6b may be different in

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granular versus dysgranular portion of S1 (Deschênes et al., 1998).

Typical indicators (i.e., ionotropic glutamate receptors, synapses close to cell bodies, depressing synapses) show that L5 of S1 provides POm with driving input. This is compatible with a feedforward role, i.e., this pathway carries information up the brain network hierarchy. By opposition, typical indicators (facilitating synapses on distal dendritic domains, with both ionotropic and metabotropic glutamate receptors) support a modulatory role for S1 L6a afferents to VPM. Therefore, this pathway is likely to transmit feedback down the brain hierarchy (Reichova and Sherman, 2004; Sherman and Guillery, 1996). Synapses from L6b require better characterization before similar roles can be attributed to this pathway (Hoerder-Suabedissen et al., 2018).

L6 CT projections are similar to cortico-cortical projections in that they are characterized by a highly variable conduction time, with some very long delays (Kelly et al., 2001; Kwegyir-Afful and Simons, 2009). By opposition, L5 CT (collaterals) have a fast conduction time, similar to the TC projections (Miller, 1996). The variable conduction time in L6 CT projections has been hypothesized to allow the modulation of the temporal dynamics of TC cells across time scales (Briggs and Usrey, 2008).

Synaptic variations suggest that these afferents have different spatial distribution within VB: the rostral part of this complex is innervated by small CT terminals, whereas its caudal region contains both small and large CT terminals. This complex further contains a shell-like region that is

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characterized by large terminals (Liao et al., 2010).

Although in general, patterns of connectivity are similar across modalities, some differences exist. For example, in the auditory system, the FO (i.e., MGNv) has been shown to receive driving ascending input, whereas the HO (i.e., MGNd) is receiving ascending modulatory input (Lee and Sherman, 2010). Such segregation is less evident in the somatosensory system for which both driving and modulatory ascending afferents target POm (Mo et al., 2017).

6.3 External inhibition

Because most dorsal thalamic nuclei only have a small proportion of local inhibitory interneurons, a substantial part of their inhibition comes from external sources, mainly from Rt but also from other sources (Figure 11).

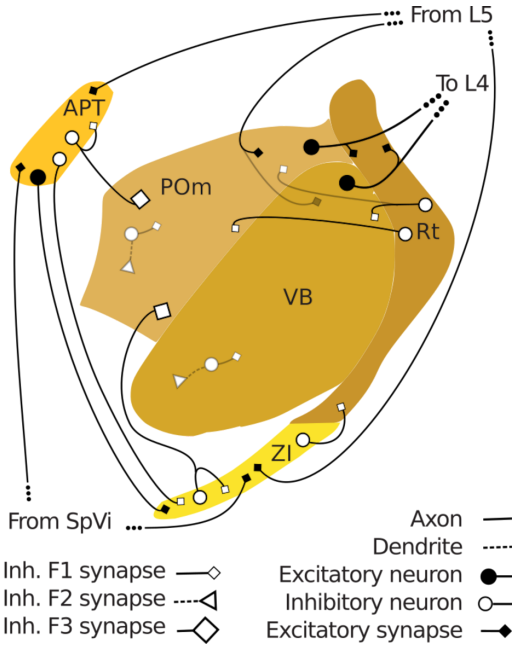

Figure 11. Inhibitory circuits of the somatosensory thalamus.

ZI, a ventral thalamic region contiguous with Rt, and particularly its PV+

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ventral portion, is an important source of inhibition for HO (Bartho et al., 2002; Bokor et al., 2005; Giber et al., 2008; Lavallée et al., 2005). It receives projections from L5 cells (Mitrofanis and Mikuletic, 1999) and from ascending afferents (e.g., from SpVi) (Lavallée et al., 2005), but not from dorsal thalamus (Bartho et al., 2002). ZI innervates large proximal HO dendrites with clustered giant boutons (major axis up to 6-8 um), establishing multiple release sites. These boutons form glomeruli with large excitatory boutons from L5 afferents (Bartho et al., 2002). Hence, ZI-thalamic inhibition seems to be very potent and focal, as opposed to Rt inhibition which is likely to have a more diffuse and modulatory effect (small boutons, generally single release sites, sparsely distributed across dendritic domains). ZI projections generally avoid small-size distal dendrites targeted by L5 projections (Bartho et al., 2002). Further, there is indirect but solid evidence that incertal but not Rt boutons have pre-synaptic type II muscarinic acetylcholine receptors. Although such receptors are nearly absent from VPL and VPM (except for the most caudal part), they constitute about half of the GABAergic terminals in PO, highlighting what is likely to be a considerable impact of ZI on the activity of this nucleus (Bartho et al., 2002).

Projections from the APT are very similar to those from ZI. They project only to HO forming large multi-synaptic boutons similar to incertal ones (Bokor et al., 2005; Giber et al., 2008; Lavallée et al., 2005) and designated as F3 terminals (Wanaverbecq et al., 2008) to emphasize their difference from F1 and F2 terminals found in the thalamus. As for ZI, and as opposed to Rt, APT has rich re-entrant GABAergic connectivity. However, as opposed to ZI, APT

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has similar connectivity with ascending and descending thalamic afferents (Lavallée et al., 2005) and sends no projections to Rt (Bokor et al., 2005; Cavdar et al., 2006).

APT and ZI are likely working in concert for controlling the activity in HO since APT projects to ZI with both GABA+ and GABA- boutons. Further, the APT-thalamic pathway is characterized by large and potent synapses (Bokor et al., 2005), whereas the APT-ZI pathway seems to have a milder modulatory effect and has smaller boutons with one or two synapses (Giber et al., 2008), suggesting a certain level of segregation between these two pathways. The existence of these parallel inhibitory pathways led to the proposal of an extrareticular system for the focal inhibitory control of HO, as opposed to a more modulatory control of the thalamus by Rt (Bokor et al., 2005). Nevertheless, this extrareticular system is likely to work in synergy with reticular inhibition since a ZI-Rt pathway has been reported in rats (Cavdar et al., 2006).

7 Outlook: Gap and opportunities

7.1 A need for further data integration and system interoperability

Initial investigations of the TC system allowed establishing fundamental and structuring dichotomic concepts such as driver/modulatory afferents, FO/HO nuclei, core/matrix projections, and feed-forward/feedback inhibition. These concepts provide guidelines for extrapolating the vast amount of information required for understanding and modeling such a complex system using the unavoidably limited amount of observations that can be collected

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experimentally. In particular, although this review focuses on the somatosensory system, most properties of the TC loop in this system (e.g., the existence of a topological organization) can be generalized across sensory modalities and then fine-tuned to take into account peculiarities of given modalities.

To understand the biophysics of the TC loop, we can increasingly rely on high-resolution and high-throughput experimental recording methods. However, the potential of these new methods will be fully harnessed only if we manage to pool together quantitative experimental results from various sources. Such a pooling requires the experimental results to be systematically contextualize using open-access resources, like standard coordinate systems (e.g., the CCF (Oh et al., 2014)), atlases (e.g., the Waxholm Space Atlas of the Sprague Dawley Rat (Papp et al., 2014), the Allen Mouse Brain Connectivity Atlas (Oh et al., 2014)), ontological terms (e.g., the Neuroscience Information Framework Standard Ontology (Imam et al., 2012)), systematic curation of published data (O'Reilly et al., 2017), and interoperable neuroinformatics platforms (e.g., the Blue Brain Nexus; https://bluebrainnexus.io/). In particular, point-to-point connection probabilities atlas based on data such as those stored in the Allen Mouse Brain Connectivity Atlas would prove invaluable. We also need to link spatial coordinates (i.e., not only whole brain regions) with quantitative values (i.e., not only dichotomic concepts) across cellular dimensions (e.g., electrophysiological behavior, morphological type, gene expression, protein expression), for example by embedding them as vectorial fields within shared

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spatial atlases. The fact that the topological variability shown in Figure 7 could only be represented schematically rather than in a numerically accurate way is symptomatic of the absence of such resources. Since these results are not provided in a common spatial framework, they cannot be integrated accurately in a single space allowing cross-fertilization of studies (e.g., inferring the precise relationship between bursting types and somatotopy).

Reaching such a level of data integration is essential to tackle fundamental issues like the high experimental variability, the lack of reproducibility, the interspecies differences, the developmental trajectories, and the differences due to diseases and idiosyncratic conditions. Using standard frameworks to provide such a formal contextualization is necessary to support the meta-analyses required to extract reliable conclusions from highly variable experimental results such as cell densities (see Figure 5). Unfortunately, not all required frameworks are yet available, and those currently available often need ongoing improvements (e.g., better sub-parcellation of atlases, refinement of ontologies). The advent of the “big science” approach might support the costly and often under-appreciated development of such resources but would require deep cultural changes in our way to evaluate scientific contribution and merit.

7.2 Outstanding knowledge gaps

A few outstanding gaps in our current knowledge are worth highlighting, as for example the rather shallow understanding we have of interneurons in other nuclei than LGN. Aside from the widely different proportions that have been reported in section 4.3, almost nothing is known about their

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electrophysiological properties, their connectivity, their morphologies, and their functional role. Also puzzling is the report of non-GABAergic neurons in Rt (Cavdar et al., 2013). Further, only a few paired-recording studies have investigated the inhibition between interneurons and TC cells comprehensively, with none reporting on the short-term plasticity dynamics of IPSP at the interneuron-TC synapse. Similarly, little is known about reticular to interneuron connectivity in rodents.

Thalamic glial cells have also been the focus of very few studies, even though we know that they work in synergy with thalamic neurons, for example by disinhibiting VB TC neurons (Copeland et al., 2017). Reliable modeling of neuro-glio-vascular interactions will only be possible after these cells are experimentally characterized in much more detail.

Further quantitative and high-resolution information about connectivity is also necessary for neurons involved in the TC loop. It is challenging, with the current state of the art, to infer a precise and comprehensive picture of how synaptic boutons are distributed within thalamic nuclei and individual morphologies. Without this information, connectivity within biophysically-detailed models can only be roughly approximated, with undetermined consequences on network activity. Much more information is also needed to derive precise space-aware estimations of the prevalence of the microconnectivity patterns described in Figure 8. These need to be assessed not only structurally, but also functionally since they are likely modulated by CT activity, e.g., by facilitating the response of a group of cells through NMDA spikes or by inhibiting a group through extrareticular

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pathways.

7.3 Future perspective

On the bright side, impressive methodological developments are promising fast progress on long-standing issues. For example, the sparsity and variability in stereological studies reporting cell densities (Keller et al., 2018) is likely to be soon resolved by whole-brain approaches relying on novel techniques such as brain clearing (Kim et al., 2017; Murakami et al., 2018). Also, high-throughput whole-brain sparse labeling and imaging of brain cells should greatly improve the thoroughness of our cell morphology sampling (Gong et al., 2016). Furthermore, it will support the reconstruction of much more complete (i.e., not cut by the slicing performed during patch-clamp experiments) morphologies (Economo et al., 2016; Reardon, 2017). For example, the MouseLight project at Janelia Research Campus has recently made available 1,000 complete cell morphologies, with long range axonal projections spanning large portions of the mouse brain (Winnubst et al., 2019). The availability of morphologies with complete axonal projections will be invaluable for large-scale modeling and may have a profound impact on our way to view the TC system.

Furthermore, since its introduction over a decade ago, optogenetics has allowed researchers to design *in vivo* experimental protocols that provided a strong foundation to decorticate neuronal networks in more natural conditions (Deisseroth, 2015). These advances have been further supported by the recent development of miniaturized imaging equipment, such as miniscope and GRIN lenses (Ghosh et al., 2011), which made calcium

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imaging possible in freely behaving animals (Zhang et al., 2019). Similarly analyzing extracellular potentials with Neuropixel probes (Jun et al., 2017), will likely improve significantly our understanding of dynamics in the TC loop during its normal mode of operation. With these *in vivo* experimental tools, we can now probe the inner workings of sleep, sensory processing, behavior, and further, the counterparts of these mechanisms in thalamus-implicated disease states like epilepsy, schizophrenia, and autism. These experimental advances combined with fast-paced improvement in modeling methodologies and the steady increase of available computational power are paving the way for great leaps in our understanding of the TC system.

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