The vibrissa sensorimotor system of rodents: A view from the sensory thalamus

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The rat vibrissa system, with its tactile hairs and their associated neuronal architecture, is a prototypical sensorimotor system for the study of active sensation. While nearly all mammalian species have vibrissae, many rodent species have specifically evolved the ability to sweep their vibrissae for dynamic exploration of the environment (Knutsen et al., 2006; Metha and Kleinfeld, 2004; Metha et al., 2007). Thus two aspects of signaling are involved in the vibrissa sensory pathway: one that signals touch and the other that signals self-motion (Kleinfeld and Deschênes, 2011; Prescott et al., 2011). Here we focus on the parallel streams of vibrissa information processing that are involved in vibrissa signaling (**Figure 1**) with a focus on the different signaling pathways to the thalamus and their roles in the behavior of rodents.

Background

On each side of the rodent's snout, in a region called the mystacial pad, there are five rows of vibrissae that form an ordered array of low-threshold mechanoreceptors (**Figure 1A**). Trigeminal ganglion cells that innervate these mechanoreceptors respond to motion of only one vibrissa. The spatial arrangement of the vibrissae within the pad is mapped into homotopic aggregates of neurons from the trigeminal nuclei (Ma and Woolsey, 1984) (**Figure 1B**), up through the ventral posterior medial (VPM) nucleus of the thalamus (Van der Loos, 1976) (**Figure 1C**), and onto layer 4 of vibrissa primary somatosensory (vS1) cortex (Woolsey and Van der Loos, 1970) (**Figure 1D**). In mice, aggregates of neurons in vS1 cortex consist of clusters of stellate cells surrounding a 'hollow' core that is filled with dendrites, axons, and glial cells. Thence the term "barrel" was used to describe their structure (**left image, Figure 1D**). By extension, the cellular aggregates in VPM thalamus and in the trigeminal brainstem subnuclei are denoted barreloids and barrelettes, respectively (**Figures 1B,C**). Thus each vibrissa forms the start of a labeled line that includes a trigeminal barrelette, a thalamic barreloid, and a cortical barrel. This morphology makes the vibrissa system of rodents one of the most valuable models for research in sensory physiology, development, and studies of experience-dependent synaptic plasticity. The advent of transgenic mice and the development of new imaging techniques have further contributed to promote the popularity of this somatosensory system (Luo et al., 2008; 2018).

Ascending streams of vibrissa information

Tract tracing studies and studies that combined electrophysiological recording with single cell labeling have led to the discovery of separate pathways of vibrissa information processing – designated as the lemniscal, extralemniscal, and paralemniscal pathways (**Figure 1C**). The lemniscal and extralemniscal pathways relay vibrissa information through different sectors of VPM thalamus, while the paralemniscal pathway transits through the posterior group (Po) of the thalamus (for reviews see Pouchelon et al., 2012; Deschênes and Urbain, 2016).

The lemniscal pathway. The lemniscal pathway arises from two populations of trigeminothalamic neurons. The first population consists of small-sized neurons that are clustered in modules, i.e., the barrelettes, within nucleus principalis (**red arrow, Figures 1B,C**). These cells have receptive fields that are dominated by a single vibrissa and they account for about 75 percent of the projection cells in nucleus PrV (Minnery and Simons, 2003). They project only to the contralateral VPM thalamic nucleus, where they emanate small bushy terminal fields, which are approximately 80 µm in diameter, in the homologous barreloid. Sensory transmission along the lemniscal pathway retains a fine-grained map of vibrissa representation. Cells within a given PrV barrelette innervate the whole of a barreloid (**left image, Figure 1C**) and their projections show little convergence. On average, a VPM relay cell receives input from only one to two PrV neurons (Castro-Alamancos, 2002; Deschênes et al., 2003; Arsenault and Zhang, 2006). Synaptic transmission is mediated by large-sized perisomatic synapses that ensure a fast and reliable relay of information (Spacek and Lieberman, 1974; Williams et al., 1994). These barreloid cells project to layers 4 and 6a in the granular zones of vS1 cortex (**Figure 1D**).

The second population of trigeminothalamic neurons consists of large-sized neurons in trigeminal nucleus PrV, whose soma is located in the septa between the barrelettes (Henderson and Jacquin, 1995; Lo et al., 1999) (**blue arrow, Figures 1B,C**). These neurons have multivibrissa receptive fields and project to the dorsal aspect of the barreloids near the border with Po thalamus, which is referred to as the "head" of the barreloids, and more sparsely to Po thalamus itself (Veinante and Deschênes, 1999). Thus, in contrast with the vast majority of barreloid cells whose receptive field is dominated by a single vibrissa, those situated in the head of barreloids respond equally well to multiple vibrissae (Ito, 1988; Sugitani et al., 1990; Urbain and Deschênes, 2007). These multivibrissa-responsive cells project preferentially to layers 4 and 6a in the dysgranular zone of vS1 cortex (Furuta et al., 2009) (**Figure 1D**).

The discovery of a multi-vibrissa pathway that transits through the head of the VPM barreloids (Urbain and Deschênes, 2007) raised the possibility that septal cells derive their receptive field input from this subpopulation of VPM neurons (blue; **Figures 1C,D**). Indeed, septal cells maintain their multi-vibrissa receptive field and response properties after brainstem lesion that prevents vibrissa input from activating the paralemniscal pathway. Conversely, lesion of the lemniscal pathway nearly completely abolishes vibrissa responses throughout vS1 cortex. Finally, the labeling of single VPM cells revealed that multi-vibrissa cells in the head of the barreloids project principally to the dysgranular regions of vS1 cortex (Furuta et al., 2009). In summary, barreloid cells project to layers 4 and 6a throughout vS1 cortex via two separate streams that innervate the granular and dysgranular zones, respectively.

Prior studies in alert head-restrained rodents reported that VPM cells encode both self-generated vibrissa motion and touch (Moore et al., 2015; Urbain et al., 2015). Yet no clear spatial relationship was found between the location of a neuron within VPM and the modulation of its firing rate. The coding and mixing of these touch and self-motion signals is an area of active research, with thalamic signals now imaged through the release of glutamate throughout all layers of cortex (Liu et al, 2019a).

The extralemniscal pathway. The extralemniscal pathway differs from the lemniscal pathway in that thalamic cells exhibit multi-vibrissa receptive fields that are independent of input from the PrV (Bokor et al., 2008). This pathway arises from cells located in the caudal sector of SpVI (SpVIc) (Veinante et al., 2000), that project to the VPMvl region of the thalamus, a crescent-shaped region that approximately corresponds to the lower tier of VPM thalamus (**brown arrow, Figure 1C**). In contrast with the small size of the terminal field of nucleus PrV axons in a barreloid, i.e., a diameter of ~ 80 µm (Veinante and Deschênes, 1999), individual SpVIc axons form larger, rostrocaudally oriented terminal fields in VPMvl thalamus, i.e., size ~ 100 µm by 250 µm (Veinante et al., 2000). This suggests a higher degree of input convergence on VPMvl neurons.

Relay cells in VPMvl thalamus project principally to the second somatosensory (S2) cortical area and more sparsely to the dysgranular zone of S1 cortex by means of axon collaterals (Pierret et al., 2000) (**Figure 1D**). The projection foci are dense in layers 4 and 6 of S2 cortex, and moderate in layers 3, 4, and 6 of S1 cortex. A single study has addressed the role of this latter pathway (Yu et al., 2006). It was proposed that the extralemniscal pathway

conveys vibrissa-contact signals for object localization in the whisking field (Yu et al., 2006). This result was obtained in anesthetized rats by means of artificial whisking, i.e., rhythmic electrical stimulation of the facial nerve (Szwed et al., 2003). Additional experiments in alert rats are required to validate this suggestion, although object localization is lost by transient inactivation of vS1 cortex (O'Connor et al., 2010a).

The paralemniscal pathway. The paralemniscal pathway arises from large-sized, multi-vibrissa cells located in the rostral sector of subnucleus SpVI (SpVIr). In Po thalamus, SpVIr axons terminate principally in a shell-like region over the dorsomedial aspect of VPM thalamus, where they make large synaptic contacts with the proximal dendrites of relay neurons (Lavallée et al., 2005). The labeling of single axons that emanate from different parts of Po thalamus revealed heterogeneous neuronal populations that, collectively, project to the striatum and across the somatomotor regions of the neocortex, including S1, S2, and motor cortices (Deschênes et al., 1998; Ohno et al., 2012). The laminar distribution of terminal fields varies across areas, but layers 1 and 5a are the most densely innervated.

It was shown that Po thalamus contains a map of all body parts, with the vibrissae represented in the most lateral sector near the VPM border (**green region, Figure 1C**), where cells receive vibrissa input from trigeminal subnucleus SpVI, and the hindlimb represented in the most medial sector near the intralaminar nuclei (Diamond et al., 1992). It is currently unclear whether Po neurons that are responsive to different body parts have similar projection patterns. It must be emphasized that Po thalamus, as delineated in most stereotaxic atlases of rodents, is a large region with disparate prethalamic inputs and distinct clusters of relay cells, each characterized by a specific pattern of axonal projections to cortex, striatum, and amygdala (Alloway et al., 2013; Ohno et al., 2012). Like the pulvinar in primates, this thalamic region remains ill-characterized both in terms of chemo-architecture and neuronal input-output relationships.

While Po thalamic cells receive monosynaptic input from vibrissa-responsive trigeminal SpVIr neurons, they respond only weakly to vibrissa deflection. The responses are of much lower magnitude than those observed in VPM thalamus and occur at long latencies, i.e., 16 - 20 ms (Diamond et al., 1992; Sosnik et al., 2001). The reason for this weak response is that Po neurons receive a mixture of excitatory and feedforward inhibitory inputs. Most of the trigeminal axons that innervate Po thalamus also project to the ventral division of zona incerta (ZIv) (Bartho et al., 2002), and GABAergic ZIv cells project to Po neurons (Veinante et al., 2000).

Silencing ZIv reinstates short-latency sensory transmission through Po thalamus (Trageser and Keller, 2004; Lavallée et al., 2005). Thus the relay of vibrissa inputs through Po thalamus relies on disinhibition, i.e., inhibition of the inhibitory incerto-thalamic pathway. The behavioral conditions under which disinhibition operates and the types of vibrissa message that are relayed through Po thalamus are open questions.

Many dispelled conjectures complicate the understanding of the paralemniscal pathway. It was proposed that the paralemniscal pathway conveys information about whisking kinematics (Yu et al., 2006). However, subsequent studies found that encoding of whisking along the paralemniscal pathway is relatively poor (Moore et al., 2015; Urbain et al., 2015). It was also proposed that the paralemniscal pathway is specifically activated upon noxious stimulation (Masri et al., 2009; Frangeul et al., 2014). Yet, it has never been shown that trigeminal interpolaris cells that respond to vibrissa deflection are also activated by noxious stimuli. Lastly, a recurring notion is that vibrissa input to the dysgranular regions of vS1 cortex process paralemniscal inputs. Although this proposal was inconsistent with the observation that the response of Po neurons to vibrissa deflection lags that of septal cells (Armstrong-James and Fox, 1987; Diamond et al., 1992; Brumberg et al., 1999), it has lingered in the literature for want of a better explanation.

A novel perspective on the function of the paralemniscal pathway was recently obtained on the basis of a virus-based tract tracing study. We observed that SpVIr cells that project to Po thalamus also innervate a number of regions involved in the control of autonomic functions and in the facial expression of emotional reactions. This suggests that the paralemniscal pathway is not involved in sensory processing per se, but in signaling the valence of orofacial inputs, and the triggering of adaptive behavioral reactions (Elbaz et al., 2021).

Are there other trigeminothalamic pathways? A thalamic projection from the oralis subnucleus of the trigeminal complex (SpVO) arises from large cells with multi-vibrissa receptive field (Jacquin and Rhoades, 1990; Veinante et al., 2000). It is the least abundant trigeminothalamic projection, and also the least studied. It terminates in the most posterior part of the thalamus, right in front of the pretectum, and also in a caudal thalamic region intercalated between the pretectum and the medial geniculate nucleus. These thalamic regions are known to receive multisensory inputs, i.e., somatic, visceral, nociceptive, auditory, and to project to the perirhinal cortex, striatum, and amygdala (Groenewegen and Witter, 2004). Neurons in subnucleus oralis also provide a substantial projection to the superior colliculus. Although

electrophysiological data are not yet available, we deem it likely that the subnucleus oralis projection constitutes a pathway to associate multiple sensory inputs, and forward this information to the amygdala and limbic cortical areas involved in emotional reactions.

The caudalis subnucleus of the spinal trigeminal complex (SpVC) contains both mono- and multi-vibrissa responsive cells (Renehan et al., 1986). Yet there is no evidence to date that these cells project to the thalamus.

Inhibitory control of thalamic relay cells.

The VPM and Po thalamus in rodents do not contain local circuit GABAergic cells. Inhibitory inputs arise from three sources: the reticular thalamic nucleus (RTn), the ZIv, and the anterior pretectal nucleus (Barthó et al., 2002; Bokor et al., 2005). Individual RTn cells receive input from thalamic relay cells and from layer 6 corticothalamic cells. Individual nRT cells project to specific sectors of VPM and Po thalamus that relay vibrissa information from the lemniscal, extralemniscal and paralemniscal pathways (Pinault et al., 1995). While RTn terminals distribute over the distal half of the dendritic trees both in VPM and Po, incertal and pretectal axons make large synaptic contacts on the soma and proximal dendrites of Po cells.

Organization of corticothalamic pathways

Corticothalamic inputs arise from cortical layers 5 and 6. In the vibrissa system of rodents, the projection emanating from layer 5 cells is a collateral projection from long-range axons that project to the brainstem. These axons do not supply branches to the thalamic reticular nucleus nor to neurons in VPM thalamus. Rather, they arise from layer 5b in vS1 cortex and project exclusively to Po thalamus, where they make large synaptic contacts with the proximal dendrites of relay neurons. In contrast, layer 6 corticothalamic cells project to both VPM and Po thalamus (Bourassa et al., 1995; Killackey and Sherman, 2003). Those projecting to VPM thalamus are located in the upper part of layer 6, i.e., layer 6a, across the granular and dysgranular zones of vS1 cortex. Those projecting to Po thalamus reside in the lower part of layer 6, i.e., layer 6b, across the granular and dysgranular zones of S1 cortex, and in layer 6a of the dysgranular zone of S1 cortex. In addition, Po thalamus and the head of the barreloids receive corticothalamic input from layer 6 of the vibrissa motor cortex (Urbain and Deschênes, 2007). All layer 6 corticothalamic axons give off collaterals in the thalamic reticular nucleus and innervate profusely the distal dendrites of thalamic relay cells.

It is often said that the corticothalamic projections are organized in a manner that reciprocates the spatial distribution of thalamocortical pathways. Yet, over the years some inconsistencies have been reported between the principle of reciprocity and the actual organization of corticothalamic projections. For instance, layer 6 cells of the vibrissa motor cortex innervate both Po thalamus and the dorsal aspect of the thalamic barreloids (Urbain and Deschênes, 2007). Yet, there is no evidence that barreloid cells project to the motor cortex. Also, the vibrissa motor and premotor cortices project bilaterally in the thalamus, although none of these projections were shown to be matched by bilateral thalamocortical projections (Deschênes et al., 1998; Alloway et al., 2008). In view of these exceptions, it was proposed that the organization of corticothalamic connections complies with a more fundamental rule, called the rule of parity (Deschênes et al., 1998). This rule states that the distribution of layer 6 corticothalamic projections reciprocates the branching patterns of prethalamic afferents.

Corticothalamic axons make loops with the thalamocortical fibers. Yet, which elements in a loop act as the feedback as opposed to the feedforward path is largely a matter of viewpoint. It is reasonable to consider corticothalamic pathways as the feedback pathways in situations where sensory stimuli are delivered to a head-restrained or an anesthetized animal (Kleinfeld et al., 2002). Yet when animals search for specific stimuli, such as when foraging, the inverse viewpoint likely prevails as cortical activity models the desired stimulus and the corticothalamic pathway projects this pattern to thalamus. The rule of parity considers thalamus in terms of comparing the desired and stimulus generated input, a viewpoint that is in line with psychophysical and behavioral evidence that perception is an active process intimately linked to the motor activities of the animal. A comprehensive expose of this rule and its functional implications is found in the review by Deschênes et al. (1998).

Microvibrissae

The rat's microvibrissa somatosensory system is characterized by a vibrissa density that is about 40-times greater than that of the mystacial macrovibrissae (Brecht et al., 1997). The large expanse of cortex devoted to representation of the microvibrissae points to the ethological importance of this fine-grained tactile system, which remains largely unexplored. We know of no systematic study that examined the encoding of signals from the microvibrissae in the brainstem and thalamus.

Video analysis shows that when a rat contacts an unexpected object with its macrovibrissae, it orients his nose to the nearest contact, and dabs against the object with its microvibrissae at a rate of about 8 Hz (Grant et al., 2012; Parmiani et al., 2018). This rhythmic tactile sampling is phase-locked to sniffing and to movement of the nose (Kurnikova et al., 2017). It was suggested that the microvibrissae are critically involved in object recognition and texture discrimination, but are not essential for spatial tasks (Brecht et al., 1997). The robust and reliable encoding of differences in object textures by microvibrissa-responsive neurons in barrel cortex supports this proposal (Kuruppath et al., 2014).

Functional representation in barrelettes, barreloids, and barrels

Neuronal receptive fields for touch within PrV barrelettes, VPM barreloids, and cortical barrels are dominated by a single principal vibrissa. What kinematic features are mapped by analogy with space-time patterns along pathways in the visual system? It was reported that cells with similar angular preference cluster together within a barrel or a barreloid in anesthetized rodents (Bruno et al., 2003; Timofeeva et al., 2003; Andermann and Moore, 2006), but no systematic map of angular tuning has yet emerged. The use of passive vibrissa deflection in anesthetized animals represents a major limitation in these studies, particularly as angular tuning may be secondary to encoding the phase of self-motion in the whisk cycle (Curtis and Kleinfeld, 2009). As neurons along the lemniscal pathway robustly encode both touch and rhythmic whisking (Moore et al., 2015; Urbain et al., 2015), the whisking phase and vibrissa set-point may be key parameters to consider. Inroads on the encoding of touch (Jadhay et al., 2009; O'Connor et al., 2010a; O'Connor et al., 2010b) and touch relative to self-motion (Chung et al., 2020; Curtis and Kleinfeld, 2009; Isett and Feldman, 2020; Severson et al., 2017), albeit not set-point, have been made in cortex. The mapping of touch kinematics and the logic of the interaction of the self-motion signal and set-point represent work in progress at the level of VPM thalamus (Liu et al., 2019b). Results obtained by means of advanced two-photon microscopy to image thalamocortical axons within a barrel (Liu et al., 2019a) suggest that phase in the whisk cycle is mapped in a continuous path around a barrel, consistent with past studies on orientation preference (Furuta et al., 2011).

Open questions and missing data

In the present review we pointed out several anatomical and physiological issues that remain unanswered concerning the transmission of signals to and through thalamic nuclei in the vibrissa system (**Figure 1**). Until recently, most researches have focused on thalamus and cortex, with little attention paid to the brainstem trigeminal subnuclei that give rise to the ascending pathways. These subnuclei are richly interconnected and contain inhibitory circuits that operate both pre- and post-synaptically (Furuta et al., 2008; Bae and Yoshida, 2011). Although experimental studies of sensory processes in brainstem trigeminal nuclei are technically challenging, they are critical to understand the role of the vibrissa system in rodents' behavior.

It is worth reminding that vibrissae are very sensitive organs. Without sensory filtering at the very first relay stations the ascending pathways of vibrissa information would be overdriven. This could have disastrous consequences not only on sensory discriminative performance, but also on the overall level of emotional stress of the animal. In this regard, we recall that sensory trigeminal nuclei receive inhibitory input from the Kolliker-Fuse nucleus (Geerling et al., 2017) an upper brainstem region involved in the control of autonomic reactions. The inhibitory connections from the Kolliker-Fuse nucleus may well gate sensory responses (Elbaz et al., 2021).

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Figure caption

Figure 1. Schematic of the ascending pathways of vibrissa information processing. Abbreviations: PrV, principal trigeminal nucleus; SpVO, spinal nucleus oralis; SpVIr and SpVIc, rostral and caudal divisions of spinal nucleus interpolaris, respectively; SpVM, spinal nucleus muralis, SpVC, spinal nucleus caudalis; VPM, ventral posterior medial nucleus of dorsal thalamus; VPMvl, ventrolateral aspect of the ventral posterior medial nucleus of dorsal thalamus; Po, medial division of the posterior group nucleus; RTn, nucleus reticularis; VPL, ventral posterior lateral nucleus of dorsal thalamus.

(A) The periphery consists of vibrissae that are rhythmically swept by muscles in the mystacial pad and detection of touch by pressure sensors in the follicle. The image of the mystacial pad is adapted from Haidarliu et al. (2010) and that of the follicle is adapted from Whiteley et al. (2015).

(B) The trigeminal subnuclei in the medulla receive input from the follicles in the mystacial pad that is transmitted by neurons in the trigeminal ganglion. The photomicrograph of barrelettes is unpublished work from Martin Deschênes, the photomicrograph of the trigeminus is adapted from Furuta et al. (2018),

(C) The three main thalamic pathways. The photomicrograph of the barreloids in the core region of VPM thalamus is adapted from Haidarliu and Ahissar (2001).

(D) The cortical target regions of the main thalamic pathways. The photomicrographs of vS1 cortex is unpublished work from Martin Deschênes.

D

A Periphery — Mystacial Pad — Follicle

Trigeminal ⬤ ganglion

Multivibrissa PrV cells **Multivibrissa SpVIc cells**
Monovibrissa PrV cells **Multivibrissa SpVIr cells**

B Brainstem — Barrelettes

Rostral — PrV — SpVO — SpVIr — SpVIc — SpVM — SpVC — Caudal

lateral

C Thalamus — Barreloides

VPL — VPMvl — VPM — RTn — Po
Lemniscal

VPL — VPMvl — VPM — RTn — Po
Paralemniscal

VPL — VPMvl — VPM — RTn — Po
Extralemniscal

D Cortical layers — Barrels

Lemniscal organization
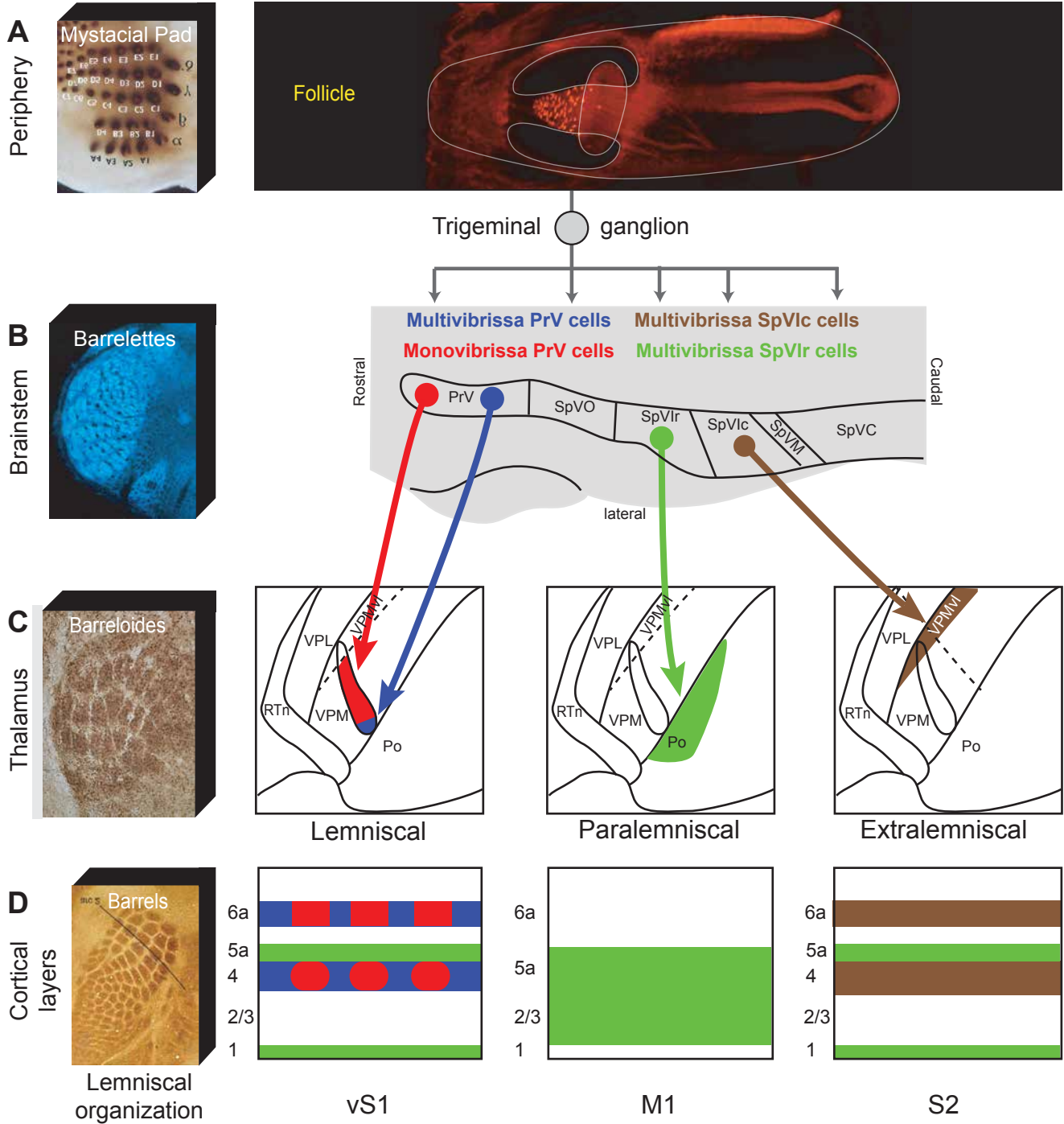
6a / 5a / 4 / 2/3 / 1 — vS1

6a / 5a / 2/3 / 1 — M1

6a / 5a / 4 / 2/3 / 1 — S2

Figure 1. Deschênes and Kleinfeld