The Role of the Principal Sensory Nucleus in Discriminative Touch

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Specialized facial somatosensory organs have evolved in diverse groups of animals, and the sense of touch that these organs transduce is important for normal behavior. The principal sensory nucleus of the spinal trigeminal complex is the first relay for facial discriminative touch in the central nervous system. Much of the work done on this nucleus is done in rodents, where the ability to trace the central representations of whiskers follicle innervation has been a useful tool for experimenters. Questions remain about the role of the nucleus, from uncertainties about the basic anatomy to its role in forming the disproportionate representation of the body seen in the cortical somatosensory maps. Comparative neurobiology points out that some non-rodent animals with specialized trigeminal somatosensory organs, such as the star-nosed mole, have a much larger principal sensory nucleus than one would expect for a mammal of their size. Complementing rodent work with studies on these species has the potential to help resolve puzzles about the entire spinal trigeminal complex, and the principal sensory nucleus in particular.

Keywords: *Somatosensory, trigeminal, segmentation, principal sensory nucleus, Barrels, star-nosed mole*

Introduction

Facial somatosensory specializations help animals navigate their world. Examples include whiskers on the face rodents and seals[1, 2], corpuscles of Herdst and Grandry on the beak of ground-probing birds[3, 4], push-rod receptors on the bills of montremes[5], integumentary sense organs on the jaws of crocodilians[6], and Eimer's organs on the noses of talpid moles[7]. These adaptations are associated with exploration, foraging and feeding[8, 9]. The co-evolution of sense organs and central processing centers is a theme in neurobiology[10, 11]. Accordingly, when researchers have looked at the first relay of the trigeminal somatosensory stream, these specialized trigeminal touch organs tend to be paired with central specializations[12-15].

The spinal trigeminal complex (STC) is the main target for the primary somatosensory receptors innervating the scalp, face and oral structures. The complex consists of the principal sensory nucleus (PrV) at the most rostral position and the spinal trigeminal nucleus (STN) more caudally. The latter consists of three subnuclei with subnucleus pars oralis (SpVo), subnucleus pars interpolaris (SpVi), and subnucleus pars caudalis (SpVc) found at progressively more caudal positions, respectively[16, 17]. SpVc merges with the dorsal horn of the spinal cord at its most caudal extent. The complex receives most of its sensory input from the somatosensory components of the trigeminal nerve (but also from the somatosensory components of the facial, glossopharyngeal and vagus nerves)[16]. Upon entering the brainstem, the trigeminal branch splits into an ascending branch that projects to the PrV and a descending branch that projects to the subdivisions of the STN.

Traditionally, there is a perception that in the somatosensory brainstem there is a division of labor so that the PrV mediates light touch sensation and the STN mediates pain[18]. In this view, the PrV is analogous to the dorsal column nuclei and the STN to the dorsal horn[19, 20]. Broadly, there is truth in the vital importance of the PrV to discriminative touch and the STN, especially the more caudal regions, to pain, but a strict view of non-converging labeled lines has weak support. This article will focus on the PrV, but it would be misleading to present the nucleus as if it were completely independent from the STN. Therefore, the STN will be mentioned where appropriate.

Form and Function

Ramón y Cajal illustrated trigeminal afferent axons branching to form an ascending path to the PrV and a descending path to the STN[21]. He writes that he cannot be sure that all of these axons bifurcate because he cannot rely on the

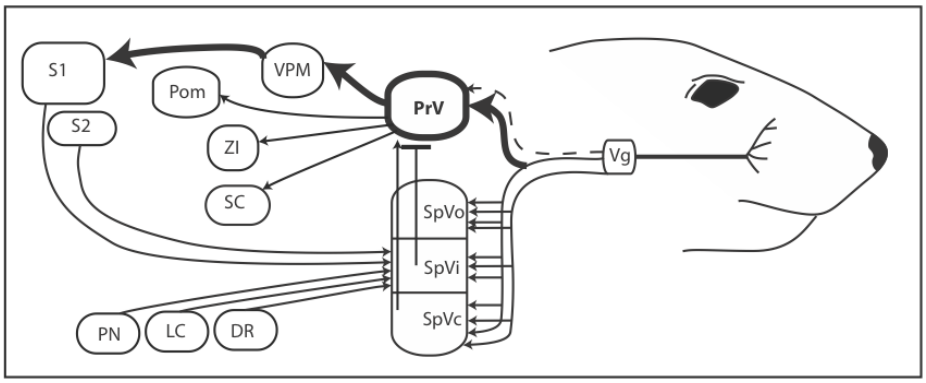

Figure 1: *Schematic of main connections of the principal sensory nucleus (PrV) and the regulatory input directed through spinal trigeminal nucleus pars interpolaris (SpVi).* The dotted line represents an unconfirmed class of sensory neurons projecting solely to the PrV. Thick lines represent the main pathway for low-threshold mechanoreception to the cortex. DR, dorsal raphe nucleus; LC, locus coeruleus; PN, Pontine nucleus; Pom, medial posterior nucleus; SC, superior colliculus; SpVc, spinal trigeminal nucleus pars caudalis; SpVo, spinal trigeminal nucleus pars oralis; ZI, zona incerta.

silver stain as an unbiased technique, but many, if not all, of the fibers he saw bifurcated. In a reinvestigation with silver stains Anstrom states he found the bifurcating fibers Ramón y Cajal reported, as well as descending non-bifurcating fibers projecting to only the STN[22]. He wrote that he did not observe, but could not rule out the possibility of, ascending non-bifurcating fibers projecting only to the PrV. Presumably, if these fibers exist, they would be mechanosensory axons that project exclusively to the PrV.

Another anatomist found such fibers. Windle, like Ramón y Cajal and Anstrom, used silver stains, but his studies were on fetal pigs instead of fetal and young mice[23]. He found three sub-populations of trigeminal afferents: 52% of axons bifurcated, 42% (mostly thin fibers) descended without bifurcating, and 6% (mostly thick fibers) ascended without bifurcating. He struggled to explain why other investigators did not observe large diameter non-bifurcating ascending fibers. One possibility he does not mention is that mice, with vibrissa used for whisking, and pigs, with a large glabrous nose used for rooting in soil, differ in their facial somatosensory specializations. Since the mechanoreceptors in these specializations differ, the animals may have different proportions of bifurcating and non-bifurcating trigeminal afferents.

Subsequent literature on ascending non-bifurcating axons is sparse, though the perception that this pathway exists is maintained in modern reviews and texts[24-27]. One method for studying projection patterns of sensory neurons in the brainstem is interaxonal injections of tracer combined with reconstruction of the labeled axons. This has been used in the STC with interaxonal injections of the neuronal tracers horseradish peroxidase or neurobiotin into the spinal trigeminal tract. Unfortunately, the injections are almost always at the level of SpVo or SpVi[28-33], a method which could not isolate an ascending non-bifurcating population. A less biased technique would use interaxonal injections upstream of the bifurcation, as done by Shigenaga et al.[34], or to inject a far-reaching tracer into single ganglion cells, as Jaquin et al.[35] piloted in a methods paper. Neither study found ascending non-bifurcating axons. The absence of this class could be because such neurons are not present in rodents. However, given that neurons with the ascending non-bifurcating branching pattern made up only 6% of trigeminal afferents in pigs, a combined sample size of 12 axons in rodents is unlikely to represent sufficient sampling to warrant a strong conclusion that these cells are absent in rodents.

Within the PrV, SpVo and SpVi the somatotopic map of the face is inverted so that afferents from the mandibular branch project dorsally, the maxillary branch intermediately and the ophthalmic branch ventrally[28, 31]. The anterior receptors are represented medially and the more posterior receptors,laterally. The arrangement in the SpVc is less well understood. Some studies find that the dorsal-ventral representation is unchanged but the medial-lateral representation is flipped, so that the anterior receptors are represented laterally and the more posterior receptors, medially[17, 36-38]. They also find that in SpVc there is rostral-caudal skew that results in the more rostral afferents being represented more rostrally in the nucleus. This arrangement is reminiscent of the rostral-caudal mapping of dermatomes found in the dorsal horn for the rest of the body. Despite this work, reviews sometimes depict the SpVc as organized like the other subdivisions[26], and recently the somatotopy of SpVc has reemerged as an issue[37]. It is noteworthy that there is still confusion about basic anatomy of the STC.

In addition to the main sensory input from primary sensory neurons, the PrV receives modulatory input from the STN and the cortex. Inhibitory GABAergic interneurons from the SpVi and excitatory glutamatergic interneurons from the SpVc project to the PrV[40]. These connections let the STN influence the sensitivity of the PrV[41]. Projections

from the primary and secondary somatosensory areas (S1 and S2) to the STC could also facilitate top-down reduction of PrV sensitivity[42-43]. In rodents, the cortex-STN-PrV pathway is thought to be particularly important during active whisking, when the somatosensory signals induced by body movement, and not by the characteristics of a substrate, are irrelevant. Such a circuit could explain how the sensitivity of the PrV is reduced during active whisking[44]. Other inputs are from the pontine tegmental nucleus[45-46], the raphe nucleus[47] and the locus coeruleus[48]. These likely reflect modulation of sensitivity based on the animal's level of alertness.

From the PrV, neurons project mainly to the contralateral ventral posterior medial nucleus (VPM) of the thalamus, which sends strong projections to S1[12,49-51]. This trigeminal lemniscal pathway is particularly notable in rodents because every station on this pathway (the PrV, the VPM and S1) has a pattern of cell-dense patches that correspond in a one-to-one manner with the whiskers on the animal's snout, termed barrelettes[17], barreloids[51], and barrels[12] in each location, respectively. We will return to barrels later in the essay. Other important direct projections are to zona incerta[52], the posterior medial nucleus of the thalamus[49] and the superior colliculus[53]. These projections likely contribute to the regulation of movement. The main connections of the PrV are summarized in **Figure 1**.

Electrophysiological work in a variety of species complements the above anatomical findings. As would be expected from the termination patterns of large diameter bifurcating axons branching to every STC subdivision, the PrV and the STN contain mechanosensory neurons[14,54-58]. Likewise, the anatomy shows that many small diameter fibers are non-bifurcating descending axons. If these are nociceptive c-fibers, then electrophysiological studies should find the STN enriched with nociceptive neurons. Indeed, electrophysiological studies that test for it fail to find nociceptive neurons in the PRV, but isolate them in STN[54,56,59-61].

Another promising area for animal studies is to use the power of genetic manipulations in model species to dissect the pathways of mechanoreceptors. For example, Li et al.[62] drove expression of reporter proteins in different classes of low-threshold mechanoreceptors in order to follow sensory neurons from the receptors in the skin to their projections in the dorsal horn. The same techniques are yet to be applied to neurons projecting to the dorsal column nuclei or to the STC. Both studies would be valuable. In the whisker pathway, it would be interesting to see if the different classes of low-threshold mechanoreceptors have unique projection patterns to the subdivisions of the STC, which has so far been undetected with electrophysiology and tract tracing.

Human case studies provide strong results that support the view of parallel pain and touch pathways. Lesions in the PrV cause deficits in touch sensation with sparing of temperature sense and nociception in the face[63], while lesions in the SpVc spare touch sensation but usually lead to the loss of nociception and temperature perception[18]. Thus, surgical damage to this area is a treatment for intractable orofacial pathogenic pain. With case studies such as these providing most of the background for the understanding of the human trigeminal system, a recent fMRI study was surprising. The study looked for changes in the blood oxygen level in humans who were experiencing noxious and non-noxious cutaneous and muscle stimulation to their face. As expected, noxious cutaneous and noxious muscle stimulation elicited changes in regions of the STN, but unexpectedly, the noxious muscle stimulation also elicited activation in PrV[64].

These unexpected results showing integration of pain and sensory information in the brainstem fit with a history of confusion about trying to connect the anatomical data, the electrophysiological data and now the fMRI data — which all show some integration of low-threshold mechanoreception and nociception — with human case studies, which show a strong division of touch and pain sensation between the nuclei[18,22,64]. One problem is that lesion studies rely on eliminating an entire node of a network, which provides strong but crude results. Another problem is that there is a push to make labeled lines for pain and touch explain the anatomical divisions of the STC, despite evidence that the divisions will not fit well into those categories. That debate, however, is beyond the scope of this article (see [65] for review).

Comparative neurobiology

Rodents have been seen as well suited for studies of the trigeminal touch pathway because their barrel system is more amenable to experimentation than non-patterned areas. The cortical barrels are impressive. For example, in rats, barrels cover 20% of S1, a total area of 9 mm^2 [66]. The development of this pattern is dependent on an intact PrV[67]. As othes have pointed out, it is odd that all the input for such a large cortical representation is funneled through a small PrV[54], 0.56mm^3 in the case of a rat[13]. Part of the resolution is that the cortex also receives connections from the

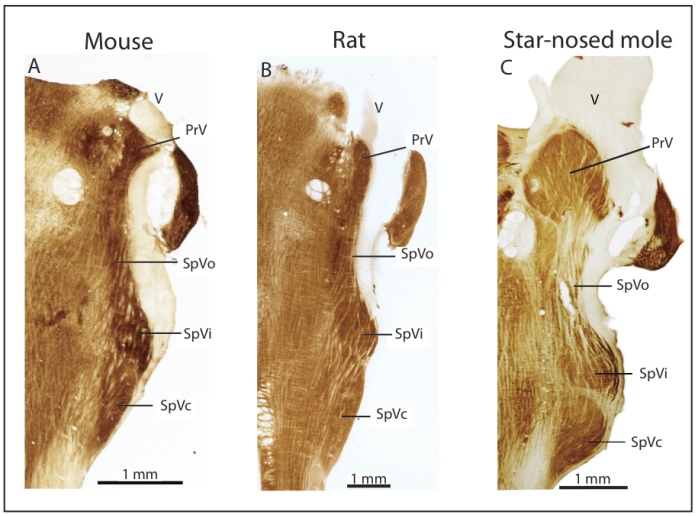

Figure 2: *Cytochrome oxidase stained sections of a mouse, rat and star-nosed mole brainstem cut in the horizontal plane.* Chosen sections maximized the volume of the principal sensory nucleus (PrV). Compared to the mouse and the rat, the star-nosed mole has a large PrV. SpVc, spinal trigeminal pars caudalis; SpVi, spinal trigeminal pars interpolaris; SpVo, spinal trigeminal pars oralis.

STN. Specifically, the caudal portions of SpVi project to the ventrolateral portion of the VPM in the thalamus. The VPM projects to the inter-barrel space, termed septa, in the cortex[68].

In rats, the volume of the SpVi is 1.66mm^3, almost three times larger than the PrV, and has more distinct barrelettes than the PrV[17,69]. Earlier we saw that the SpVi has a role in modulating sensory sensitivity based on directed movements of the whiskers. A large part of rodent exploratory behavior is active whisking — coordinated movements of the six muscles innervating each whisker pad to move the whiskers against the surface being examined[2,70-72]. All this suggests that rats and other rodents are good models for studying the SpVi, particularly because the subnucleus relates to active sensory behavior. But other animals may be better suited for investigating the PrV.

Comparative studies point out that in some species with elaborate somatosensory trigeminal sensory organs, the PrV is hypertrophied[9,14]. The case of the star-nosed mole is particularly informative because of the amount already known about its nervous system. The star consists of 22 fleshy appendages covered with Eimer's organs. Eimer's organs are composed of regular geometric arrangements of Merkel cell-neurite complexes, laminated corpuscles and free nerve-endings[7]. The star can be moved forward as a whole, and groups of appendages can be extended to bring the organ surface into contact with a substrate[73]. When moles forage, they rapidly move the star, touching it to the surfaces of the damp soil of their habitat to locate small food items in the mud[74]. There is a behavioral preference to use the two medial ventral rays when inspecting potential food items[75]. The neuroanatomical correlate of that preference is a larger representation of that ray in S1, and smaller receptive field size in the representation of the medial ventral rays than in the other rays[73,76]. The behavioral preference and the increased resolution suggest those rays as a somatosensory analog of the retina's fovea[75].

To put the size of the star-nosed mole PrV into perspective, the absolute volume of the PrV of a 55g star-nosed mole is larger than the PrV of a 274g rat — it is about 630% the size expected based on the proportions of a rat[13-14]. In comparison, the SpVi subdivision of the star-nosed mole is only about 50% larger than expected[9] (unpublished result). Acknowledging that the comparisons are crude and cover a wide taxonomic range, the results still show that the star-nosed mole has a large PrV even when compared to other somatosensory specialists (**Figure 2**).

The size of the PrV in the star-nosed mole is likely related to the exceptional spatial resolution of the star. Multi-unit receptive fields in the cortex average 0.82 mm^2 in the non-foveal part of the star and 0.52 mm^2 in the foveal regions, which are both smaller than receptive fields reported for primate fingertips[76-78]. If the PrV is the nucleus for fine touch, the extraordinary resolution of the star would be expected to distinguish this nucleus. There is already evidence that this is the case: within the PrV, as in the cortex, the medial ventral rays have a larger representation than the other rays. Interestingly, the greater size of the representation of the foveal rays in the cortex and PrV is not explained by greater innervation of these rays[14]. Combined with the smaller receptive fields in foveal than in non-foveal areas in S1, this suggests that within the lemniscal pathway foveal afferents converge less than the afferents for other rays.

Finding that a behaviorally important area of skin is over-represented in the central nervous system is not new[79]. But finding that the size of the somatosensory representation cannot be predicted by counting the number of fibers innervating that structure and multiplying by a constant "afferent scaling factor" is special[80]. This result is important because it suggests the mole PrV, and perhaps the rest of the lemniscal pathway, could be used to address questions about how the central over-representation of a foveal area of a sensory epithelium comes about.

Conclusion

The role of the PrV, compared to other regions of the STC is relatively understudied. The oversight is surprising given its vital role in organizing the somatosensory cortex. The lack of focus on the PrV might be due to the relatively unimpressive PrV in rodents compared to other trigeminal somatosensory specialists. There are many unresolved questions that could be addressed with comparative work. Just some include: Anatomically, what contributes to a hypertrophied PrV? Are there unique afferents? Is there less convergence? Within a nucleus, what contributes to the "foveal" area of higher resolution? Understanding these points will inform us on the forces that link the evolution of sensory surfaces and their central representations.

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This article finds tests the relationship between whisker innervation and cortical barrel area in six strains of mice breed for their different whisker patterns. The authors find that within a strain there is a linear relationship between the variables, but the slope of the relationship differs between strains. The existence of a linear relationship can be contrasted with case in the star-nosed mole.

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