

Central Projections of Trigeminal Afferents Innervating the Face in Naked Mole-Rats (*Heterocephalus glaber*)

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ABSTRACT

In this study, we examined the topography of projections from facial afferents to the trigeminal brainstem nuclear complex (TBNC) in naked mole-rats using the neuronal tracer CTB-HRP. Tracer injections were made in a ventral to dorsal sequence that included the tooth pulp and dental ligament, ventral buccal pad, vibrissae, and the forehead. Labeled terminals were identified throughout the rostrocaudal extent of the TBNC, including the principal nucleus (Pr5), pars oralis (Sp5O), pars interpolaris (Sp5I), and pars caudalis (Sp5C) of the spinal trigeminal nucleus. Injections that labeled afferents from the tooth pulp and dental ligament resulted in heavy transport to dorsomedial portions of the TBNC, whereas injections made into progressively more dorsal regions of the face resulted in labeled terminals progressively more ventral and lateral in the nuclei. Injections that included dental afferents also labeled the mesencephalic nucleus of V, whereas injections into the skin of the face labeled cell bodies in the facial nucleus, and in most cases the motor nucleus of 5. Dental afferents in more rostral portions of the TBNC were coextensive with a cytochrome oxidase-dense region visible in alternate sections processed for chemoarchitecture. *Anat Rec*, 291:988–998, 2008. © 2008 Wiley-Liss, Inc.

Key words: dental; teeth; somatosensory; tooth pulp; pain

Abbreviations used: I/II = spinal cord layer 1/2; 4V = fourth ventricle; 7 = facial motor nucleus; 7n = facial nerve; 8n = vestibular root of cranial nerve 8; 10 = dorsal motor nucleus of vagus; 12 = hypoglossal nucleus; Acs5 = accessory motor trigeminal nucleus; Acs7 = accessory facial nucleus; Amb = ambiguous nucleus; CGPn = central gray pons; Cu = cuneate nucleus; DC or DCN = dorsal cochlear nucleus; DM = dorsomedial; DTgC = dorsal tegmental nucleus, central; DTgP = dorsal tegmental nucleus, pericentral; ECu = external cuneate nucleus; g7 = genu of the facial nerve; Ge5 = gelat layer caudal sp5 nuc; Gr = gracile nucleus; icp = inferior cerebellar peduncle; io = inferior olive; LC = locus coeruleus; LPBC = lateral parabrachial nucleus, central; LRt = lateral reticular nucleus; LSO = lateral superior olive; LVe = lateral vestibular nucleus; mcp = middle cerebellar peduncle; Me5 = mesencephalic 5 nucleus; me5 = mesencephalic 5 tract; mlf = medial longitudinal fasciculus; Mo5 = motor trigeminal nucleus; MPB = medial parabrachial nucleus; MVe = medial vestibular nucleus; MVeMC = medial vestibular nucleus, magnocellular; MVePC = medial vestibular nucleus, parvocellular; MVPO = medioventral periolivary nucleus; PCRtx = parvocellular reticular nucleus, alpha; PDTg = posterodorsal tegmental nucleus; Pr = prepositus nucleus; Pr5 = principal trigeminal nucleus; Pr5DM = dorsomedial subnucleus of Pr5; Pr5VL = ven-

trolateral subnucleus of Pr5; py = pyramidal tract; pyx = pyramidal decussation; RtTg = reticulotegmental nucleus of the pons; s5 = sensory root of trigeminal nerve; scp = superior cerebellar peduncle; SGe = supragenual nucleus; SO = superior olive; Sol = solitary nucleus; sp5 = spinal trigeminal tract; Sp5C = spinal 5 nucleus, caudal subnucleus; Sp5I = spinal 5 nucleus, interpolar subnucleus; Sp5O = spinal 5 nucleus, oral subnucleus; SPO = superior paraolivary nucleus; SpVe = spinal vestibular nucleus; Su5 = supratrigeminal nucleus; Tz = nucleus of trapezoid body; VCP = ventral cochlear nucleus, posterior; Ve = vestibular nucleus; VL = ventrolateral; vsc = ventral spinocerebellar tract; X = nucleus X.

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Naked mole-rats (*Heterocephalus glaber*) live in dark underground tunnels and depend primarily on somatosensation for exploring their environment. Their eyes are small and have only sparse projections to the lateral geniculate nucleus and superior colliculus (Crish et al., 2006). Their ears are also small and tuned primarily to low frequencies (Heffner and Heffner, 1993). Not surprisingly, however, their somatosensory system is expanded. Mole-rats have sensory vibrissae on their face and body, extending all the way to the end of their tail. They also have large incisors used for digging extensive underground tunnels, for carrying young, for exploring and moving objects, and of course for chewing food (Fig. 1). Both the facial vibrissae and the incisors have large representations in primary somatosensory cortex (S1). S1 itself is 50% larger (as a proportion of total neocortex) in mole-rats compared with laboratory rats (Catania and Rempel, 2002). Within S1, the two contralateral incisors take up a remarkable 30% of the body representation (Catania and Rempel, 2002; Henry et al., 2006). This expansion of the dental representation seems to reflect the importance of the front teeth in mole-rat behavior.

Although previous investigations have revealed the detailed mapping of mechanoreceptors into mole-rat somatosensory cortex, little is known about the organization of the trigeminal sensory complex in the brainstem, where important mechanoreceptors initially project. This area is of particular interest because recent studies have revealed an extensive reorganization of the tooth representation in mole-rat somatosensory cortex after tooth extraction (Henry et al., 2005). Previous studies of cortical reorganization following deafferentation have implicated altered connectivity in brainstem nuclei as an important component of the altered topography at higher central nervous system levels (Sengelaub et al., 1997; Jain et al., 2000). It is possible that altered brainstem connectivity plays a role in the reorganization of mole-rat neocortex after tooth loss as well. One goal of the present study was to describe the normal pattern of connectivity to provide a framework for interpreting deafferentation experiments. In addition, the projections and organization of tooth pulp afferents in the brainstem are of general interest because of their potential role in neuropathic disorders that result in persistent orofacial pain or phantom tooth sensations (Bates and Stewart, 1991; Marbach, 1993a–c, 1996; Marbach and Rapheal, 2000; Tassinari et al., 2002; Clark, 2006).

To investigate how facial afferents project to the brainstem, we made injections of the anatomical tracer cholera toxin subunit B conjugated to HRP (CTB-HRP) into the tooth pulp and skin of different areas of the face. Our goal was to determine how these projections in mole-rats are organized and to compare the projection patterns with those found in other species.

MATERIALS AND METHODS

Eight adult mole-rats were used to determine the connectivity of dental and facial mechanoreceptors. All animal procedures followed National Institutes of Health guidelines and were performed according to the standards set by the Animal Welfare Act and the Vanderbilt University Institutional Animal Care and Use Commit-



Fig. 1. A naked mole-rat (*Heterocephalus glaber*) showing the lack of fur, small eyes and specialized incisors.

tee. The animals were anesthetized with ketamine hydrochloride and xylazine diluted in distilled water at a dosage of 15–20 mg/kg and 0.6–1.0 mg/kg, respectively. Body temperature was maintained with a calibrated heating pad with temperature feedback. All instruments and drapes were sterilized with a steam autoclave. To examine afferent projections from the tooth pulp and dental ligament, the ventral jaw region was thoroughly

cleaned with a surgical scrub (Betadine) and ETOH. After the animal reached a surgical plane of anesthesia, a small incision was made along the ventral jaw in the rostral-caudal plane and the skin was retracted from the mandible with forceps. A small hole (approximately 1 mm) was drilled into the mandible and underlying incisor using a dental drill with a round bur attachment. A small injection (approximately 2 μ l) of 2% CTB-HRP (in sterile saline) was made in the hole using a Hamilton microliter syringe. The hole was then covered with dental adhesive and the skin was closed with sterile nylon or vetbond. The surgical procedure lasted less than 30 min. Topical antibiotics (bacitracin zinc, neomycin, polymyxin b-pramoxine HLC) and analgesics (bupivacaine) were applied to the wound immediately after the surgery and the following day. For tracers injected into the buccal pad, vibrissa pad, and forehead, animals were anesthetized with isoflurane in an induction chamber, and multiple small injections (1.5 to 2.5 μ l) of 2% CTB-HRP (in sterile saline) were made in the skin area of interest using a Hamilton microliter syringe. The procedure generally lasted less than 5 min. Injection areas were marked on a schematic of the face. After a postsurgical survival time of 48 hr, the animal was given an overdose of sodium pentobarbital and perfused with 0.9% saline followed by 2–4% paraformaldehyde. The brain was removed, and the brainstem and trigeminal nerves and ganglia were immersed in 30% sucrose in phosphate buffer for 12 hr. Sections were cut coronally on a freezing microtome at 50 μ m. Brainstem sections were alternatively processed for the metabolic enzyme cytochrome oxidase (CO; Wong-Riley, 1978) or processed for label with tetramethylbenzidine (TMB) using the protocol developed by Gibson and colleagues (1984). Trigeminal nerve sections were also processed for label with TMB. Representative sections containing labeled cell bodies and axon terminals were reconstructed using a camera lucida and superimposed on sections processed for CO. By matching blood vessel patterns and tissue artifacts, the pattern of connections was related to architectonic boundaries. Final composites of labeling superimposed on architectonic boundaries of representative sections were rendered using Adobe Illustrator CS3.

RESULTS

The results of our investigation show the topography of somatosensory inputs from facial mechanoreceptors to the brainstem, revealing afferent terminals throughout the rostro-caudal extent of the brainstem trigeminal nuclear complex (TBNC), which includes the principal nucleus (Pr5) and the spinal trigeminal nuclei: oralis (Sp5O), interpolaris (Sp5I), and caudalis (Sp5C). Labeled terminals were identified as far caudal as the upper cervical vertebrae and throughout the more rostral trigeminal nuclei, tapering off at the anterior-most aspect of Pr5.

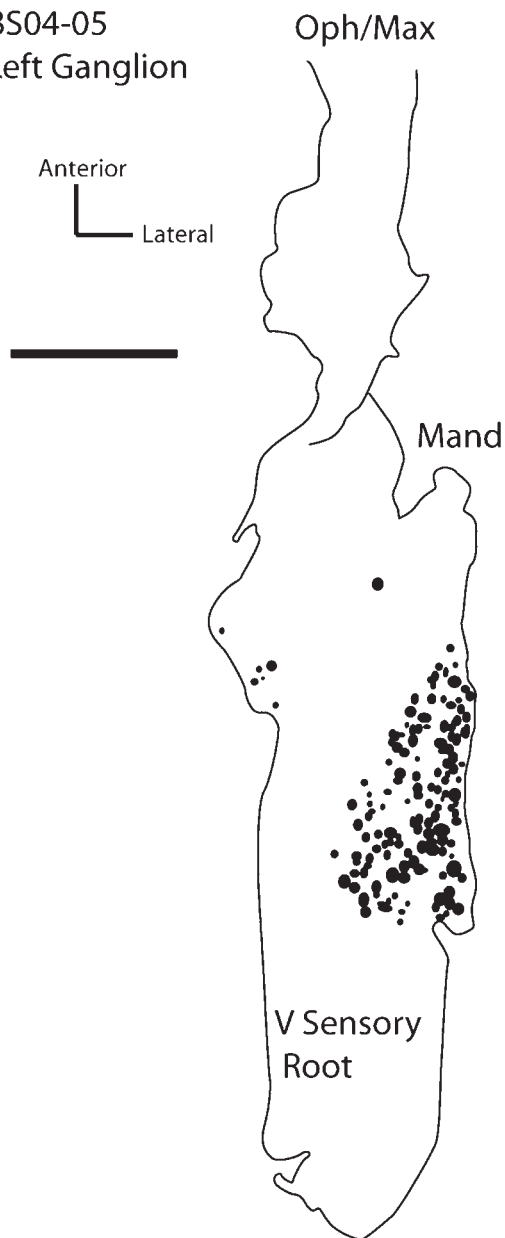
We also processed the ganglia for TMB to reveal the distribution of cell bodies of labeled afferents. Label was located exclusively in the ipsilateral trigeminal ganglion. In the case of labeled afferents from the tooth pulp and dental ligament, cell bodies were confined to a region of the ganglion just posterior to the branching of the man-

dibular division of the trigeminal nerve (Fig. 2A). Injection of tracer in the buccal pad resulted in labeled cell bodies more anterior and medial in the ganglion, including regions anterior to the branching of the mandibular division (Fig. 2B). This trend is consistent with previous investigations of somatotopic organization of the trigeminal ganglion, which suggest that the most ventral, mandibular regions (lower lip and lower incisor) on the face are represented at the more posterior part of the ganglion, whereas more dorsal regions (e.g., the buccal pad) on the face are represented in more anterior regions of the ganglion (Gregg and Dixon, 1973; Waite and Permetier, 1991; Leiser and Moxon, 2006).

Within the brainstem, injections of tracer into different areas of the face resulted in transported label that was distributed in different regions of the trigeminal brainstem complex. Injections that labeled the tooth pulp and dental ligament resulted in relatively heavy transport of label to the dorsomedial-most portion of all four subdivisions of the TBNC (Fig. 3). Labeled terminals had the smallest distribution in pars caudalis (Sp5C: Fig. 3J–M) terminating in the most medial and dorsal region and including laminae I and II. Within more rostral areas of the TBNC, label was distributed more widely, though still localized to dorsomedial areas. Within Sp5I, much of the label was confined to a CO-dense region located at the dorsomedial end of the nucleus (DM in Fig. 3H). Some of the densest label was found at the dorsomedial extent of the Sp5I/Sp5O junction (Fig. 3E), though Pr5 was also heavily labeled (Fig. 3A,B). Several cells were also labeled in the mesencephalic nucleus of V (Fig. 3A).

Injections into the buccal pad region were made in the ventral-medial region of the face close to the lower incisor (Fig. 4B). Labeled terminals were found throughout the TBNC, but in a more lateral region compared with the lower incisor afferents. This distinction was least obvious for Sp5C, where labeled buccal pad afferents overlapped with corresponding regions from the lower incisor afferents (Fig. 4H,I). However in Sp5I, Sp5O, and Pr5, the CO-dense region that contained heavy label from the incisor afferents was largely devoid of terminals from the buccal pad (Fig. 4A–G). Buccal pad labeled trigeminal ganglion cells were restricted to the ipsilateral ganglion. Despite the ipsilateral distribution of labeled ganglion cells, there was a sparse labeling of terminals in the contralateral TBNC, primarily in the outermost, dorsal layers of Sp5C (Fig. 4H). Contralateral label was only found in the buccal pad cases and may represent the decussation of fibers at the level of the brainstem, as previously suggested for rats (Pfaffner and Arvidsson, 1982; Jacquin et al., 1990). In addition, label from the buccal pad cases was found in the ipsilateral facial nucleus, trigeminal accessory nucleus, and trigeminal motor nucleus (Fig. 4A–D). This labeling (Fig. 5J–L) can also be seen directly superimposed on adjacent sections from the same animal case stained for cytochrome oxidase (Fig. 5A–I) to reveal the chemoarchitecture.

Injection of tracer into the more dorsal portion of the face containing the macrovibrissae (Fig. 6B) resulted in a shifted region of labeled afferents in the TBNC compared with injections into the tooth and buccal pad areas (Fig. 6A–I). The areas that were most heavily labeled by injections into the incisor were largely devoid of label from the vibrissae. Label was instead concentrated more

ABS04-05
Left Ganglion

Tooth/Jaw Injection

BBS04-09
Left Ganglion

Buccal Pad Injection

Fig. 2. Localization of labeled cell bodies in the mole-rat ipsilateral trigeminal ganglion following tracer injection into the lower incisor area (A) and the buccal pad (B). Each panel represents a single section through the middle of the ganglion. Scale bars = 1 mm.

laterally and ventrally in the nuclei. The most medial and dorsal (DM) region of Sp5C was devoid of labeling (Fig. 6G–I), as was the DM area of Sp5I, Sp5O and Pr5 (Fig. 6A–F). As in the buccal pad cases, labeled cells were observed in the facial nucleus and facial nerve fibers (7n) were labeled (Fig. 6C–E).

The most dorsal injection site, on the forehead (Fig. 7B), resulted in a further shift of labeled afferents toward the most ventrolateral portion of the TBNC (Fig. 7A–I). Labeled regions containing afferent terminals in Sp5C were located in lateral portions in the most caudal sections examined (Fig. 7G–I), and

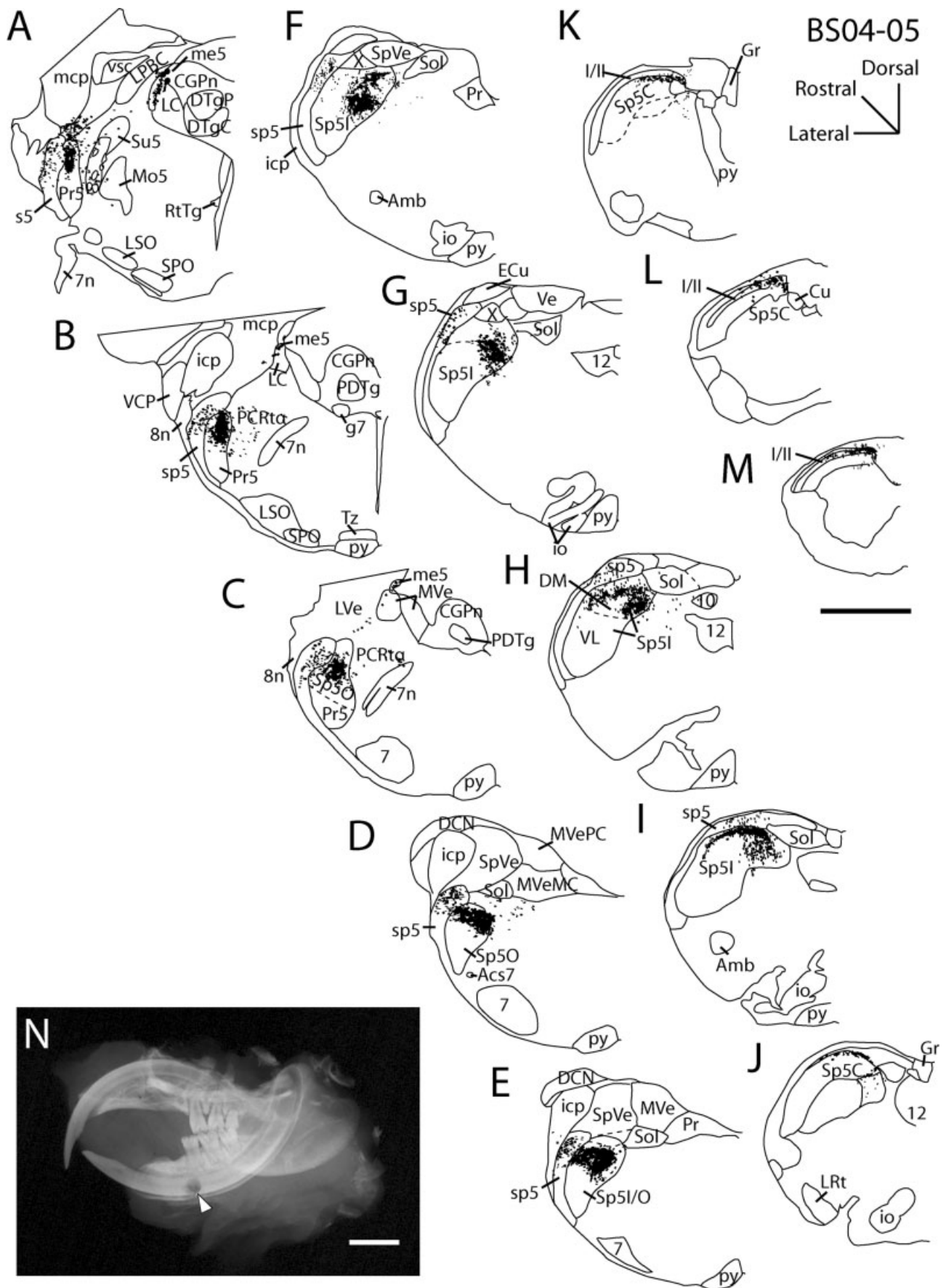


Fig. 3. Central projections from the lower incisor periodontal ligament and tooth pulp. **A–M:** Reconstructed coronal tissue sections show different levels of the TBNC. Labeled afferents were found in all four subnuclei of the ipsilateral TBNC (A–M) and in the mesencephalic

nucleus (A, solid black dots). **N:** X-ray of mole-rat head, showing location of injection into the lower incisor and including the surrounding connective tissue (white arrow). Scale bar = 1 mm in A–M, 3 mm in N.

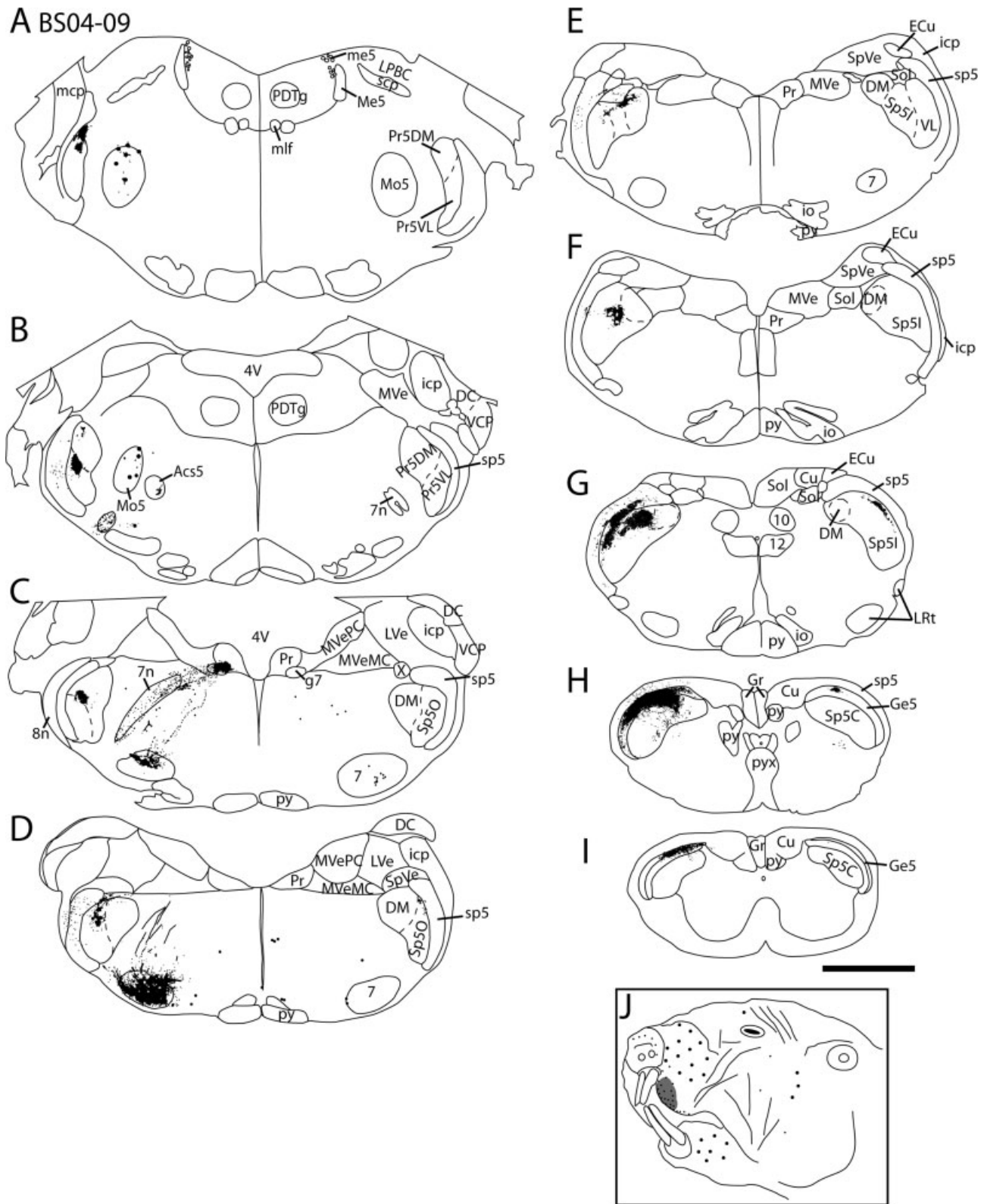


Fig. 4. Central projections from the buccal pad. **A-I**: Reconstructed coronal tissue sections showing different levels of the TBNC. Labeled afferents were found in all four ipsilateral subnuclei of the

TBNC (**A-I**) and in portions of contralateral subnuclei caudalis (**H**), interpolaris (**G**), and oralis (**D**). See Figure 5 for adjacent CO sections. **J**: Diagram showing site of injection in buccal pad. Scale bar = 1 mm.

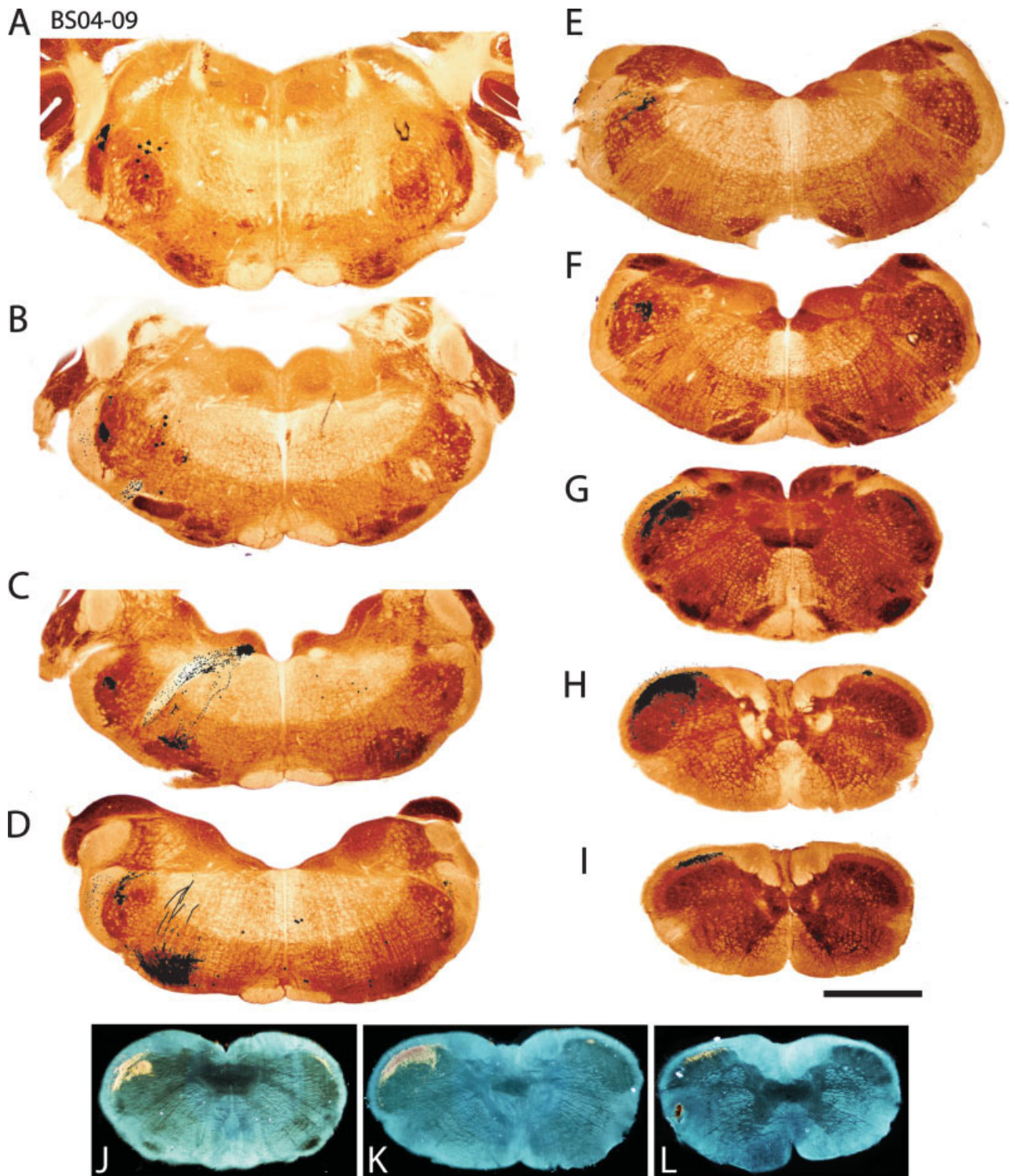


Fig. 5. **A-I:** Central projections from the buccal pad (black) directly superimposed on adjacent cytochrome oxidase-stained sections to show histochemical characterization of nuclei of the TBNC in which labeling occurred. See Figure 4 for labeled subdivisions. **J-L:** Darkfield images of CTB-HRP labeling for sections adjacent to G-I. Scale bar = 1 mm.

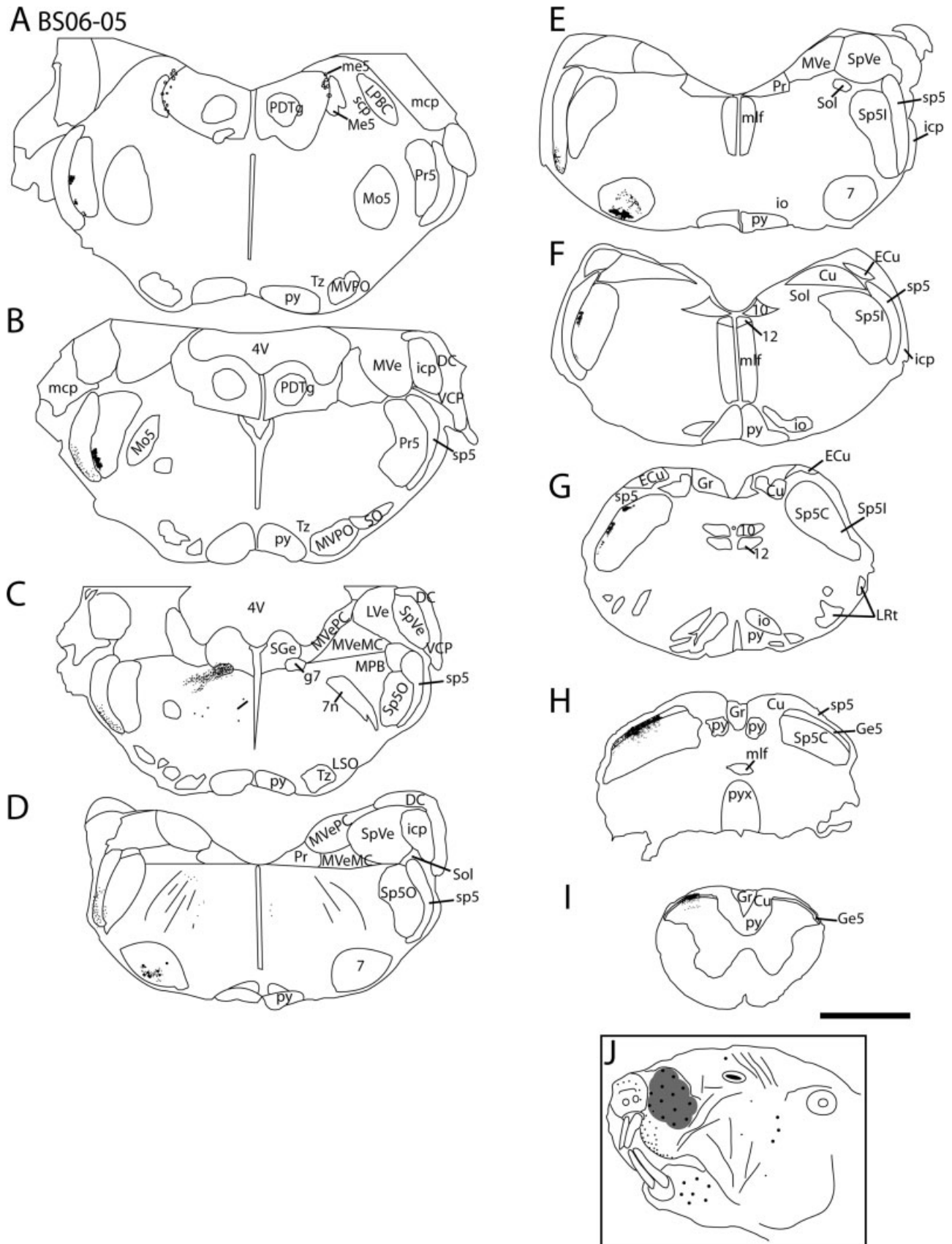


Fig. 6. Central projections from the mystacial vibrissal pad. **A-I**: Reconstructed coronal tissue sections showing different levels of the TBNC. Labeled afferents were found in all four ipsilateral subnuclei of the TBNC. **J**: Diagram showing site of injection in vibrissal pad. Scale bar = 1 mm.

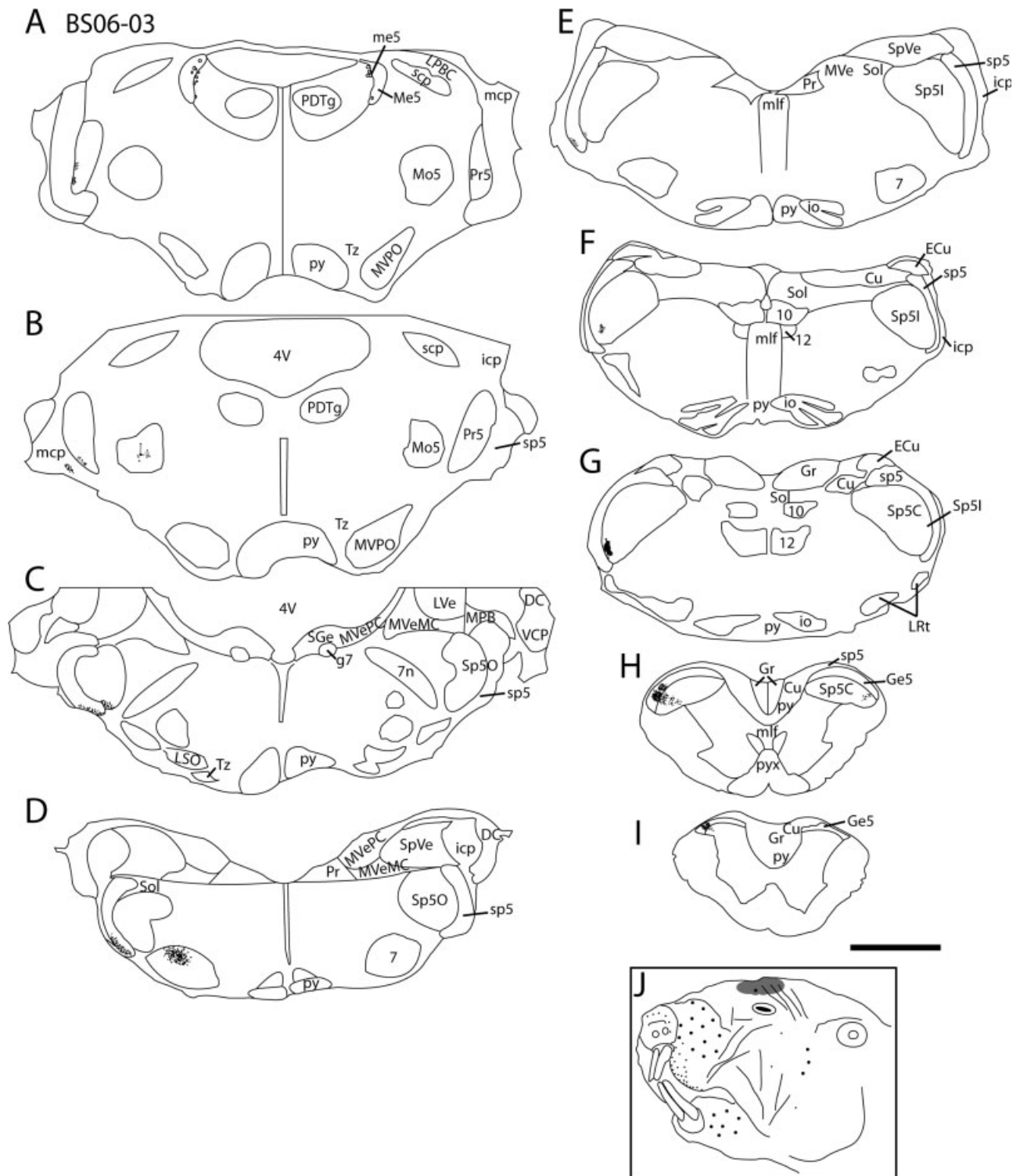


Fig. 7. Central projections from the forehead. **A–I**: Reconstructed coronal tissue sections showing different levels of the TBNC. Labeled afferents were found in all four ipsilateral subnuclei of the TBNC. **J**: Diagram showing site of injection in the forehead. Scale bar = 1 mm.

progressively more ventrally and laterally in expanded regions of label for the nuclei at the Sp5C/Sp5I juncture (Fig. 7E–G) and throughout Sp5O and Pr5 (Fig. 7A–D). The labeled regions in the TBNC

were smallest for this injection site, presumably reflecting the lower innervation density for the skin of the forehead compared with the vibrissae and oral regions.

DISCUSSION

In this investigation, we examined the topography of afferent projection zones from the face of naked mole-rats. A topographic progression was apparent in the distribution of terminals in the TBNC. Specifically, as the injection sites progressed from the lower incisor (including tooth pulp and dental ligament) to the adjacent buccal pad, to more dorsal vibrissae, and finally to the forehead, the resulting terminal fields, which extended rostrocaudally throughout the TBNC, progressed from the dorsomedial region of the nuclei to the ventromedial region of the nuclei. These results are consistent with previous investigations of trigeminal projections to the brainstem. For example, Marfurt and Turner (1984) investigated tooth pulp afferents from the maxillary molar tooth in rats, and revealed projections that extended throughout the rostrocaudal extent of the TBNC, but were concentrated in the dorsal and medial portions of the nuclei. Our procedure differed from Marfurt and Turner's, in that our injection into the tooth was not confined to the pulp chamber. Rather, it included both the incisor pulp chamber and the underlying connective tissue to label both pulpal and periodontal ligament afferents. This may in part account for the greater number of afferents labeled in the present investigation. In addition, we used CTB-HRP to investigate connectivity, rather than WGA-HRP, as used by Marfurt and Turner. Thus we may have labeled a greater proportion of larger diameter mechanoreceptive fiber and fewer nociceptors (Robertson and Arvidsson, 1985). This would be consistent with findings at the cortical level. Mole-rats have a greatly enlarged representation of the incisors in the neocortex (Henry et al., 2006), and thus may have a relatively large projection from dental mechanosensory afferents to the TBNC compared with other species. In more rostral areas of the TBNC, the area of labeled terminals from dental afferents was generally concentrated in a cytochrome oxidase-dense region visible in adjacent sections (DM; Fig. 3H). Recent investigations of the somatosensory cortex of mole-rats and laboratory rats have revealed a series of cytochrome oxidase-dense modules coextensive with the incisor representations at the cortical level (Remple et al., 2003; Henry et al., 2006), and this could be reflected in the brainstem as well. In laboratory rodents, modular representations of sensory surfaces have been found in both neocortex (cortical barrels; Woolsey and Van der Loos, 1970) and the TBNC (Belford and Killackey, 1979; Ma, 1991).

The injections of tracer into the tooth and jaw region also labeled several neurons in the mesencephalic nucleus of V (Fig. 3A). This was expected given the previously characterized projections from the mesencephalic nucleus to the dental ligament in other species (Cody et al., 1974; Gonzalo-Sanz and Insausti, 1980; Byers and Dong, 1989; Zhang et al., 1992). The majority of mechanoreceptors innervated by these fibers are thought to be ruffini-like endings concentrated in the lower (proximal) levels of the ligament, carrying information about tooth contact during mastication (Byers and Dong, 1989). This is likely an important pathway in mole-rats, given their use of front teeth for digging extensive underground tunnels through soil of variable composition.

As injections were made further dorsally, the area of labeled terminals in the brainstem moved more laterally and ventrally. This is consistent with several previous

investigations of the face representation in mammals, which have demonstrated that more ventral regions of the face are represented predominantly in the more medial and dorsal areas of the TBNC, whereas more dorsal portions of the face are generally represented more laterally and ventrally (Darian-Smith and Mayday, 1960; Gordon et al., 1961; Nord, 1967; Grant and Arvidsson, 1975; Yokota and Nishikawa, 1977, 1980; Arvidsson, 1982). In the case of laboratory rats and mice, transported label from tracer injections into the whiskerpad reveal that the ventral vibrissae on the face (e.g., row E) project to more dorsomedial areas in TBNC, whereas more dorsal vibrissae on the face (e.g., row A) project to more ventrolateral regions (Arvidsson, 1982). The topography is perhaps most obviously demonstrated by the pattern of barrelettes in the brainstem (Belford and Killackey, 1979), which reflects the topographic organization of whiskers on the face, much like barrels in the neocortex. Such preparations show the vibrissae pattern (with the exception of Sp5O) in the TBNC, where the barrelettes representing the more dorsal vibrissae (row A) are visible more ventrally, whereas the barrelettes representing the more ventral vibrissae (row E) are visible more dorsally. For the anterior-posterior dimension of the face, more caudal vibrissae are represented more laterally in the brainstem, whereas the more anterior vibrissae are represented more medially. We did not investigate this dimension of the projection pattern in mole-rats, and no barrelettes were observed in the brainstem of naked mole-rats. Although barrels have been observed in the neocortex of mole-rats (Henry et al., 2006), these were less distinct than those demonstrated in laboratory rats and mice. In addition, barrelettes are best observed in juvenile animals and may be difficult to discern in adult mole-rats such as those observed in the present study.

Finally, the topography of projections from facial afferents in mole-rats is consistent with previous investigations of neocortex, where the ventral buccal pad representation has been identified adjacent to the more rostral representation of the lower incisor (Henry et al., 2006). Extraction of the lower incisor results in later reactivation of the neocortex by buccal pad afferents and other surrounding facial structures (Henry et al., 2005). The present study suggests deafferentation of the lower incisor could deactivate a relatively large region of the brainstem. Although some investigations suggest that dental afferents are not remodeled in the brainstem following deafferentation (Shortland et al., 1995), other investigations of rat hindlimbs and primate hands indicate that some fibers in the brainstem sprout following deafferentation of adjacent regions. These few fibers could reactivate large areas of neocortex as ascending pathways diverge (Sengelaub et al., 1997; Jain et al., 2000). More study is needed to determine whether this mechanism could account for reorganized dental areas observed following deafferentation in mole-rats.

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