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The Dorsal Column Nuclei Neuroanatomy Reveals A Complex Sensorimotor Integration and Distribution Hub

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Abstract

The dorsal column nuclei (DCN) are organised by both somatotopy and modality, and have a diverse range of afferent inputs and projection targets. The functional organisation and connectivity of the DCN implicate them in a variety of sensorimotor functions, beyond their commonly accepted role in processing and transmitting somatosensory information to the thalamus, yet this is largely underappreciated in the literature. In this review, we examine the morphology, organisation, and connectivity of the DCN and their associated nuclei, to improve understanding of their sensorimotor functions. First, we briefly discuss the receptors, afferent fibres, and pathways involved in conveying tactile and proprioceptive information to the DCN. Next, we review the modality and somatotopic arrangements of the constituents of the dorsal column nuclei complex (DCN-complex), which includes the gracile, cuneate, external cuneate, X, and Z nuclei, and Bischoff's nucleus. Finally, we examine and discuss the functional implications of the myriad of DCN-complex projection targets throughout the midbrain, and hindbrain, in addition to their modulatory inputs from the cortex. The organisation and connectivity of the DCN-complex suggest that these nuclei should be considered a complex integration and distribution hub for sensorimotor information.

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Abbreviations

CuN: Cuneate nuclei

cCuN: Cuneate nuclei caudal zone

mCuN: Cuneate nuclei middle zone

rCuN: Cuneate nuclei rostral zone

DCN: dorsal column nuclei – gracile (inclusive of Bischoff's nucleus) and cuneate nuclei

DCN-complex: dorsal column nuclei complex – gracile (inclusive of Bischoff's nucleus), cuneate, and external cuneate nuclei, nuclei X and Z

DDC: direct dorsal column pathway

GrN: gracile nuclei

cGrN: Gracile nuclei caudal zone

mGrN: Gracile nuclei middle zone

rGrN: Gracile nuclei rostral zone

IC: inferior colliculus

InC: Intercollicular region

LAC: lemniscal adjunct channel

MLLC: main line lemniscal channel

PAG: periaqueductal grey

PO: posterior group of the thalamus

PG: pontine grey

PSDC: postsynaptic dorsal column pathway

PV: parietal ventral area of the anterior parietal cortex

RF: receptive field

SC: superior colliculus

VL: Ventrolateral nucleus of the thalamus

VP: ventroposterior nuclei of the thalamus

VPL: ventroposterior lateral nucleus of the thalamus

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Introduction

Somatosensation involves a complex group of senses that gather information about physical attributes of the external world and the body's internal physical state. It is essential for functions like texture discrimination, object manipulation, directing attention, regulating movement, avoidance behaviours, sensing pain and temperature, and affective touch. These diverse roles necessitate somatosensory information transmission to many brain structures, specialised for these different functions. The brainstem dorsal column nuclei (DCN) are recognised as a processing centre for touch and proprioceptive information ascending from the periphery to the somatosensory cortex. However, the DCN contain diverse cell groups that project to a myriad of targets throughout the brain and perform specialised roles in somatosensory processing and sensorimotor integration. An excellent review of the DCN organisation and projection targets was produced by Berkley *et al.* (1986), in an effort to increase understanding of their functional significance. However, in the more than 30 years since this review, knowledge of the functional organisation and connectivity has greatly increased, warranting synthesis.

Typically, the DCN are considered to comprise the cuneate nuclei (CuN) and gracile nuclei (GrN), but there are several adjacent nuclei occasionally included. These are the external cuneate nuclei (ECuN), the nucleus of Bischoff (BN), nuclei X (NuX), and nuclei Z (NuZ) (**Figure 1**). Here, we use the term *the dorsal column nuclei* (*DCN*) to refer only to the GrN and the CuN combined (BN is assumed to be part of the GrN). When including the ECuN, NuX, and NuZ we refer to *the dorsal column nuclei complex* (*DCN-complex*) (Mountcastle, 1984; Berkley *et al.*, 1986). We refer to each of the respective cell groups as the plural nuclei, rather than the singular nucleus (e.g. dorsal column nuclei, gracile nuclei, cuneate nuclei), as they are considered separate nuclei on either side of the midline (except for Bischoff's nucleus). **Figure 1** summarises the arrangement of the DCN-complex.

Elucidating the architecture and interconnectedness of brain structures is essential to understanding their function independently, and as components of a system. Here, we review the morphology,

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organisation, and afferent and efferent connections of the DCN-complex, with discussion of functional implications. A comprehensive review of the DCN structural characteristics reveals that the DCN should be considered an essential integration and distribution hub for sensorimotor information. In a broader context, regarding the DCN-complex as a distribution hub for bodily somatosensory information entering the brain, substantiates this region as an ideal target for a future neural prosthesis to restore sensorimotor function after spinal injury. First, we briefly discuss the mechanoreceptors for transducing somatosensory information and the pathways this information takes to the DCN.

Peripheral receptors

Touch and proprioceptive stimuli are transduced by mechanoreceptors converting mechanical deformation of various tissues into electrical impulses. These mechanoreceptors reside in skin, muscles, tendons, and ligaments and each have specialised end organs with associated afferent types. Here, we briefly describe the structure and functional properties of somatosensory mechanoreceptors and associated afferents, but there are several excellent reviews on this topic providing greater detail (Johnson, 2001; Johansson & Flanagan, 2009; Darian-Smith, 2011; Abraira & Ginty, 2013; Zimmerman *et al.*, 2014).

Glabrous skin

Glabrous skin is specialised for discriminative touch and predominates on the palmar and plantar sides of mammalian hands and feet, respectively. There are four types of afferent fibres and associated end organs found in mammalian glabrous skin: slowly adapting (SA) type 1 and 2 (SA1 and SA2), and rapidly adapting (RA; also called fast adapting) type 1 and 2 (RA1 and RA2). All four afferent types are classed as Aβ fibres, which are myelinated large diameter fibres with fast conduction velocities (16-100 m/s) (Abraira & Ginty, 2013). Conduction velocities are species-dependent, however, as humans (Knibestöl, 1973), monkeys (Perl, 1968), and cats (Brown & Iggo, 1967; Burgess *et al.*, 1968) have fibres that reach the upper limits of this range, while rat Aβ fibres can conduct up to ~70 m/s (Sanders & Zimmermann, 1986; Handwerker *et al.*, 1991; Leem *et al.*, 1993). Slowly adapting afferents produce a characteristic

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sustained, slowly decreasing action potential firing rate, to maintained mechanical skin indentation. Rapidly adapting afferents respond best to dynamic skin deformation changes, and their responses to sustained stimuli show a rapid decrease in firing rate (Johansson & Flanagan, 2009). Type 1 afferents are characterised by their small receptive fields (RFs), and superficial location in the dermis or epidermis, and are ideally suited for conveying spatial patterns of skin indentation. Type 2 afferents are characterised by large receptive fields and are typically located deeper in the dermis.

The four afferent types can also be defined by the specialised end-organs that they associate with. SA1 afferents terminals are known to associate closely with Merkel receptors (Iggo & Muir, 1969; Munger *et al.*, 1971; Halata *et al.*, 2003) and RA1 afferents associate with Meissner's corpuscles (Cauna & Ross, 1960). These two afferent types work complementarily to facilitate fine tactile discrimination. SA2 afferents are thought to associate with Ruffini endings, although this remains controversial (see (Abraira & Ginty, 2013) for discussion), and they respond best to skin stretch (Knibestöl, 1975). RA2 afferent terminals associate with Pacinian corpuscles, respond best to high frequency vibrations (40-400 Hz), and are extremely sensitive to small and fast mechanical skin deformations (Johansson *et al.*, 1982; Bell *et al.*, 1994).

Hairy skin

The same four afferent types can be found in hairy skin. There are additional Aβ RA afferents that form circumferential endings around many hairs. These are referred to as Aβ field units and respond best to gentle stroking of large fields of hairy skin (Bai *et al.*, 2015). Other Aβ RA and SA fibres associate with hair follicles with longitudinal lanceolate endings and Merkel cell complexes, respectively (Li *et al.*, 2011; Abraira & Ginty, 2013; Jenkins & Lumpkin, 2017). In addition to Aβ fibres, slower-conducting fibres also associate with hair follicles. Aδ fibres are thinly myelinated and have intermediate conduction velocities (5-30 m/s), and C-fibres are unmyelinated and have the slowest conduction velocities (0.2-2 m/s) (Abraira & Ginty, 2013). These fibres show intermediate adaptation characteristics between SA and RA, form lanceolate endings around hair follicles, and are thought to play a role in affective touch (Löken *et al.*, 2009; Li *et al.*, 2011).

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Muscles and joints

Afferents that respond to changes in muscle length, tendon tension, and joint movement are associated with proprioception. Muscle length is conveyed by specialised muscle fibres called muscle spindles, which are innervated by primary (Group Ia) and secondary (Group II) spindle afferent fibres. Tendon tension is conveyed by Golgi tendon organs (Group Ib fibres) that respond best to isometric contractions that produce a load on a tendon and weakly respond to changes in muscle length (Edin & Vallbo, 1990a, b; Jami, 1992). Finally, joint receptors respond to joint movement, pressure over the joint capsule, or contraction of muscles inserted in the capsule (Macefield, 2005; Proske & Gandevia, 2012). The end organs associated with these joint afferents are Ruffini-like endings, Pacinian-like corpuscles and Golgi organs in ligaments (Grigg, 1994). These afferents respond best at the end of the joint's movement range with SA characteristics (Grigg, 1994). Group I fibres have very fast conduction velocities (30-120 m/s), whereas Group II fibres conduct more slowly (15-80 m/s) (Cheney & Preston, 1976; Wei *et al.*, 1986; Scott, 1990; De-Doncker *et al.*, 2003). As with Aβ cutaneous fibres, rat proprioceptive fibres represent the lower end of this conduction velocity spectrum, whereas cats and primates have higher conduction velocities.

Spinal cord pathways to the dorsal column nuclei complex

Somatosensory information bound for the DCN-complex, ascends the spinal cord via multiple different paths. The pathway taken by afferent fibres is determined by the modality of the afferents, and whether they have receptive fields on the upper or lower body.

The direct dorsal column pathway

The best known of the ascending pathways to the DCN-complex is the direct dorsal column pathway (DDC), in which primary afferents, transmitting tactile and proprioceptive information, ascend the spinal cord in the dorsal columns (DCs) and terminate on second order neurons in the ipsilateral DCN. The DCs comprise the gracile and cuneate fasciculus (GF and CF), which are white matter tracts in the dorsal funiculus, housing lower and upper body afferents, respectively. Afferents entering the spinal cord at the most caudal dorsal roots ascend medially, and successive entry of afferents at more rostral

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spinal roots maintain their order of entry by ascending in progressively more lateral portions of the DCs (Whitsel *et al.*, 1970; Smith & Deacon, 1984).

A modality-based organisation within the DCs coexists with the somatotopic organisation (Niu *et al.*, 2013). Hindlimb Group I and II muscle and tendon afferents leave the DC to synapse onto second order neurons in the nucleus dorsalis (sometimes referred to as Clarke's column) (Bloedel & Courville, 2011) and most, if not all, SA1 afferents seem to disappear from the DCs as they ascend to the DCN (Whitsel *et al.*, 1969; Whitsel *et al.*, 1970; Abraira & Ginty, 2013). Therefore, above mid-thoracic levels it appears that mostly RA primary afferents are found in the GF, while proprioceptive-related afferents from the upper body are found laterally in the CF (Luo *et al.*, 2009; Niu *et al.*, 2013). This partly agrees with modality-based organisation in the DCN (Dykes *et al.*, 1982), thalamus (Dykes *et al.*, 1981), and somatosensory cortex (Kaas *et al.*, 1979). However, further investigation is necessary to confirm the arrangement of specific fibre types ascending in the DDC. Critically, SA responses are commonly recorded in the DCN, yet these fibres apparently leave the DC at mid-thoracic levels, and DCN RA responses are recorded in response to forelimb tactile stimuli, yet RA afferents have been reported to be relatively sparse or absent in the CF and CN.

The postsynaptic dorsal column pathway

Complementary to the DDC fibres, some axons entering the spinal cord synapse onto second order neurons in laminae III, IV, and V of the dorsal horn, that have ascending axons in the DCs and terminate in the ipsilateral DCN-complex (Uddenberg, 1968; Rustioni, 1973; Angaut-Petit, 1975a; Rustioni & Kaufman, 1977; Brown & Fyffe, 1981; Enevoldson & Gordon, 1989; Abraira & Ginty, 2013). Neurons in this so-called postsynaptic dorsal column pathway (PSDC) receive inputs from a mixture of tactile, proprioceptive, and visceral afferents, and a small population respond to noxious mechanical stimuli (Angaut-Petit, 1975b; Jankowska *et al.*, 1979; Abraira & Ginty, 2013). PSDC neurons, therefore, may play a role in integrating somatosensory information, as they can receive convergent inputs from more than one modality (Angaut-Petit, 1975b; Jankowska *et al.*, 1979; Abraira & Ginty, 2013).

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The dorsal aspect of the lateral funiculus

Some afferents synapse onto second order neurons in the dorsal horn and then ascend the spinal cord in the dorsal aspect of the lateral funiculus (dLF) (Pompeiano & Brodal, 1957; Landgren & Silfvenius, 1971; Dart & Gordon, 1973; Magherini *et al.*, 1974; Magherini *et al.*, 1975; Nijensohn & Kerr, 1975; Johansson & Silfvenius, 1977a, c, b; Gordon & Grant, 1982). Many of these axons from T6 and below are dorsal spinocerebellar tract (DSCT) neurons with cell bodies in the nucleus dorsalis. Neurons comprising the DSCT convey lower body proprioceptive information (Group I and II muscle afferents) and terminate in the ipsilateral cerebellum, but they also send collaterals to the ipsilateral, and a small proportion to the contralateral, DCN-complex (Landgren & Silfvenius, 1971; Johansson & Silfvenius, 1977a; Low *et al.*, 1986; Mantle-St. John & Tracey, 1987). There are also axons ascending to the DCN-complex within the dLF that are not part of the DSCT (Dart & Gordon, 1973; Johansson & Silfvenius, 1977b; Gordon & Grant, 1982; Low *et al.*, 1986), which likely make up the spinomedullothalamic tract. Little is known about this pathway, but it is described to comprise axons from neurons with cell bodies in dorsal horn lamina IV, which respond to stimulation of deep structures and cutaneous SA afferents from the upper and lower body. Therefore, this tract may house second order SA neurons that are activated by the SA primary afferents reported to leave the DDC at mid-thoracic levels. The primary targets of the spinomedullothalamic tract are NuX and NuZ.

The dorsal column nuclei complex

The following review will examine the GrN and the CuN in detail, but we will first introduce the ECuN, BN, and NuX and NuZ, for which, compared to the DCN, there is relatively little information and reported inconsistencies.

External cuneate nuclei

The ECuN lie dorsolateral to the CuN and originate around the level of obex (**Figure 1A, B**). The ECuN receives inputs from deep structures (muscles, tendons, and joints) of the upper body and forelimbs, via the DCs, and is largely composed of second-order cerebellar-projecting neurons. This cuneocerebellar pathway is the primary source of cerebellar inputs from upper-body deep structures

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and is an upper-body equivalent of the DSCT (Paxinos *et al.*, 2012). The ECuN mostly contains neurons with large cell bodies and its border with the rostral CN is often indistinguishable due to the population of large cells common to both nuclei. However, ECuN neural population typically appear more compact and homogenous than the reticulated appearance of rostral CuN (Bermejo *et al.*, 2003). The ECuN shows no evidence of topographic divisions defined by cell morphologies or neuronal response characteristics, but its somatotopic arrangement and projection targets are discussed in later sections.

Bischoff's nucleus

Sometimes a slender group of cell bodies at the brainstem midline is identified between the GrN, named Bischoff's nucleus (BN) (Bischoff, 1899), which receives afferents exclusively from the tail (**Figure 1A, B**). BN has been described in rats (Bermejo *et al.*, 2003), raccoons (Johnson Jr *et al.*, 1968), opossums (Robards, 1979), primates (Chang & Ruch, 1947), and possibly the cat (Kruger *et al.*, 1961), but is not typically considered separate from the GrN. When BN is identified, it is described as originating at the spinomedullary junction and extending rostrally to the caudal border of area postrema, and is separated from the GrN by GrF fibres ventrally and laterally (Johnson Jr *et al.*, 1968; Bermejo *et al.*, 2003).

Large BN are found in some vertebrates that lack hind limbs, such as manatees (Sarko *et al.*, 2007), or that have well-developed prehensile tails, such as pythons (Molenaar, 1976). Sea lions also appear to have a large, clearly separated BN (Sawyer *et al.*, 2016), but like in the spider monkey (Chang & Ruch, 1947) it is not a thin midline structure, as described by Bischoff.

Nuclei X and nuclei Z

Two small nuclei, named nuclei X (NuX) and nuclei Z (NuZ) by Pompeiano and Brodal (1957), are sometimes considered part of the DCN-complex (Mountcastle, 1984; Mantle-St. John & Tracey, 1987). These nuclei do not have a clearly defined functional role but are likely involved in integrating and transmitting hindlimb (NuX also receives forelimb inputs) proprioceptive and cutaneous information to the thalamus and cerebellum. However, these nuclei are not consistently identified, and their inputs and projection targets have not been well characterised.

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NuX comprise small to medium-sized loosely scattered cells found rostral to the ECuN (**Figure 1A, B**) (Brodal & Pompeiano, 1957) in rats (Mantle-St. John & Tracey, 1987; Paxinos & Watson, 1998), cats (Johansson & Silfvenius, 1977b), raccoons (Ostapoff & Johnson, 1988), and nonhuman primates (Albright & Friedenbach, 1982; Pearson & Garfunkel, 1983), but is rarely identified in humans (Kaas, 2004), likely because it is difficult to identify histologically. NuX receive secondary afferents responsive to activation of ipsilateral hindlimb muscles, joints, and skin, which are primarily collaterals of DSCT neurons from the nucleus dorsalis (Landgren & Silfvenius, 1971; Johansson & Silfvenius, 1977b; Low *et al.*, 1986; Mantle-St. John & Tracey, 1987; Ostapoff *et al.*, 1988). In raccoons, NuX also receives some input from forelimb deep afferents that ascend in the dLF (Ostapoff & Johnson, 1988), but it is unclear if these are primary or secondary afferents, or whether the same inputs are found in other species.

NuZ lies rostrolateral to the GrN (**Figure 1A, B**), and has been identified in rats (Low *et al.*, 1986), cats (Landgren & Silfvenius, 1971; Johansson & Silfvenius, 1977a, c; Asif & Edgley, 1992), raccoons (Ostapoff *et al.*, 1988; Ostapoff & Johnson, 1988), nonhuman primates (Albright & Friedenbach, 1982), and humans (Sadjadpour & Brodal, 1968). Like NuX, NuZ receives ipsilateral hindlimb secondary afferents, which are predominantly DSCT collaterals from the dLF and respond to activation of muscles, joints, and skin (Landgren & Silfvenius, 1971; Magherini *et al.*, 1974; Magherini *et al.*, 1975; Johansson & Silfvenius, 1977a, c; Low *et al.*, 1986; Asif & Edgley, 1992). Interestingly, some NuZ afferents appear to have cell bodies in lamina 10 of the dorsal horn (Low *et al.*, 1986), but their function is unknown and they have not been described in other studies. Finally, some fibres that terminate in NuZ travel in the DCs, but whether these are primary or secondary afferents is unconfirmed (Hand, 1966; Johansson & Silfvenius, 1977a, b).

Gracile nuclei

The GrN are groups of cell bodies in the dorsal medulla that primarily receive inputs from the lower limbs and lower trunk. They have elongated, parallel cell arrangements lying either side of the midline

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and originate near the dorsal aspect of the spinomedullary junction. The cross-sectional area of the GrN is largest caudal to obex and tapers rostrally, ending just rostral to obex (**Figure 1A, B**). The GrN are mostly bordered ventrally by the nuclei solitarius, and the CuN laterally (Bermejo *et al.*, 2003; Paxinos *et al.*, 2012). Medially, the two sides of the GrN are separated from each other by a thin layer of GrF fibres and BN, if present (see BN section above; **Figure 1A, B**) (Bermejo *et al.*, 2003). At its rostral extremity the GrN borders NuZ, which is sometimes confused with the rostral portion of the GrN due to the similar appearance and projection targets (Quy *et al.*, 2011).

The GrN were originally thought to be a simple relay for tactile information being transmitted to the thalamus and subsequently the cortex, for conscious perception (Therman, 1941). However, investigations from the past several decades depict the GrN as a heterogeneous cell population that acts as a hub for processing tactile and proprioceptive information and distributing it throughout several different sensorimotor systems (Berkley et al 1986). GrN cells are arranged in distinct populations, with different cell types, population densities, receptive field sizes, response modalities, and projection targets (Gordon & Paine, 1960; Gordon & Seed, 1961; Gordon & Jukes, 1964b, a; Boivie, 1978; Dykes *et al.*, 1982; Berkley *et al.*, 1986; Noriega & Wall, 1991; Qi & Kaas, 2006). The most salient of the population differences has led to the separation of the GrN approximately into thirds along its rostrocaudal extent, named the rostral, middle, and caudal zones (**Figure 1A, B**, **Table 1**).

Rostrocaudal zones

Rostral gracile nuclei

The rostral gracile nuclei (rGrN) (**Figure 1A, B**) have a reticulated appearance, with a mix of large and small cell bodies of various shapes (**Table 1**). In the cat, Dykes *et al.* (1982) found that rGrN cells predominantly respond to stimulation of deep structures, with smaller populations of cells driven by mixed cutaneous and Pacinian-like inputs (**Table 1**). rGrN cells typically have large RFs (Gordon & Paine, 1960; McComas, 1963; Gordon & Jukes, 1964b), consistent with the predominance of deep inputs, or potentially due to primary afferent convergence onto rGrN cells. Rostral GrN RFs are mostly

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on the proximal lower limb and axial lower body regions and the majority are RA (**Table 1**) (Dykes *et al.*, 1982; Luo *et al.*, 2009; Niu *et al.*, 2013).

Middle gracile nuclei

The gracile nuclei middle zone (mGrN) (**Figure 1A, B**) is characterised by dense cell clusters, surrounded by a medial, dorsal, and lateral 'shell' region of reticulated appearance (**Figure 1A**) (Berkley *et al.*, 1986; Bermejo *et al.*, 2003). Cells in the clusters region of the mGrN mostly have small or medium-sized, round cell bodies and small RFs compared to rostral and caudal GrN cells (**Table 1**) (Gordon & Paine, 1960; Gordon & Seed, 1961; McComas, 1963). The RFs of mGrN cluster neurons are predominantly found on distal body parts, particularly the toes, while the surrounding reticulated regions include cells with larger RFs on more proximal body parts. mGrN cells predominantly receive RA cutaneous inputs (Dykes *et al.*, 1982; Luo *et al.*, 2009; Niu *et al.*, 2013).

The mGrN clusters are best visualised using histochemical staining of the mitochondrial enzyme cytochrome oxidase (CO), which shows areas of high metabolic synaptic activity (Mjaatvedt & Wong-Riley, 1988; Wong-Riley, 1989). The clusters are salient in several species of primates (Noriega & Wall, 1991; Strata *et al.*, 2003; Qi & Kaas, 2006), raccoons (Johnson Jr *et al.*, 1968), and are present, but less clear, in cats (Kuypers *et al.*, 1961; Kuypers & Tuerk, 1964; Hand, 1966). In rats, Crockett *et al.* (1996) showed that a GrN middle region was cytoarchitecturally distinct from the rostral and caudal regions, but clear CO clusters were absent. Rather, there is weak evidence of irregular cell clusters, described as 'vertical slabs' in the rostrodorsal region of the GrN, but this pattern was inconsistent across rats (Bermejo *et al.*, 2003). Ventral to the clusters is another reticulated zone that preferentially receives deep afferents, but this region is more apparent in the CuN.

Caudal gracile nuclei

The caudal GrN zone (cGrN) (**Figure 1A, B**) has predominantly medium and large, round cells that do not show obvious clustering, and some multipolar or fusiform neurons scattered throughout (**Table 1**). The cGrN cells hav very large RFs from the entire body with less defined somatotopy, compared to

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mGrN, and the largest proportion of Pacinian-like cell responses of the three rostrocaudal zones (Dykes *et al.*, 1982).

Cuneate nuclei

The CuN lie lateral to the GrN on either side of the brainstem and contain heterogeneous cell groups that receive afferent input from the upper limbs and trunk. The CuN originate at the spinomedullary junction where they are separated from the GrN dorsomedially by CuF fibres (**Figure 1A, B**). Rostrally, the CuN and the GrN meet as the gracile and cuneate fascicular fibres become sparser just caudal to obex. At the level of area postrema the CuN are bordered by the nucleus solitarius complex ventromedially, the ECuN dorsolaterally, and the spinal trigeminal nuclei ventrolaterally (Paxinos & Watson, 1998; Bermejo *et al.*, 2003). The most rostral portion of the CuN is displaced slightly more laterally compared to the middle region and ends at a juncture with NuX and NuZ, and the ECuN (**Figure 1A, B**).

Early investigations in the cat and rat, determined that these nuclei have only two divisions with different cytoarchitecture in the rostral and caudal zones (Kuypers & Tuerk, 1964; Keller & Hand, 1970; Basbaum & Hand, 1973), afferent inputs (Keller & Hand, 1970), and top-down cortical inputs (Kuypers & Tuerk, 1964). However, these rostrocaudal divisions were revised to a tripartite arrangement including rostral, middle, and caudal zones, analogous to their GrN counterparts, in macaques (Biedenbach, 1972), cats (Cheema *et al.*, 1983; Berkley *et al.*, 1986), raccoons (Rasmusson, 1988), and rats (Maslany *et al.*, 1991; Maslany *et al.*, 1992).

Rostrocaudal zones

Rostral cuneate nuclei

The rostral cuneate nuclei (rCuN) (**Figure 1A, B**) division is characterised by a reticulated arrangement of large cell bodies and many small cell bodies, grouped throughout bundles of the CuF, which mostly have large RFs on the proximal and axial upper body (Cheema *et al.*, 1983; Bermejo *et al.*, 2003). The rostral border of rCuN meets NuX and NuZ and intermingles with ECuN dorsolaterally (**Figure 1A, B**). It can be difficult to observe a clear separation between the rCuN and ECuN, as both contain similar

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populations of large cell bodies (Bermejo *et al.*, 2003) and primarily respond to stimulation of deep structures (**Table 1**) (Dykes *et al.*, 1982; Cheema *et al.*, 1983). However, the rCuN receive more cutaneous afferents than the ECuN and almost exclusively display SA characteristics.

Middle cuneate nuclei

The middle cuneate nuclei (mCuN) are the largest and densest CuN zones (Heino & Westman, 1991; Bermejo *et al.*, 2003). The mCuN are predominantly made up of medium and small cells, with a higher proportion of medium-sized neurons compared to caudal and rostral CuN zones (**Table 1**) (Cheema *et al.*, 1983). The mCuN can be subdivided into three zones – the shell, the clusters, and the ventral zone – which are summarized for rats, cats, raccoons, and macaques in the **Figure 1C**.

Like the mGrN, the mCuN cluster zone has dense, roughly ovoid, groups of cell bodies, separated by cell-poor CuF fibre septa, best visualised by their CO activity (Florence *et al.*, 1989; Crockett *et al.*, 1993). Dense somatotopically organised cutaneous afferent terminals primarily from the distal forelimbs target these clusters. Cluster neurons are characterised by having the smallest RFs relative to rostral and caudal CuN, and are specialised for processing and transmitting precise discriminative touch information (**Table 1**) (Cheema *et al.*, 1983; Li *et al.*, 2012). All four species have a mCuN cluster region (**Figure 1C**) (Johnson Jr *et al.*, 1968; Cheema *et al.*, 1983; Florence *et al.*, 1989; Maslany *et al.*, 1991; Maslany *et al.*, 1992; Crockett *et al.*, 1993; Crockett *et al.*, 1996; Li *et al.*, 2012), but it is often called the *pars rotunda* in primates (Ferraro & Barrera, 1935).

The mCuN shell region has dense fields of non-clustered cell bodies displaying high CO activity, which is common to all four species (**Figure 1C**) (Li *et al.*, 2012). Typically, afferents from proximal upper body regions terminate in the mCuN shell, and cells in this region have larger RFs and respond to a mixture of tactile and proprioceptive stimuli.

Interestingly, the cat ventral mCuN shows dense unclustered CO labelling and receives inputs from primary afferents that innervate both deep and cutaneous structures of the proximal and axial upper body, but is dominated by responses to proprioceptive stimuli (**Table 1**) (**Figure 1C**) (Rosen, 1969;

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Millar & Basbaum, 1975; Dykes *et al.*, 1982; Nyberg & Blomqvist, 1982; Cheema *et al.*, 1983; Nyberg & Blomqvist, 1984; Jasmin *et al.*, 1985). In primates, a ventral and lateral region of mCuN named the pars triangularis (Ferraro & Barrera, 1935) exhibits the same characteristics as the cat ventral mCuN (**Figure 1C**) (Hummelsheim & Wiesendanger, 1985; Hummelsheim *et al.*, 1985). In raccoons a so-called "tongue" or "bridge" region at the ventrolateral portion of mCuN forms a bridge of cells with the ECuN (**Figure 1C**). The bridge region receives muscle afferent terminals and contains cells responsive to muscle stretch from the proximal and axial upper body (Johnson Jr *et al.*, 1968). The similarities of the pars triangularis, the bridge region, and the ventral zone suggest that they are homologous structures and, here, we consider them the same functional region referred to as ventral CuN. Finally, a recent report in rats reported that they did not find any proprioceptive responses in the ventral CuN (Li *et al.*, 2012), and it is unclear if they have an analogous ventral zone.

Caudal cuneate nuclei

The cCuN has a reticulated appearance, predominated by neurons with small cell bodies, but there is also a mixed population of medium and large neurons, which are mostly found in the dorsal portion (**Table 1**) (Cheema *et al.*, 1983). Primary afferent fibre terminals are less discretely arranged in cCuN compared to mCuN (Florence *et al.*, 1989; Maslany *et al.*, 1992). cCuN neurons have large RFs and respond with a mix of RA and SA characteristics from skin, muscles, and joints of the digits, arm, and upper trunk (Dykes *et al.*, 1982; Cheema *et al.*, 1983). Compared to middle and rostral CuN zones, a relatively large proportion of cells in the caudal zone show Pacinian-like responses. Like mCuN, cCuN appears to have a ventral region with a larger proportion of cells responding to passive movement of the elbow and shoulder joints, and respond almost exclusively with SA characteristics (**Table 1**) (**Figure 1**) (Dykes *et al.*, 1982; Cheema *et al.*, 1983).

In summary, the DCN have clear morphological and modality-based segregation in three rostrocaudal zones, as well as cross-sectional segregation, particularly in the middle region. The clusters receive almost exclusively cutaneous afferents from the distal limbs and are specialised for precise discriminative touch. The shell, rostral, and caudal DCN have mixed cell populations, RFs on more

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proximal and axial body regions, and appear to receive afferent types of all modalities. The ventral regions extend the rostrocaudal length of the DCN and predominantly receive deep inputs. Finally, the caudal zones excluding the ventral portion appear to have the largest proportion of Pacinian-like responses of the three zones. The GrN and CuN rostrocaudal zones have similar attributes but, notable differences are the preponderance of RA afferents terminating in the GrN, and the more defined clusters, shell, and ventral regions of the CuN (**Table 1**) (**Figure 1**).

Dorsal column nuclei somatotopy

The DCN were first shown to be somatotopically organised by Kruger *et al.* (1961) by electrophysiologically mapping the peripheral RFs of DCN neurons in cats. Using a variety of electrophysiological and labelling methods a stereotyped map was confirmed by others, with a mediolateral progression of tail, foot, lower leg, and upper leg representation in the GrN, followed by the ulnar forelimb, digits and hand/forepaw, radial forelimb, shoulder, and neck in the CuN (**Figure 2**). DCN somatotopy is present throughout the rostrocaudal zones, but is best defined in the middle regions, and poorly defined in the rostral and caudal zones. The stereotyped map has been demonstrated in several mammalian species including cats (Millar & Basbaum, 1975; Dykes *et al.*, 1982; Nyberg & Blomqvist, 1982; Jasmin *et al.*, 1985; Nyberg, 1988), rats (Nord, 1967; Maslany *et al.*, 1991; Li *et al.*, 2012), sheep (Woudenberg, 1970), raccoons (Johnson Jr *et al.*, 1968; Rasmusson, 1988, 1989), squirrels (Ostapoff *et al.*, 1983), opossums (Hamilton & Johnson, 1973), and non-human primates (Florence *et al.*, 1988; Culberson & Brushart, 1989; Florence *et al.*, 1989, 1991; Xu & Wall, 1996, 1999; Strata *et al.*, 2003; Qi & Kaas, 2006). Most of the lower and upper trunk representation lies in a transition zone between the GrN and the CuN (**Figure 2**). The neck, ear, and posterior head are represented most laterally in the CuN (Johnson Jr *et al.*, 1968; Millar & Basbaum, 1975; Li *et al.*, 2012), in a transition zone between the CuN and the face representation in the spinal trigeminal nuclei. While the stereotyped map holds true in most cases, there are some crucial differences among species, particularly related to the orientation of the hind and forelimb digits, which are discussed in the following paragraphs.

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Gracile nuclei

Although the somatotopic arrangement of the GrN is relatively consistent across species, the organisation of the hind paw/foot is variable. In the rat, cat, and raccoon toes 1-5 (T1-T5) are arranged in a lateral to medial line near the dorsal surface of the GrN (**Figure 2**) (Kruger *et al.*, 1961; Nord, 1967). The footpads are represented dorsally, with the toes and the dorsal surface of the foot represented in progressively more ventral zones (**Figure 2**) (Johnson Jr *et al.*, 1968; Millar & Basbaum, 1975; Maslany *et al.*, 1991). However, the toes of non-human primates including galagos, owl monkeys, squirrel monkeys, and macaques are represented in the medial region of the GrN, in a crescent shape with T5 dorsolateral relative to the other toes and T1 ventromedial (**Figure 2**) (Strata *et al.*, 2003; Qi & Kaas, 2006). Even among these primate species there is moderate variability in foot representation (see Qi and Kaas (2006)).

In the mCuN clusters, different body regions are represented in specific CO-dense clusters (Nyberg, 1988; Rasmusson, 1988; Florence *et al.*, 1989, 1991; Noriega & Wall, 1991; Crockett *et al.*, 1993; Xu & Wall, 1996, 1999). However, in the GrN, sometimes more than one toe or other body region is represented in the same cluster, and afferents from specific body regions may terminate in several CO-dense clusters along the rostrocaudal extent of the GrN (Strata *et al.*, 2003; Qi & Kaas, 2006).

Interestingly, in one rat study the lateral to medial arrangement of T1 andT4 was shown to completely reverse several times throughout the rostral caudal axis in the same rat, such that at some levels, T1 was most medial and T4 (and presumably T5) was most lateral (Maslany *et al.*, 1991). Although this phenomenon has not been shown in other studies, asymmetry in rat electrophysiological GrN surface recordings (Loutit *et al.*, 2017; Loutit *et al.*, 2019), and variability in cat hindlimb projection maps have also been reported (Millar and Basbaum, 1975).

Cuneate nuclei

The glabrous skin of the forepaw/hand digits were initially reported to be represented at the dorsal surface of the CuN in cats (Kruger *et al.*, 1961), and rats (Nord, 1967). Later electrophysiology and labelling studies mostly confirmed this in cats, showing the digit pads represented almost linearly with

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digits 1-4 (D1-D4) lateral to medial and the palmar pad dorsal to the digit representation (**Figure 2**) (Millar & Basbaum, 1975; Nyberg & Blomqvist, 1982; Nyberg, 1988). The original rat somatotopic map proposed by Nord (1967) resembles that shown in the cat, but has been updated by more accurate electrophysiological mapping combined with horseradish peroxidase and CO labelling. The newer maps show D1-D5 representation rotated about 90 degrees ventral and lateral from Nord's map, in a crescent shape with the convex side facing dorsolaterally (**Figure 2**) (Maslany *et al.*, 1991; Li *et al.*, 2012). The palmar pads are represented medial to the digits, while the dorsal forepaw is represented at the dorsal border of the CuN, which is similar to that shown in raccoons (**Figure 2**) (Johnson Jr *et al.*, 1968; Rasmusson, 1988), and opossums (Hamilton & Johnson, 1973). In non-human primates including galagos, marmosets, and squirrel monkeys, digit representation is dorsal and lateral to the palmar pads (Florence *et al.*, 1991; Xu & Wall, 1996; Strata *et al.*, 2003), resembling that of the rat and raccoon. However, representation of the hand in macaques appears to be turned upside-down relative to the abovementioned species with the digits represented ventromedially to the palmar and dorsal hand (**Figure 2**) (Culberson & Brushart, 1989; Florence *et al.*, 1989). The functional significance of the different hand representation in macaques is unclear, but it appears that a similar arrangement is also likely in humans (Florence *et al.*, 1989). Potentially, this flipped macaque arrangement positions the digit representation closer to ventral mCuN which receives a preponderance of descending cortical inputs and ascending deep afferent inputs, which may enhance tactile discrimination and/or grasping abilities. Further investigation is needed to explore these possibilities.

Interestingly, the crescent-shaped digit representation appears to correlate with animals that exhibit grasping behaviours e.g. monkeys, rats, and raccoons (**Figure 2**). The raccoon is a particularly interesting example, as it is phylogenetically closer to cats and sheep, but its crescent mCuN digit representation is more like grasping animals than its genetic neighbours.

External cuneate nuclei

The ECuN have a somatotopic map of deep structures from the forelimbs and upper body, but comparatively little is known about this map. Early macaque and cat degeneration studies found ECuN

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afferents terminating in a topographic arrangement, with afferents entering the spinal cord in upper cervical segments terminating in caudal and ventral ECuN, and afferents from successively lower spinal segments terminating progressively more rostral and dorsal (Ferraro & Barrera, 1935; Liu, 1956). Later, more precise electrophysiological mapping and afferent tracing studies of the ECuN demonstrated a so-called 'musculotopic' map, with individual muscles, or functionally related muscle groups, represented topographically in rats, cats, and raccoons (Johnson Jr *et al.*, 1968; Rosen, 1969; Campbell *et al.*, 1974; Dykes *et al.*, 1982; Nyberg & Blomqvist, 1984; Bakker *et al.*, 1985; Jasmin *et al.*, 1985; Abrahams & Swett, 1986). The muscles of the distal forelimb are represented medially and ventrally in the ECuN, and proximal forelimb and axial muscles represented progressively lateral and dorsal. In the lateral portion, the neck is represented ventral to the shoulder and upper trunk. This arrangement was also found to be displaced along the rostro caudal axis of the ECuN, with neck muscle afferents represented in the rostro lateral ECuN, the proximal arm and shoulder muscles caudal, and the forearm and forepaw muscles more caudally still (Johnson Jr *et al.*, 1968; Campbell *et al.*, 1974; Nyberg & Blomqvist, 1984; Jasmin *et al.*, 1985). Interestingly, to our knowledge a detailed musculotopic map has not been described in primates.

Generally, ECuN cells with distinct functional roles are intermingled, such that afferent terminal distributions of flexor and extensor muscles of the arm appear to overlap (Jasmin *et al.*, 1985), but individual ECuN cells only respond to a single muscle or a group of agonistic muscles (Campbell *et al.*, 1974). However, the proximity of cells responding to antagonistic muscles seems well suited to facilitate communication between these groups. Therefore, ECuN cells could potentially influence their antagonistic muscle counterparts, situated nearby within the ECuN, or some other intermediate processing mechanism.

Dorsal column nuclei projection targets and connections

The DCN have a complex and diverse population of projection targets throughout the brain and spinal cord. This suggests that these nuclei act not as simple relays, but as processing and distribution hubs

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for ascending somatosensory information. Berkley *et al.* (1986) produced an excellent review of the DCN projection targets and separated them into three broad systems: a cortical system, a cerebellar system, and a spinal cord system. In this review, we will adopt these categorisations as a framework to discuss the interconnectedness of the DCN below.

The cortical system

Ascending somatosensory information from the DCN-complex reaches somatosensory primary and unimodal cortical regions via the thalamus. These cortical destinations include Brodmann's areas 3b (also known as the primary somatosensory cortex (S1)), 3a, 1, and 2 in the anterior parietal cortex and somatosensory association areas including the secondary somatosensory cortex (S2) and the parietal ventral area (PV) (also referred to as the fourth somatosensory cortex (S4) in some species). Areas 3a and 3b primarily, but not exclusively, receive proprioceptive and cutaneous information, respectively, and each contain a separate somatotopic map of the entire body. Areas 1 and 2 have larger RFs and complex response properties.

The cortical system proposed by Berkley *et al.* (1986) includes three subsystems with different DCN-complex neural populations, separated by their thalamic intermediate targets and subsequent cortical targets (**Figure 3**). The first and most commonly described cortical subsystem is the pathway for discriminative touch information through the ventroposterior lateral nucleus (VPL) of the thalamus. The second subsystem conveys proprioceptive information through a region along the border of VPL and ventrolateral nucleus (VL) of the thalamus. The third subsystem conveys multimodal information from the DCN-complex to the posterior group (PO) of the thalamus.

Reports vary as to the proportion of DCN-complex neurons that project to the thalamus, but they appear to make up the largest proportion of DCN-complex neurons (Gordon & Seed, 1961; Blomqvist, 1980; Ellis Jr & Rustioni, 1981; Rustioni *et al.*, 1984; Kemplay & Webster, 1989; Bermejo *et al.*, 2003). DCN neurons included in the cortical system are, therefore, considered the dominant DCN population.

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Cortical subsystem 1

The first cortical subsystem involves the well-known dorsal column-medial lemniscus system. The subsystem comprises mostly medium-sized round DCN cells of the clusters region, and a small proportion from rostral and caudal DCN, that project through the medial lemniscus (ML) to the contralateral VPL of the thalamus (**Figure 3**). The DCN-VPL projections terminate somatotopically with the opposite medial-lateral (due to the fibres crossing the midline) and dorsal-ventral (upside-down) orientation of the DCN somatotopic map. Therefore, GrN projections terminate rostral and lateral to CuN projections, and distal body parts are represented ventrally, with more proximal body parts dorsally (Schroeder & Jane, 1971; Feldman & Kruger, 1980; Massopust *et al.*, 1985; Villanueva *et al.*, 1998). The VPL is sometimes referred to as part of the "core" region of the thalamic ventroposterior nucleus (the ventroposterior medial nucleus is also included) and has discrete clusters separated by cell-poor septa (Qi *et al.*, 2011), analogous to the DCN clusters region.

The DCN-VPL projection is commonly thought to be exclusively contralateral, but, interestingly, Wree *et al.* (2005) found a moderate (5%) population of DCN cells that project to the ipsilateral VPL in rats. Ipsilateral-projecting neurons are found throughout the GrN, and in rCuN and mCuN, but are almost completely absent from cCuN (**Figure 3**). The authors did not speculate on the functional significance of this ipsilateral population and we do not know whether it is present in other species besides rats.

Congruent with the role of the DCN clusters and thalamic VPL regions in processing and transmitting discriminative touch information, neurons in VPL project heavily onto cortical areas 3b and 1, but also onto areas 3a and 2 (**Figure 3**).

Cortical subsystem 2

The second cortical subsystem comprises neurons conveying proprioceptive information, with cell bodies in NuZ and NuX, ventral CuN, and the ECuN (**Figure 3**). These neurons project via the ML to a proprioceptive region of the contralateral thalamus, which has been referred to by many names (see Berkley (1983) and Padberg *et al.* (2009) for discussion). The borders of the region are difficult to ascertain and vary between species, but in the cat, Berkley *et al.* (1986) referred to it as the border of

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VPL and the anterior thalamic motor nuclei. This region forms a shell around the anterior border of VPL, so we will refer to it as the VPL shell region, like Jones and Friedman (1982). The lack of evidence for GrN projections to the VPL shell may be because the GrN appears to receive few deep inputs (**Table 1; Figure 1,3**) (Whitsel *et al.*, 1969; Whitsel *et al.*, 1970; Dykes *et al.*, 1982; Niu *et al.*, 2013). Instead, DSCT axon collaterals and the spinomedullothalamic tract project to NuX and NuZ, which appears to be the main route by which lower body proprioceptive-related information reaches the VPL shell.

Projections from the ECuN to the VPL shell are present in rats (Mantle-St. John & Tracey, 1987), raccoons (Ostapoff *et al.*, 1988), and monkeys (Boivie & Boman, 1981; Pearson & Garfunkel, 1983), but not cats (Rosen, 1969; Berkley *et al.*, 1986). Like the somatotopic arrangement of the mCuN clusters (see Dorsal column nuclei somatotopy, cuneate nuclei section), the ECuN-thalamic projections in rats, raccoons, and monkeys, but not cats, further supports the notion that the DCN are functionally organised for dexterous limb and digit control in these animals, as noted by Ostapoff *et al.* (1988). Raccoons are more phylogenetically similar to cats than to rats or monkeys, yet cats lack ECuN-thalamic connections, and have different somatotopic DCN organisation, which correlate to their lack of forepaw dexterity.

Like DCN-VPL connections, afferents conveying upper body information from the ECuN and ventral CuN neurons project to the medial portion of the VPL shell, while afferents conveying lower body information from NuZ and NuX neurons project to the lateral portion, showing some somatotopic organisation (Grant *et al.*, 1973; Johansson & Silfvenius, 1977b; Pearson & Garfunkel, 1983; Berkley *et al.*, 1986; Mantle-St. John & Tracey, 1987; Ostapoff *et al.*, 1988; Ostapoff & Johnson, 1988). Each of these DCN-complex regions are known to carry information related to proprioception, which is congruent with VPL shell neurons responding to proprioception-related stimuli. The primary target of VPL shell neurons is area 3a, but some projections also terminate in areas 2 and 3b (Clemo & Stein, 1983; McHaffie *et al.*, 1988; Padberg *et al.*, 2009). The role of this cortical subsystem is to convey proprioceptive information from the entire body to the somatosensory cortex.

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Cortical Subsystem 3

The third proposed group within the cortical system is a population of DCN-complex neurons that project to the contralateral posterior group (PO) of the thalamus via the ML (**Figure 3**). The PO contains a complete somatotopic representation of the contralateral body surface, albeit with large RFs, and appears to play a role in processing both nociceptive and innocuous touch information (Guilbaud *et al.*, 1977; Brinkhus *et al.*, 1979; Diamond *et al.*, 1992). Direct DCN-PO projections derive from a small population of neurons scattered throughout the DCN (Lund & Webster, 1967; Hand & Van Winkle, 1977; Berkley, 1980; Feldman & Kruger, 1980; Itoh *et al.*, 1984; Berkley *et al.*, 1986). Inputs from the DCN are mostly found in dorsal PO with GrN neurons terminating lateral and rostral compared to CuN terminals (Berkley, 1980; Villanueva *et al.*, 1998).

A possible indirect DCN-PO pathway via the intercollicular region of the tectum (InC) has also been suggested (Itoh *et al.*, 1984; Berkley *et al.*, 1986). There is a dense, roughly somatotopic connection between DCN neurons (excluding the cluster zone) and the InC (RoBards *et al.*, 1976; Schroeder & Jane, 1976; Björkeland & Boivie, 1984; Wiberg & Blomqvist, 1984a; Wiberg *et al.*, 1987). Neurons in a region of the InC that roughly overlaps with terminals from DCN neurons send projections to the lateral division of PO (Itoh *et al.*, 1984). These projections are bilateral, but numbers of ipsilateral connections far outweigh contralateral ones. Direct DCN-PO terminations are denser in medial PO, while the possible indirect terminations are focused in lateral PO (Hand & Van Winkle, 1977; Berkley, 1980).

The function of either the direct or indirect DCN-PO pathways is not clear. The PO projects to cortical areas 1, 2, 3b, S2, and PV (**Figure 3**) (Burton & Jones, 1976; Naito & Kawamura, 1982; Roda & Reinoso-Suárez, 1983; Stein *et al.*, 1983; Padberg *et al.*, 2009), which suggests a role beyond precise discriminative touch. Both the PO and the InC also receive dense reciprocal inputs from the PV (McHaffie *et al.*, 1988). Top-down inputs from PV to the superior colliculus (SC) are essential for development and function of multisensory integration in the SC (McHaffie *et al.*, 1988; Stein *et al.*, 2014), so perhaps the top-down PV-InC and/or PV-PO connections serve a similar function.

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The nucleus reuniens

Villanueva et al (1998) found a group of neurons in the CuN that project bilaterally to the nucleus reuniens (NR) of the rat thalamus. We have not included this DCN-thalamic connection as a major pathway, as this appears to be the only example of these projections. However, such a connection has interesting functional implications. The NR is found at the ventral midline of the thalamus, above the third ventricle, and is the largest of the midline thalamic nuclei (Griffin, 2015). The DCN-NR projections terminate mostly in the dorsal NR, which is an area that predominantly projects to CA1 of the hippocampus (Dolleman-van Der Weel & Witter, 1996). It is not clear whether the CuN projections terminate directly onto cells that project to the NR, but their colocalization may indicate a pathway for information from the DCN to access the limbic system. The NR interactions with the hippocampus form a reciprocal network with the medial prefrontal cortex and contribute to spatial working memory (Griffin, 2015) and contextual memories for discriminating dangerous and safe contexts (Ramanathan *et al.*, 2018). The CuN-NR connection might convey somatosensory information to this network, which is used for spatial working memory.

Cortical inputs

In addition to the diverse ascending projections of the DCN, they also receive descending input from the sensorimotor cortex. Cortical-DCN axons are collaterals from both corticospinal and corticobulbar neurons that travel in the pyramidal tract and originate in cortical layer V (**Figure 4**) (Rustioni & Hayes, 1981; Martinez *et al.*, 1995). The corticofugal projections are functionally matched, such that motor (primary motor cortex (M1); area 4) and proprioceptive (area 3a) cortical regions send most projections to the proprioceptive-related region in the ventral DCN (Kuypers, 1958; Kuypers *et al.*, 1961; Gordon & Jukes, 1964a; Kuypers & Tuerk, 1964; Cheema *et al.*, 1983; Cheema *et al.*, 1985). Similarly, discriminative touch-related cortical and DCN regions are reciprocally connected, as area 3b sends projections primarily to the DCN cluster regions (Kuypers, 1958; Kuypers *et al.*, 1961; Gordon & Jukes, 1964a; Kuypers & Tuerk, 1964; Cheema *et al.*, 1983; Cheema *et al.*, 1985). Cortical areas 1 and 2 also project primarily onto rostral DCN, but also to the CuN shell, and sparsely to the cluster regions (Cheema *et al.*, 1985; Bentivoglio & Rustioni, 1986). Like ascending afferents, cortical-DCN inputs are

somatotopically organised, such that neurons representing a body region in the cortex project to neurons representing the same body region in the CuN (Cheema *et al.*, 1983; Cheema *et al.*, 1985).

Cortical inputs to the DCN are primarily excitatory, mediated by glutamate, but can also have inhibitory effects via DCN inhibitory interneurons (Aguilar *et al.*, 2003). When a group of DCN cells are activated by peripheral stimuli, the group of cells with overlapping RFs are also excited by corticofugal inputs to amplify the signal. Surrounding cells with non-overlapping RFs are simultaneously inhibited, thus disinhibiting any lateral inhibition caused by neighbouring afferents and potentially reducing the RF size of the sensory input (Aguilar *et al.*, 2003). Cortical-DCN connections appear to play a role in modulation of activity during movement and in enhancing ascending tactile information. For a review of the corticofugal connections, proposed neuronal circuitry, and neurophysiology see Mariño *et al.* (1999).

The cerebellar system

Berkley *et al.* (1986) named a second DCN system *the cerebellar system*. This system includes a diverse array of projection targets and interconnected regions including the tectum, pretectum, inferior olive, pontine grey, red nucleus and zona incerta, in addition to direct connections to the cerebellum. Generally, the DCN-complex neurons involved in the cerebellar system are varied in morphology and primarily found in the ECuN, DCN areas outside the clusters regions, and NuX, and only sparsely, if at all from the cluster regions.

Cerebellum

Somatosensory regions of the cerebellum are somatotopically arranged. There are two body maps – one predominantly in the anterior lobes and the other in the posterior lobes – with axial body regions represented medially in the vermis, and distal body parts represented more laterally in the paravermal region.

The most direct route by which the cerebellum receives information from peripheral afferents is via the ECuN (for the upper limb) and lamina VI and VII of the spinal cord (lower limb) via the DSCT and

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ventral spinocerebellar tract (VSCT). Both these ascending spinocerebellar tracts carry proprioceptive fibres that travel via the inferior (DSCT) or superior (VSCT) cerebellar peduncle to terminate in the ipsilateral cerebellum. Interestingly, the VSCT axons cross twice; once near the spinal level of entry, then they re-cross in the medulla. Although the DSCT send some collaterals from hindlimb afferents to NuX and NuZ, both the DSCT and VSCT predominantly bypass the DCN-complex altogether, so will not be covered in the remainder of this section. The cerebellum also receives inputs via a less direct route from other DCN-complex regions for the upper (CuN and NuX) and lower limbs (GrN, NuX and NuZ).

External cuneate nuclei

The ECuN-cerebellar pathway is the dominant group of projections from the DCN-complex to the cerebellum. Cerebellar projecting cells in the ECuN are relatively large and homogenous and convey forelimb proprioceptive information to the somatosensory cerebellum via mossy fibres input (**Figure 5**) (Quy *et al.*, 2011).

Caudal ECuN neurons that respond to hand and arm movement project to the caudal aspect of lobule V and the rostral paramedian lobule, whereas rostral ECuN neurons, which have a higher proportion of neurons responding to neck and should movement, project to rostral lobule V and the caudal paramedian lobule (Rinvik & Walberg, 1975; Quy *et al.*, 2011). ECuN projections have also been reported to other lobules IV, VI, and IX (Somana & Walberg, 1980). Besides the abundance of ipsilateral projections, a smaller number of ventral and lateral ECuN cells – regions that typically respond to movement of axial body regions (Campbell *et al.*, 1974) – project to the contralateral anterior lobe vermis, likely through the restiform body, and crossing the midline in the cerebellar white matter (Haring & Rowinski, 1982; Gerrits *et al.*, 1985). These contralateral projections to the axial body representation in the vermis correspond to the projections from ECuN neurons that respond to axial muscles just to either side of the midline.

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Cuneate nuclei

The cerebellum is also the target of ipsilateral CuN projections (**Figure 5**) (Cooke *et al.*, 1971a; Cooke *et al.*, 1971b; Cerminara *et al.*, 2003; Quy *et al.*, 2011). CuN-cerebellar neurons are found almost exclusively in rCuN, with some in the mCuN shell (Haring & Rowinski, 1982), and are typically much smaller than thalamic projecting CuN neurons (Cheek *et al.*, 1975; Rinvik & Walberg, 1975; Somana & Walberg, 1980; Mantle-St. John & Tracey, 1987). These neurons have large RFs, are almost all RA, and receive inputs from deep and cutaneous afferents (Cooke *et al.*, 1971a; Cooke *et al.*, 1971b; Cerminara *et al.*, 2003).

In the cat, the DCN-complex inputs are segregated in the cerebellum by their modalities, such that cutaneous and proprioceptive fibres project to superficial and deeper portions of the folia, respectively (Cooke *et al.*, 1971b; Ekerot & Larson, 1972; Rinvik & Walberg, 1975; Cerminara *et al.*, 2003). However, proprioceptive and cutaneous inputs from CuN and ECuN were found to be overlapping in the cerebellum of raccoons, suggesting that these animals do not have the same discrete modality segregation within folia (Haring & Rowinski, 1982). It is unclear whether modality segregation in the cerebellar folia is a feature of other mammals.

The rCuN-cerebellar neurons send axons that pass by the ECuN and through the restiform body, and mostly terminate in the ipsilateral lobule IV, V, VI, VIIIA, and the paramedian lobule, which corresponds to the cerebellar regions that are also the target of ECuN terminals (Gordon & Horrobin, 1967; Cooke *et al.*, 1971b; Cheek *et al.*, 1975; Rinvik & Walberg, 1975; Somana & Walberg, 1980). Based on electrophysiological responses, Cooke *et al.* (1971b) noted that rCuN-cerebellar neurons appear to bifurcate and project to both forelimb cerebellar body schemas in lobule V and the paramedian cerebellar lobes, which is corroborated by some weak anatomical evidence (Cheek *et al.*, 1975; Haring & Rowinski, 1982). However, a double-labelling study is needed to confirm these results, and it is unclear what their function might be. Like the ECuN, the CuN send some contralateral projections to the anterior lobe of the cerebellum, which travel via the ipsilateral restiform body and cross the midline through the cerebellar white matter (Cheek *et al.*, 1975; Haring & Rowinski, 1982).

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Gracile nuclei

Compared to the ECuN and CuN, the GrN have few projections to the cerebellum (Somana & Walberg, 1980; Quy *et al.*, 2011). The paucity of GrN-cerebellar connections is likely because most cells from the lower body, conveying information to the cerebellum, travel via second order DSCT or VSCT neurons originating in the nucleus dorsalis and dorsal horn lamina VII, respectively (Ito & Itō, 1984; Quy *et al.*, 2011). The GrN-cerebellar projections are ipsilateral and, like the CuN, originate predominantly from rGrN, with some cells projecting from the shell and ventral aspects of mGrN (**Figure 5**) (Cheek *et al.*, 1975; Rinvik & Walberg, 1975; Somana & Walberg, 1980; Quy *et al.*, 2011). These cells project to the vermal and paravermal parts of anterior lobules I, II, IV and V (Gordon & Horrobin, 1967; Cheek *et al.*, 1975; Rinvik & Walberg, 1975).

DCN-complex dual cerebellar-thalamic projections

Authors of some early electrophysiology and degeneration studies tentatively suggested that there might be DCN-complex neurons that send dual projections to both the thalamus and cerebellum (Gordon & Seed, 1961; Johnson Jr *et al.*, 1968). This was refuted, however, by several electrophysiological studies that were unable to activate DCN-complex neurons from both thalamic and cerebellar stimulation (Gordon & Horrobin, 1967; Cooke *et al.*, 1971a; Cooke *et al.*, 1971b; Haring *et al.*, 1984). A comprehensive double-labelling study in rats subsequently confirmed that DCN-complex neurons project either exclusively to thalamus or cerebellum, but not both (Mantle-St. John & Tracey, 1987). This suggests that the somatosensory information requirements for processing in thalamic and cerebellar systems are different.

Inferior olive

The inferior olives (IO) provide an error signal that the cerebellum can use to reduce mismatches between sensory input matching the body's current status, and a target movement. They can be separated into the principle olive, medial accessory olive, and the dorsal accessory olive (DAO). The rostral portion of the dorsal accessory olive (rDAO) receives inputs from the DCN and sends projections to the intermediate anterior lobe and paramedian lobule of the cerebellum (Armstrong *et al.*, 1974; Brodal *et al.*, 1975; Groenewegen *et al.*, 1975; Bloedel & Courville, 1981; Molinari, 1984).

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The rDAO receives projections from two distinct populations within the CuN: one from rCuN and another from cCuN (**Figure 5**) (McCurdy *et al.*, 1992; McCurdy *et al.*, 1998). These cells tend to form clusters, but are not part of the DCN clusters zone (Molinari *et al.*, 1996). The cCuN population forms a contiguous nucleus with cells in lamina VI of the dorsal horn of C1 and C2 to form a spinal-cCuN column. Cells in the spinal-cCuN column send the densest input to IO, projecting contralaterally to the rDAO via internal arcuate fibres (Ebbesson, 1968; Molinari *et al.*, 1996; McCurdy *et al.*, 1998). The DCN-IO input regions are somatotopically organised such that the medial border of the rDAO has cutaneous RFs from the distal forelimb and receives most of its input via the caudal part of the spinal-cCuN input column (Berkley & Hand, 1978a; Molinari *et al.*, 1996). The densest input to the trunk and shoulder region of rDAO comes from the rostral portion of the spinal-cCuN column (McCurdy *et al.*, 1998). The transitional forelimb region of rDAO, inclusive of the paw/hand, wrist and upper forelimb, receives roughly equal input from the whole spinal-cCuN column.

Interestingly, rDAO projecting cells in rCuN appear to be quite different to those of the spinal-cCuN column. The rCuN group projects bilaterally to the rDAO forelimb and trunk regions (Gerrits *et al.*, 1985; Alonso *et al.*, 1986; McCurdy *et al.*, 1998). However, rDAO neurons are only activated by contralateral stimuli, so given that the rCuN population project bilaterally to rDAO it seems unlikely that they provide the main excitatory drive to rDAO, but serve some other role (McCurdy *et al.*, 1998).

The DCN also send projections to the caudal half of the contralateral medial accessory olive and caudal DAO. Both regions project to the cerebellar vermis (Brodal & Brodal, 1981; Azizi & Woodward, 1987). These neurons are found in the DCN shell regions and rostra and caudal DCN, and their project patterns appear to be more variable than those to the rDAO (Boesten & Voogd, 1975; Berkley & Hand, 1978a; Molinari, 1984; Gerrits *et al.*, 1985; McCurdy *et al.*, 1998).

Red nucleus

The red nucleus (RN) receives motor system inputs from the cortex and cerebellum and is involved in motor control and potentially motor learning. The DCN project roughly somatotopically onto the contralateral magnocellular region of the red nucleus (RNmag) (**Figure 5**) (Robinson *et al.*, 1987). GrN

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cells project to the ventral lateral RNmag, while CuN cells project to the dorsal medial RNmag (Berkley & Hand, 1978b). The densest DCN-RNmag projections arise from the ventral caudal DCN (Robinson *et al.*, 1987).

The DCN also receive a small amount of reciprocal input from the contralateral RN, which appear to come from large cells in the RNmag, which give rise to the rubrospinal tract (Edwards, 1972; Berkley *et al.*, 1986; Robinson *et al.*, 1987; McCurdy *et al.*, 1992; McCurdy *et al.*, 1998). Evidence from the cat suggest that fibres from the RN pass around the lateral edge of the ECuN and then move medially to predominantly terminate in rCuN and cCuN, with sparse terminals in amongst the clusters of mCuN (Edwards, 1972; McCurdy *et al.*, 1992). The RN-rCuN connections terminate in a semicircular shell around the ventral, medial and dorsal borders of rCuN (McCurdy *et al.*, 1992). Most connections from the RN are focused in ventral rCuN and cCuN, which coincide with terminals from the sensorimotor cortex and with cell bodies that project to the contralateral rDAO (McCurdy *et al.*, 1992). Regions of RNmag that receive inputs from, and project to, the DCN are the same.

The functional significance of the RN-DCN system has not been confirmed, but it has been shown that activation of RNmag neurons leads to a suppression of rDAO climbing fibres (Weiss *et al.*, 1990). However, the main output of RNmag is excitatory. Recently, Geborek *et al.* (2013) have shown that electrical stimulation in the CuN results in significant suppression of climbing fibre field potentials, which could be mediated by GABAergic cells in rCuN that are known to project to rDAO (Isomura & Hámori, 1988). Therefore, it seems likely that contralateral rDAO receives excitatory input from spinal-cCuN and bilateral rDAO receive inhibitory input from rCuN cells, which likely facilitates movement-related climbing fibre suppression (Geborek *et al.*, 2013).

Pontine nuclei

The pontine nuclei are precerebellar nuclei situated in the ventral pons. They receive inputs from the motor and somatosensory cortex, in addition to ascending somatosensory information, which facilitates modification of motor commands. DCN neurons project to the pontine nuclei, predominantly contralaterally, but with some ipsilateral connections (**Figure 5**) (Jane & Schroeder,

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1971; Schroeder & Jane, 1971; Swenson *et al.*, 1984; Kosinski *et al.*, 1986a; Kosinski *et al.*, 1988b; Aas, 1989). DCN-pontine projections mostly originate from the large round cells of the cluster regions in middle and caudal DCN (Kosinski *et al.*, 1988a). These are the same neurons that project onto VPL in thalamus via the ML, and DCN-pontine projections are almost entirely collaterals of these ML projections (Kosinski *et al.*, 1988b).

DCN-pontine projections terminate somatotopically, such that neurons in the GrN project to ventral regions and CuN projections terminate rostral and dorsal relative to the GrN terminations (Swenson *et al.*, 1984). Interestingly, the somatosensory and motor cortices send projections to the pontine grey (PG) in a somatotopic pattern, which partially overlaps with the DCN input terminals (Kosinski *et al.*, 1986b; Kosinski *et al.*, 1988a). Many pontine neurons show convergent inputs from both the DCN and cortex: neurons activated by peripheral tactile stimuli appear to mostly receive input from the corresponding somatosensory cortex region, while neurons activated by proprioceptive stimuli preferentially receive input from corresponding motor cortex regions (Rüegg & Wiesendanger, 1975; Rüegg *et al.*, 1977; Kosinski *et al.*, 1988a). The convergent inputs onto PG neurons are spatially differentiated, as DCN-PG afferents synapse on proximal and intermediate dendrites, while corticopontine axons terminate more distally (Mihailoff *et al.*, 1981b; Kosinski *et al.*, 1986a; Kosinski *et al.*, 1988a).

Regions of the PG receiving GrN input overlap with groups of pontocerebellar projections to vermal lobule VIII, and CuN regions overlap with pontocerebellar projections to the paramedian lobule (Mihailoff *et al.*, 1981a; Swenson *et al.*, 1984). DCN neurons appear to project onto pontocerebellar neurons that predominantly project contralaterally (although there are some ipsilateral projecting cells), resulting in an ipsilateral DCN-PG-cerebellar pathway. The function of this pathway is yet to be understood, but it is significant that the PG is a non-thalamic target that receives a reasonable amount of input from the DCN clusters region, which appears to be transmitted to the cerebellum.

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Tectum

The tectum refers to the roof of the mid brain, which includes, but is not exclusive to, the superior colliculus (SC), inferior colliculus (IC) and the intercollicular region (InC). All three collicular regions receive projections from neurons in the mixed cell populations of the rostral, shell, and ventral DCN regions (**Figure 6**) (Blomqvist *et al.*, 1978; Berkley *et al.*, 1980; Bull & Berkley, 1984).

Superior colliculus

The SC is a midbrain structure primarily involved in multisensory integration, and directing attention and the head sensory organs, and limbs toward salient stimuli. The SC in different vertebrate species receives varied afferent numbers from each sensory system congruent with their importance to the animal. The SC has a laminar structure with the visual portion in superficial layers whereas deeper layers, namely the stratum griseum intermediate and stratum griseum profundum, receive somatosensory inputs. Interestingly the deeper layers are also the target of inputs form the auditory system, cerebellum, and basal ganglia (May, 2006). The DCN-SC terminals are somatotopically arranged, such that the caudal lateral deep layers receive CuN inputs, and the caudal medial deep portion receives GrN projection terminals (Edwards *et al.*, 1979; Wiberg & Blomqvist, 1984a; Wiberg *et al.*, 1987). These projections travel via the lemniscal adjunct channel (LAC) which is an auxillary ML pathway that exits the ML to reach non-thalamic brainstem and midbrain targets. The DCN-SC LAC fibres are almost entirely contralateral (**Figure 6**), but there are some ipsilateral DCN-SC projections (Massopust *et al.*, 1985; May, 2006).

Superior colliculus inputs originate from the rostral, caudal, shell, and ventral DCN regions (Blomqvist *et al.*, 1978; Berkley *et al.*, 1980; Bull & Berkley, 1984; Wiberg & Blomqvist, 1984a; Cooper & Dostrovsky, 1985; Berkley *et al.*, 1986). Very few SC-projecting neurons are found in the DCN clusters. Rostral, caudal, and shell DCN regions are the target of primary and secondary afferents (Rustioni, 1973; Nijensohn & Kerr, 1975; Rustioni & Kaufman, 1977; Rustioni *et al.*, 1979), conveying information from deep structures and proximal cutaneous regions with large RFs, and may also receive information from noxious stimuli (Gordon & Jukes, 1964b; Rosen, 1969; Angaut-Petit, 1975b; Nyberg & Blomqvist,

1984; Hummelsheim & Wiesendanger, 1985; Hummelsheim *et al.*, 1985). This is consistent with the idea that the DCN sends multimodal somatosensory information to the SC for directing attention and triggering motor responses to salient stimuli (Blomqvist *et al.*, 1978; Nagata & Kruger, 1979).

Inferior colliculus

The IC is best known for its auditory response properties (Aitkin *et al.*, 1975; Aitkin *et al.*, 1978; Tawil *et al.*, 1983). Like the SC, the IC receives projections conveying multimodal somatosensory input from the rostral, caudal, and shell regions of the DCN (**Figure 6**) (Aitkin *et al.*, 1978; Aitkin *et al.*, 1981; Tawil *et al.*, 1983; Wiberg *et al.*, 1987). The IC has three distinct regions known as the central IC, pericentral IC, and the external IC. The DCN project via the ML LAC onto the contralateral pericentral and external IC, but minimally to the central IC (Cooper & Dostrovsky, 1985; Wiberg *et al.*, 1987). It is unclear whether the projections are somatotopic but given that projections to the SC and InC (see below) are somatotopic, it seems likely that DCN-IC projections would be similar.

The pericentral and external IC receive both somatosensory and auditory information (Aitkin *et al.*, 1978; Aitkin *et al.*, 1981; Tawil *et al.*, 1983; Wiberg *et al.*, 1987), but the function of these overlapping inputs is unknown.

Intercollicular region

The InC region sits between the IC and SC, and has a somewhat nebulous structure, but has been separated from these nuclei based on its connectivity, cytoarchitecture, and neurophysiology (RoBards *et al.*, 1976; Flink *et al.*, 1983; Wiberg & Blomqvist, 1984a, b; Danielsson & Norrsell, 1985; Danielsson & Norssell, 1986; Wiberg *et al.*, 1987). Like the SC and IC, the InC receives inputs from rostral, caudal, and, shell DCN regions, but the InC receives densest DCN input, of the three tectal regions (**Figure 6**) (Schroeder & Jane, 1976; Berkley & Hand, 1978b; Boivie, 1978; Björkeland & Boivie, 1984; Wiberg & Blomqvist, 1984a; Cooper & Dostrovsky, 1985; Wiberg *et al.*, 1987). The DCN projections terminate somatotopically such that GrN projections terminate in the caudal InC region and the CuN more rostrally (Flink *et al.*, 1983; Wiberg & Blomqvist, 1984a, b; Danielsson & Norrsell, 1985; Danielsson & Norssell, 1986; Wiberg *et al.*, 1986, 1987).

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The functional role of DCN-InC connections is unclear, but the InC receives information from afferents with small cutaneous RFs on distal body regions (Wiberg *et al.*, 1987). The main projection field of InC neurons appears to be in the PO of the thalamus (see *Cortical Subsystem 3: Posterior group of the thalamus*), which primarily projects to S2 and is reciprocally connected to the cortical PV.

Pretectum

The pretectum is a midbrain region best known for its role in visual light reflexes. The pretectal area has five characterised nuclei, of which two receive input from the DCN: the posterior pretectal nucleus, and the pars compacta of the anterior pretectal nucleus (Berkley & Hand, 1978b; Berkley & Mash, 1978; Björkeland & Boivie, 1984; Wiberg & Blomqvist, 1984b; Wiberg *et al.*, 1987). Similar to DCN-tectal neurons, DCN-pretectal neurons are located in rostral, shell, and ventral DCN regions (**Figure 6**), although the pretectal- and tectal-projections appear to derive from different neurons within these regions (Blomqvist *et al.*, 1978; Berkley *et al.*, 1980; Bull & Berkley, 1984). Terminations in the pretectal area appear to be somatotopic: GrN-pretectal projections terminate preferentially in the anterior nucleus and CuN projections terminate in the posterior nucleus (Wiberg & Blomqvist, 1984a).

Pretectum efferents project to a variety of targets, all of which are discussed in this review as targets of direct DCN projections, including the PG, RN, IO, zona incerta, and non-VPL thalamic regions (Benevento *et al.*, 1977; Berman, 1977; Abols & Basbaum, 1979; Weber & Harting, 1980; Walberg *et al.*, 1981). The DCN-pretectal connection has been suggested to be involved in multisensory integration, but a functional role is yet to be elucidated (Berkley *et al.*, 1986).

Zona Incerta

The zona incerta (ZI) is an elongated grey matter structure situated in the subthalamic region. Various types of neurons in rostral DCN project via the ML and terminate in ventral ZI (**Figure 6**) (Lund & Webster, 1967; Boivie, 1971; Hand & Van Winkle, 1977; Berkley & Hand, 1978b; Roger & Cadusseau, 1985; Berkley *et al.*, 1986; Aumann *et al.*, 1996). Projections from the CuN are more numerous and

terminate more medially, whereas GrN projections terminate more laterally (Boivie, 1971; Villanueva *et al.*, 1998).

Ventral ZI neurons, coinciding with DCN input locations, have large RFs and many respond to noxious stimulation of cutaneous and deep receptors, but whether DCN inputs are the source of these response characteristics remains unknown (Kaelber & Smith, 1979; Nicolelis *et al.*, 1992). Neurons in ZI have a variety of projection targets, of which the intermediate and deep SC seem preponderant (Ricardo, 1981; Romanowski *et al.*, 1985; Nicolelis *et al.*, 1992). Given the association with noxious responses and projection to regions like the SC, it seems that the DCN-ZI system is involved in pain signalling and perhaps orientation of sensory organs towards noxious stimuli. Interestingly, stimulation of ZI can elicit escape responses (Kaelber & Smith, 1979; Kaelber, 1981), but it is yet to be investigated whether DCN-ZI neurons can elicit these responses.

System 3: Spinal cord system

The third DCN projection subsystem proposed by Berkley *et al.* (1986) is *the spinal cord system*. More recent evidence has also revealed DCN-periaqueductal grey (PAG) projections, which we have included in the spinal cord system here, and these projections are summarised in **Figure 6**. Spinal cord inputs from the DCN originate from medium-sized neurons, with large stellate dendritic arbours, preferentially located in the ventral GrN and CuN, and between the two nuclei, and a small population scattered throughout the clusters (Kuypers & Maisky, 1975; Burton & Loewy, 1977; Enevoldson & Gordon, 1984; Berkley *et al.*, 1986; Bermejo *et al.*, 2003). The dendrites of cells outside the clusters region appear to be restricted from entering the cluster regions, whereas a small amount of spinal projecting cells are found inside the cluster region and have no restriction on their arborisation (Enevoldson & Gordon, 1984).

Spinal-projecting axons from the DCN course through both the ipsilateral DC and the dLF to terminate in the ipsilateral dorsal horn laminae I, III, IV and V (Burton & Loewy, 1977; Bromberg *et al.*, 1981; Enevoldson & Gordon, 1984; Leong *et al.*, 1984; Berkley *et al.*, 1986; Kwiat & Basbaum, 1992;

Villanueva *et al.*, 1995). A small proportion of DCN-spinal projections are collaterals of axons projecting to the thalamus (Bermejo *et al.*, 2003).

The function of the DCN-spinal projections is still unknown. However, DCN regions containing the most spinal-projecting neurons coincide with the predominant cortico-DCN input, which has led to suggestions that these neurons may be involved in a cortico-DCN-spinal modulation system for movement-related touch or proprioceptive information. Finally, the DCN-spinal target laminae, IV and V, contain origin cells of the PSDC pathway, suggesting there may be a DCN-spinal-DCN system. Many neurons in the PSDC have response properties similar to DCN cells, but with more discrete RFs, but this pathway has also been postulated to play a role in pain modulation (de Pommery *et al.*, 1984; G. J. Giesler *et al.*, 1984; Villanueva *et al.*, 1995). However, the existence of a potential DCN-spinal-DCN connection and whether it plays a role in tactile or pain processing is yet to be elucidated.

Periaqueductal grey

Surrounding the cerebral aqueduct in the tegmentum, the periaqueductal grey (PAG) receives afferents from the spinothalamic tract that transmit pain and temperature information. Interestingly, the DCN have also been shown to send contralateral projections via the ML LAC to the PAG (**Figure 6**) (Schroeder & Jane, 1971; Hazlett *et al.*, 1972; Björkeland & Boivie, 1984; Wiberg *et al.*, 1987; Villanueva *et al.*, 1998; García Del Caño *et al.*, 2004; Barbaresi & Mensà, 2016), which terminate somatotopically such that the GrN project to the ventrocaudal PAG and the CuN more rostrally (Barbaresi & Mensà, 2016).

The functional properties of these DCN-PAG neurons have not been characterised, nor has a role in pain processing been established for the DCN. However, some DCN neurons respond to, or are modulated by, noxious skin, muscle, joint, and visceral stimulation (Ferrington *et al.*, 1988; Cliffer *et al.*, 1992; Al-Chaer *et al.*, 1997; Miki *et al.*, 1997; Al-Chaer *et al.*, 1998; Schwark & Ilyinsky, 2001; Wang & Westlund, 2001; Costa-García & Nuñez, 2004; Kitagawa *et al.*, 2005; Zhao *et al.*, 2012). The PAG coordinates varied autonomic, behavioural, and analgesic responses to different situations such as

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experiencing deep visceral pain, or acute cutaneous injury, but physiological studies are needed to determine how the DCN interacts with this system.

Summary of DCN organisation

The organisation of the DCN-complex is defined by the neural populations' modality, somatotopy, and connectivity. Broadly, the DCN-complex can be summarised into predominantly, but not exclusively, tactile- and proprioception-dominated zones. The clusters and shell of the middle DCN, and caudal DCN zones, excluding the ventral regions are dominated by tactile-related information processing and transmission, whereas the ventral DCN, ECuN, and NuX and NuZ can be considered proprioceptive-dominated. The rostral DCN appears to process a relatively equal mixture of tactile and proprioception-related information. Within the tactile-dominated regions, the clusters region specifically processes and transmits spatially precise discriminative touch information from the distal limbs. The largest representation in the cluster regions is of glabrous skin, which is specialised for exploring the physical environment and provides high-quality sensory feedback necessary for dextrous motor tasks. The rostral, caudal, and shell regions process less spatially precise, multimodal information, contributing less to fine motor control, and receive a larger proportion of inputs from the proximal limbs and axial body regions.

The clusters region receives inputs from primary cutaneous afferents of the DCs, and cortical area 3b, and primarily projects onto the thalamic VPL, with some outputs to other targets, including the thalamic PO and the pontine nuclei. The multimodal rostral, shell, and caudal regions receive primary and secondary afferents from the DCs, and inputs from the RN and cortical areas 3b, 1, and 2, and project to a variety of targets including the thalamic PO, tectum, pretectum, PAG, RN, pontine nuclei, ZI, and IO. Finally, the proprioceptive-dominated regions receive inputs from the primary and secondary afferents of the DCs, the dLF, and the ventral DCN receives inputs from cortical areas 3a and 4. These neural populations primarily project to the cerebellum, the thalamic VPL shell, and the spinal cord dorsal horn.

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These organising principles show that the DCN-complex is more than a simple relay for tactile information, but rather should be considered an integration and distribution hub for tactile and proprioceptive information ascending the neuraxis to the cortex, in addition to a wide variety of targets throughout the midbrain and hindbrain.

The DCN-complex: a potential neural prosthetic target?

Current neural prosthetics can restore some movement capabilities to tetraplegics by translating brain signals that code intended movements, to control a robotic, or even paralysed, limbs (Hochberg *et al.*, 2012; Collinger *et al.*, 2013; Wodlinger *et al.*, 2014; Bouton *et al.*, 2016; Ajiboye *et al.*, 2017; Friedenberg *et al.*, 2017; Colachis *et al.*, 2018). However, provision of somatosensory feedback is essential for naturalistic movement control, but currently lacking. Intracortical microstimulation in humans has succeeded in eliciting minimal, although some, naturalistic tactile and proprioceptive sensations (Flesher *et al.*, 2016; Salas *et al.*, 2018). Recognising the DCN-complex as a distribution hub may be key to understanding how to restore naturalistic movement modulation. If stimulation is targeted higher up in the brain, much of the ascending somatosensory information that is not directly bound for the cortex will never be restored. However, if the DCN-complex is targeted, future neural prosthetic devices could artificially recreate signals bound for the myriad of targets examined here, including the cerebellum, PG, RN, IO, tectum, pretectum, and the spinal cord in addition to the tactile and proprioceptive information bound for the cortex for conscious perception. Restoring somatosensory inputs to cerebellar circuits is of particular interest, as this information is used for movement modulation and error correction. Thus, the DCN-complex may be advantageous over the cortex, as a somatosensory neural prosthetic target. Therefore, we propose that the DCN-complex warrant future investigation to restore both conscious and unconscious somatosensory functions with neural prostheses.

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References

Aas JE. (1989). Subcortical projections to the pontine nuclei in the cat. *Journal of Comparative Neurology* **282,** 331-354.

Abols IA & Basbaum AI. (1979). The posterior pretectal nucleus: Evidence for a direct projection to the inferior olive of the cat. *Neuroscience Letters* **13,** 111-116.

Abrahams V & Swett J. (1986). The pattern of spinal and medullary projections from a cutaneous nerve and a muscle nerve of the forelimb of the cat: a study using the transganglionic transport of HRP. *Journal of Comparative Neurology* **246,** 70-84.

Abraira VE & Ginty DD. (2013). The sensory neurons of touch. *Neuron* **79,** 618-639.

Aguilar J, Rivadulla C, Soto C & Canedo A. (2003). New corticocuneate cellular mechanisms underlying the modulation of cutaneous ascending transmission in anesthetized cats. *Journal of neurophysiology*.

Aitkin LM, Dickhaus H, Schult W & Zimmermann M. (1978). External nucleus of inferior colliculus: auditory and spinal somatosensory afferents and their interactions. *Journal of Neurophysiology* **41,** 837-847.

Aitkin LM, Kenyon CE & Philpott P. (1981). The representation of the auditory and somatosensory systems in the external nucleus of the cat inferior colliculus. *Journal of Comparative Neurology* **196,** 25-40.

Aitkin LM, Webster WR, Veale JL & Crosby DC. (1975). Inferior colliculus. I. Comparison of response properties of neurons in central, pericentral, and external nuclei of adult cat. *Journal of Neurophysiology* **38,** 1196-1207.

Ajiboye AB, Willett FR, Young DR, Memberg WD, Murphy BA, Miller JP, Walter BL, Sweet JA, Hoyen HA & Keith MW. (2017). Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration. *The Lancet* **389,** 1821-1830.

Al-Chaer ED, Feng Y & Willis WD. (1998). A Role for the Dorsal Column in Nociceptive Visceral Input Into the Thalamus of Primates. *Journal of Neurophysiology* **79,** 3143-3150.

Al-Chaer ED, Westlund KN & Willis WD. (1997). Nucleus Gracilis: An Integrator for Visceral and Somatic Information. *Journal of Neurophysiology* **78,** 521-527.

Albright B & Friedenbach D. (1982). The distribution of lateral funicular and cortical fibers to the dorsal column, Z and X nuclei in the prosimianGalago. *Neuroscience* **7,** 1175-1185.

Alonso A, Blanco M, Paino C & Rubia F. (1986). Distribution of neurons in the main cuneate nucleus projecting to the inferior olive in the cat. Evidence that they differ from those directly projecting to the cerebellum. *Neuroscience* **18,** 671-683.

Angaut-Petit D. (1975a). The dorsal column system: I. Existence of long ascending postsynaptic fibres in the cat's fasciculus gracilis. *Experimental brain research* **22,** 457-470.

Angaut-Petit D. (1975b). The dorsal column system: II. Functional properties and bulbar relay of the postsynaptic fibres of the cat's fasciculus gracilis. *Experimental brain research* **22,** 471-493.

Armstrong D, Harvey R & Schild RF. (1974). Topographical localization in the olivo-cerebellar projection: An electrophysiological study in the cat. *Journal of Comparative Neurology* **154,** 287-302.

Asif M & Edgley SA. (1992). Projections of group II-activated midlumbar spinocerebellar tract neurones to the region of nucleus Z in the cat. *The Journal of Physiology* **448,** 565-578.

Aumann TD, Rawson JA, Pichitpornchai C & Horne MK. (1996). Projections from the cerebellar interposed and dorsal column nuclei to the thalamus in the rat: A double anterograde labelling study. *Journal of Comparative Neurology* **368,** 608-619.

Azizi SA & Woodward D. (1987). Inferior olivary nuclear complex of the rat: morphology and comments on the principles of organization within the olivocerebellar system. *Journal of Comparative Neurology* **263,** 467-484.

Bai L, Lehnert BP, Liu J, Neubarth NL, Dickendesher TL, Nwe PH, Cassidy C, Woodbury CJ & Ginty DD. (2015). Genetic identification of an expansive mechanoreceptor sensitive to skin stroking. *Cell* **163,** 1783-1795.

Bakker D, Richmond F, Abrahams V & Courville J. (1985). Patterns of primary afferent termination in the external cuneate nucleus from cervical axial muscles in the cat. *Journal of Comparative Neurology* **241,** 467-479.

Barbaresi P & Mensà E. (2016). Connections from the rat dorsal column nuclei (DCN) to the periaqueductal gray matter (PAG). *Neuroscience Research* **109,** 35-47.

Basbaum AI & Hand PJ. (1973). Projections of cervicothoracic dorsal roots to the cuneate nucleus of the rat, with observations on cellular “bricks”. *Journal of comparative Neurology* **148,** 347-359.

Bell J, Bolanowski S & Holmes MH. (1994). The structure and function of pacinian corpuscles: A review. *Progress in Neurobiology* **42,** 79-128.

 doi:10.20944/preprints201911.0084.v1

Benevento LA, Rezak M & Santos-Anderson R. (1977). An autoradiographic study of the projections of the pretectum in the rhesus monkey (macaca mulatta): evidence for sensorimotor links to the thalamus and oculomotor nuclei. *Brain Research* **127,** 197-218.

Bentivoglio M & Rustioni A. (1986). Corticospinal neurons with branching axons to the dorsal column nuclei in the monkey. *Journal of Comparative Neurology* **253,** 260-276.

Berkley K & Hand P. (1978a). Projections to the inferior olive of the cat II. Comparisons of input from the gracile, cuneate and the spinal trigeminal nuclel. *Journal of Comparative Neurology* **180,** 253-264.

Berkley KJ. (1980). Spatial relationships between the terminations of somatic sensory and motor pathways in the rostral brainstem of cats and monkeys. I. Ascending somatic sensory inputs to lateral diencephalon. *Journal of Comparative Neurology* **193,** 283-317.

Berkley KJ. (1983). Spatial relationships between the terminations of somatic sensory motor pathways in the rostral brainstem of cats and monkeys. II. Cerebellar projections compared with those of the ascending somatic sensory pathways in lateral diencephalon. *Journal of Comparative Neurology* **220,** 229-251.

Berkley KJ, Blomqvist A, Pelt A & Flink R. (1980). Differences in the collateralization of neuronal projections from the dorsal column nuclei and lateral cervical nucleus to the thalamus and tectum in the cat: An anatomical study using two different double-labeling techniques. *Brain Research* **202,** 273-290.

Berkley KJ, Budell RJ, Blomqvist A & Bull M. (1986). Output systems of the dorsal column nuclei in the cat. *Brain Research Reviews* **11,** 199-225.

Berkley KJ & Hand PJ. (1978b). Efferent projections of the gracile nucleus in the cat. *Brain Research* **153,** 263-283.

Berkley KJ & Mash DC. (1978). Somatic sensory projections to the pretectum in the cat. *Brain Research* **158,** 445-449.

Berman N. (1977). Connections of the pretectum in the cat. *Journal of Comparative Neurology* **174,** 227-254.

Bermejo PE, Jiménez CE, Torres CV & Avendaño C. (2003). Quantitative stereological evaluation of the gracile and cuneate nuclei and their projection neurons in the rat. *Journal of Comparative Neurology* **463,** 419-433.

Biedenbach M. (1972). Cell density and regional distribution of cell types in the cuneate nucleus of the rhesus monkey. *Brain research* **45,** 1-14.

Bischoff E. (1899). Zur Anatomie der Hinterstrangkerne bei Säugethieren. *Jb Psychiat Neurol* **18,** 371-384.

Björkeland M & Boivie J. (1984). An anatomical study of the projections from the dorsal column nuclei to the midbrain in cat. *Anatomy and Embryology* **170,** 29-43.

Bloedel JR & Courville J. (1981). Cerebellar afferent systems. *Handbook of physiology* **2,** 735-829.

Bloedel JR & Courville J. (2011). Cerebellar Afferent Systems. In *Comprehensive Physiology*, ed. Terjung R, pp. 735-829.

Blomqvist A. (1980). Gracilo-diencephalic relay cells: A quantitative study in the cat using retrograde transport of horseradish peroxidase. *Journal of Comparative Neurology* **193,** 1097-1125.

Blomqvist A, Flink R, Bowsher D, Griph S & Westman J. (1978). Tectal and thalamic projections of dorsal column and lateral cervical nuclei: a quantitative study in the cat. *Brain Research* **141,** 335-341.

Boesten A & Voogd J. (1975). Projections of the dorsal column nuclei and the spinal cord on the inferior olive in the cat. *Journal of Comparative Neurology* **161,** 215-237.

Boivie J. (1978). Anatomical observations on the dorsal column nuclei, their thalamic projection and the cytoarchitecture of some somatosensory thalamic nuclei in the monkey. *Journal of Comparative Neurology* **178,** 17-47.

Boivie J & Boman K. (1981). Termination of a separate (proprioceptive?) cuneothalamic tract from external cuneate nucleus in monkey. *Brain research* **224,** 235-246.

Boivie Jr. (1971). The termination in the thalamus and the zona incerta of fibres from the dorsal column nuclei (DCN) in the cat. An experimental study with silver impregnation methods. *Brain Research* **28,** 459-490.

Bouton CE, Shaikhouni A, Annetta NV, Bockbrader MA, Friedenberg DA, Nielson DM, Sharma G, Sederberg PB, Glenn BC, Mysiw WJ, Morgan AG, Deogaonkar M & Rezai AR. (2016). Restoring cortical control of functional movement in a human with quadriplegia. *Nature* **533,** 247.

Brinkhus H, Carstens E & Zimmermann M. (1979). Encoding of graded noxious skin heating by neurons in posterior thalamus and adjacent areas in the cat. *Neuroscience letters* **15,** 37-42.

Brodal A & Pompeiano O. (1957). The vestibular nuclei in the cat. *Journal of anatomy* **91,** 438.

Brodal A, Walberg F & Hoddevik GH. (1975). The olivocerebellar projection in the cat studied with the method of retrograde axonal transport of horseradish peroxidase. *Journal of Comparative Neurology* **164,** 449-469.

Brodal P & Brodal A. (1981). The olivocerebellar projection in the monkey. Experimental studies with the method of retrograde tracing of horseradish peroxidase. *Journal of Comparative Neurology* **201,** 375-393.

Bromberg MB, Burnham JA & Towe AL. (1981). Doubly projecting neurons of the dorsal column nuclei. *Neuroscience Letters* **25,** 215-220.

Brown A & Fyffe R. (1981). Form and function of dorsal horn neurones with axons ascending the dorsal columns in cat. *The Journal of physiology* **321,** 31-47.

Brown A & Iggo A. (1967). A quantitative study of cutaneous receptors and afferent fibres in the cat and rabbit. *The Journal of physiology* **193,** 707.

Bull MS & Berkley KJ. (1984). Differences in the Neurons That Project from the Dorsal Column Nuclei to the Diencephalon, Pretectum, and Tectum in the Cat. *Somatosensory Research* **1,** 281-300.

Burgess PR, Petit D & Warren RM. (1968). Receptor types in cat hairy skin supplied by myelinated fibers. *Journal of Neurophysiology* **31,** 833-848.

Burton H & Jones E. (1976). The posterior thalamic region and its cortical projection in New World and Old World monkeys. *Journal of Comparative Neurology* **168,** 249-301.

Burton H & Loewy AD. (1977). Projections to the spinal cord from medullary somatosensory relay nuclei. *Journal of Comparative Neurology* **173,** 773-792.

Campbell SK, Parker T & Welker W. (1974). Somatotopic organization of the external cuneate nucleus in albino rats. *Brain research* **77,** 1-23.

Cauna N & Ross LL. (1960). The fine structure of Meissner's touch corpuscles of human fingers. *The Journal of Cell Biology* **8,** 467-482.

Cerminara NL, Makarabhirom K & Rawson JA. (2003). Somatosensory properties of cuneocerebellar neurones in the main cuneate nucleus of the rat. *The Cerebellum* **2,** 131-145.

Chang H-T & Ruch TC. (1947). Organization of the dorsal columns of the spinal cord and their nuclei in the spider monkey. *Journal of anatomy* **81,** 140.

Cheek M, Rustioni A & Trevino D. (1975). Dorsal column nuclei projections to the cerebellar cortex in cats as revealed by the use of the retrograde transport of horseradish peroxidase. *Journal of Comparative Neurology* **164,** 31-46.

Cheema S, Rustioni A & Whitsel BL. (1985). Sensorimotor cortical projections to the primate cuneate nucleus. *Journal of Comparative Neurology* **240,** 196-211.

Cheema S, Whitsel B & Rustioni A. (1983). The corticocuneate pathway in the cat: relations among terminal distribution patterns, cytoarchitecture, and single neuron functional properties. *Somatosensory research* **1,** 169-205.

Cheney P & Preston JB. (1976). Classification and response characteristics of muscle spindle afferents in the primate. *Journal of Neurophysiology* **39,** 1-8.

Clemo HR & Stein BE. (1983). Organization of a fourth somatosensory area of cortex in cat. *Journal of Neurophysiology* **50,** 910-925.

Cliffer KD, Hasegawa T & Willis WD. (1992). Responses of neurons in the gracile nucleus of cats to innocuous and noxious stimuli: basic characterization and antidromic activation from the thalamus. *Journal of Neurophysiology* **68,** 818-832.

Colachis SC, Bockbrader MA, Zhang M, Friedenberg DA, Annetta NV, Schwemmer MA, Skomrock ND, Mysiw WJ, Rezai AR, Bresler HS & Sharma G. (2018). Dexterous Control of Seven Functional Hand Movements Using Cortically-Controlled Transcutaneous Muscle Stimulation in a Person With Tetraplegia. *Frontiers in Neuroscience* **12**.

Collinger JL, Wodlinger B, Downey JE, Wang W, Tyler-Kabara EC, Weber DJ, McMorland AJ, Velliste M, Boninger ML & Schwartz AB. (2013). High-performance neuroprosthetic control by an individual with tetraplegia. *The Lancet* **381,** 557-564.

Cooke J, Larson B, Oscaesson O & Sjölund B. (1971a). Organization of afferent connections to cuneocerebellar tract. *Experimental brain research* **13,** 359-377.

Cooke J, Larson B, Oscarsson O & Sjölund B. (1971b). Origin and termination of cuneocerebellar tract. *Experimental brain research* **13,** 339-358.

Cooper LL & Dostrovsky JO. (1985). Projection from dorsal column nuclei to dorsal mesencephalon. *Journal of Neurophysiology* **53,** 183-200.

Costa-García M & Nuñez A. (2004). Nociceptive stimuli induce changes in somatosensory responses of rat dorsal column nuclei neurons. *Brain Research* **1025,** 169-176.

Crockett DP, Maslany S & Egger MD. (1996). Synaptophysin immunoreactivity and distributions of calcium-binding proteins highlight the functional organization of the rat's dorsal column nuclei. *Brain research* **707,** 31-46.

Crockett DP, Maslany S, Harris SL & Egger MD. (1993). Enhanced cytochrome-oxidase staining of the cuneate nucleus in the rat reveals a modifiable somatotopic map. *Brain research* **612,** 41-55.

Culberson JL & Brushart TM. (1989). Somatotopy of digital nerve projections to the cuneate nucleus in the monkey. *Somatosensory & motor research* **6,** 319-330.

Danielsson I & Norrsell U. (1985). Somatosensory, short latency activation in the intercollicular region of the cat's mesencephalon. *Acta Physiologica Scandinavica* **124,** 479-482.

Danielsson I & Norssell U. (1986). Somatosensory units in the cat's intercollicular region. *Acta Physiologica Scandinavica* **128,** 579-586.

Darian-Smith I. (2011). The Sense of Touch: Performance and Peripheral Neural Processes. In *Comprehensive Physiology*. John Wiley & Sons, Inc, Hoboken, NJ, USA.

Dart A & Gordon G. (1973). Some properties of spinal connections of the cat's dorsal column nuclei which do not involve the dorsal columns. *Brain research* **58,** 61-68.

De-Doncker L, Picquet F, Petit J & Falempin M. (2003). Characterization of Spindle Afferents in Rat Soleus Muscle Using Ramp-and-Hold and Sinusoidal Stretches. *Journal of Neurophysiology* **89,** 442-449.

de Pommery J, Roudier F & Menétrey D. (1984). Postsynaptic fibers reaching the dorsal column nuclei in the rat. *Neuroscience Letters* **50,** 319-323.

Diamond ME, Armstrong-James M & Ebner FF. (1992). Somatic sensory responses in the rostral sector of the posterior group (POm) and in the ventral posterior medial nucleus (VPM) of the rat thalamus. *Journal of Comparative Neurology* **318,** 462-476.

Dolleman-van Der Weel MJ & Witter MP. (1996). Projections from the nucleus reuniens thalami to the entorhinal cortex, hippocampal field CA1, and the subiculum in the rat arise from different populations of neurons. *Journal of Comparative Neurology* **364,** 637-650.

Dykes R, Sur M, Merzenich M, Kaas J & Nelson R. (1981). Regional segregation of neurons responding to quickly adapting, slowly adapting, deep and Pacinian receptors within thalamic ventroposterior lateral and ventroposterior inferior nuclei in the squirrel monkey (Saimiri sciureus). *Neuroscience* **6,** 1687-1692.

Dykes RW, Rasmusson DD, Sretavan D & Rehman NB. (1982). Submodality segregation and receptive-field sequences in cuneate, gracile, and external cuneate nuclei of the cat. *Journal of Neurophysiology* **47,** 389-416.

Ebbesson SO. (1968). A connection between the dorsal column nuclei and the dorsal accessory olive. *Brain research* **8,** 393-397.

Edin BB & Vallbo A. (1990a). Dynamic response of human muscle spindle afferents to stretch. *J Neurophysiol* **63,** 1297-1306.

Edin BB & Vallbo A. (1990b). Muscle afferent responses to isometric contractions and relaxations in humans. *Journal of Neurophysiology* **63,** 1307-1313.

Edwards SB. (1972). The ascending and descending projections of the red nucleus in the cat: an experimental study using an autoradiographic tracing method. *Brain research* **48,** 45-63.

Edwards SB, Ginsburgh CL, Henkel CK & Stein BE. (1979). Sources of subcortical projections to the superior colliculus in the cat. *Journal of Comparative Neurology* **184,** 309-329.

Ekerot C & Larson B. (1972). Differential termination of the exteroceptive and proprioceptive components of the cuneocerebellar tract. *Brain Research* **36,** 420-424.

Ellis Jr LC & Rustioni A. (1981). A correlative HRP, Golgi, and EM study of the intrinsic organization of the feline dorsal column nuclei. *Journal of Comparative Neurology* **197,** 341-367.

Enevoldson T & Gordon G. (1989). Postsynaptic dorsal column neurons in the cat: a study with retrograde transport of horseradish peroxidase. *Experimental brain research* **75,** 611-620.

Enevoldson TP & Gordon G. (1984). Spinally projecting neurons in the dorsal column nuclei: Distribution, dendritic trees and axonal projections. *Experimental Brain Research* **54,** 538-550.

Feldman SG & Kruger L. (1980). An axonal transport study of the ascending projection of medial lemniscal neurons in the rat. *Journal of Comparative Neurology* **192,** 427-454.

Ferraro A & Barrera S. (1935). The nuclei of the posterior funiculi in Macacus rhesus: An anatomic and experimental investigation. *Archives of Neurology & Psychiatry* **33,** 262-275.

Ferrington DG, Downie JW & W. D. Willis J. (1988). Primate nucleus gracilis neurons: responses to innocuous and noxious stimuli. *Journal of Neurophysiology* **59,** 886-907.

Flesher SN, Collinger JL, Foldes ST, Weiss JM, Downey JE, Tyler-Kabara EC, Bensmaia SJ, Schwartz AB, Boninger ML & Gaunt RA. (2016). Intracortical microstimulation of human somatosensory cortex. *Science translational medicine* **8,** 361ra141-361ra141.

Flink R, Wiberg M & Blomqvist A. (1983). The termination in the mesencephalon of fibres from the lateral cervical nucleus. An anatomical study in the cat. *Brain Research* **259,** 11-20.

Florence S, Wall J & Kaas J. (1988). The somatotopic pattern of afferent projections from the digits to the spinal cord and cuneate nucleus in macaque monkeys. *Brain research* **452,** 388-392.

Florence S, Wall J & Kaas J. (1989). Somatotopic organization of inputs from the hand to the spinal gray and cuneate nucleus of monkeys with observations on the cuneate nucleus of humans. *Journal of Comparative Neurology* **286,** 48-70.

Florence S, Wall J & Kaas J. (1991). Central projections from the skin of the hand in squirrel monkeys. *Journal of Comparative Neurology* **311,** 563-578.

Friedenberg DA, Schwemmer MA, Landgraf AJ, Annetta NV, Bockbrader MA, Bouton CE, Zhang M, Rezai AR, Mysiw WJ, Bresler HS & Sharma G. (2017). Neuroprosthetic-enabled control of graded arm muscle contraction in a paralyzed human. *Scientific Reports* **7,** 8386.

G. J. Giesler J, Nahin RL & Madsen AM. (1984). Postsynaptic dorsal column pathway of the rat. I. Anatomical studies. *Journal of Neurophysiology* **51,** 260-275.

García Del Caño G, Uria I, Gerrikagoitia I & Martínez-Millán L. (2004). Connection from the dorsal column nuclei to the superior colliculus in the rat: Topographical organization and somatotopic specific plasticity in response to neonatal enucleation. *Journal of Comparative Neurology* **468,** 410-424.

Geborek P, Jörntell H & Bengtsson F. (2013). Stimulation within the cuneate nucleus suppresses synaptic activation of climbing fibers. *Frontiers in neural circuits* **6,** 120.

Gerrits N, Voogd J & Nas W. (1985). Cerebellar and olivary projections of the external and rostral internal cuneate nuclei in the cat. *Experimental brain research* **57,** 239-255.

Gordon G & Grant G. (1982). Dorsolateral spinal afferents to some medullary sensory nuclei. *Experimental Brain Research* **46,** 12-23.

Gordon G & Horrobin D. (1967). Antidromic and synaptic responses in the cat's gracile nucleus to cerebellar stimulation. *Brain Research* **5,** 419-421.

Gordon G & Jukes M. (1964a). Descending influences on the exteroceptive organizations of the cat's gracile nucleus. *The Journal of physiology* **173,** 291-319.

Gordon G & Jukes M. (1964b). Dual organization of the exteroceptive components of the cat's gracile nucleus. *The Journal of physiology* **173,** 263-290.

Gordon G & Paine C. (1960). Functional organization in nucleus gracilis of the cat. *The Journal of physiology* **153,** 331-349.

Gordon G & Seed W. (1961). An investigation of nucleus gracilis of the cat by antidromic stimulation. *The Journal of physiology* **155,** 589-601.

Grant G, Boivie Jr & Silfvenius H. (1973). Course and termination of fibres from the nucleus Z of the medulla oblongata. An experimental light microscopical study in the cat. *Brain Research* **55,** 55-70.

Griffin AL. (2015). Role of the thalamic nucleus reuniens in mediating interactions between the hippocampus and medial prefrontal cortex during spatial working memory. *Frontiers in Systems Neuroscience* **9**.

Grigg P. (1994). Peripheral neural mechanisms in proprioception. *Journal of Sport Rehabilitation* **3,** 2-17.

Groenewegen H, Boesten A & Voogd J. (1975). The dorsal column nuclear projections to the nucleus ventralis posterior lateralis thalami and the inferior olive in the cat: an autoradiographic study. *Journal of Comparative Neurology* **162,** 505-517.

Guilbaud G, Caille D, Besson J & Benelli G. (1977). Single units activities in ventral posterior and posterior group thalamic nuclei during nociceptive and non nociceptive stimulations in the cat. *Archives italiennes de biologie* **115,** 38-56.

Halata Z, Grim M & Bauman KI. (2003). Friedrich Sigmund Merkel and his “Merkel cell”, morphology, development, and physiology: review and new results. *The Anatomical Record Part A: Discoveries in Molecular, Cellular, and Evolutionary Biology: An Official Publication of the American Association of Anatomists* **271,** 225-239.

Hamilton T & Johnson J. (1973). Somatotopic organization related to nuclear morphology in the cuneate-gracile complex of opossums Didelphis marsupialis virginiana. *Brain research* **51,** 125-140.

Hand PJ. (1966). Lumbosacral dorsal root terminations in the nucleus gracilis of the cat. Some observations on terminal degeneration in other medullary sensory nuclei. *Journal of Comparative Neurology* **126,** 137-156.

Hand PJ & Van Winkle T. (1977). The efferent connections of the feline nucleus cuneatus. *Journal of Comparative Neurology* **171,** 83-109.

Handwerker H, Kilo S & Reeh P. (1991). Unresponsive afferent nerve fibres in the sural nerve of the rat. *The Journal of physiology* **435,** 229-242.

Haring JH & Rowinski MJ. (1982). A horseradish peroxidase study of projections from the main and external cuneate nuclei to the cerebellum of the North American raccoon. *Journal of Comparative Neurology* **211,** 363-376.

Haring JH, Rowinski MJ & Pubols BH. (1984). Electrophysiology of raccoon cuneocerebellar neurons. *Somatosensory research* **1,** 247-264.

Hazlett JC, Dom R & Martin GF. (1972). Spino-bulbar, spino-thalamic and medial lemniscal connections in the american opossum, Didelphis marsupialis virginiana. *Journal of Comparative Neurology* **146,** 95-117.

Heino R & Westman J. (1991). Quantitative analysis of the feline dorsal column nuclei and their GABAergic and non-GABAergic neurons. *Anatomy and embryology* **184,** 181-193.

Hochberg LR, Bacher D, Jarosiewicz B, Masse NY, Simeral JD, Vogel J, Haddadin S, Liu J, Cash SS & van der Smagt P. (2012). Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature* **485,** 372-375.

Hummelsheim H & Wiesendanger M. (1985). Neuronal responses of medullary relay cells to controlled stretches of forearm muscles in the monkey. *Neuroscience* **16,** 989-996.

Hummelsheim H, Wiesendanger R, Wiesendanger M & Bianchetti M. (1985). The projection of low-threshold muscle afferents of the forelimb to the main and external cuneate nuclei of the monkey. *Neuroscience* **16,** 979-987.

Iggo A & Muir AR. (1969). The structure and function of a slowly adapting touch corpuscle in hairy skin. *The Journal of physiology* **200,** 763-796.

Isomura G & Hámori J. (1988). Three types of neurons in the medial cuneate nucleus of the cat. *Neuroscience research* **5,** 395-408.

Ito M & Itō M. (1984). *The cerebellum and neural control*. Raven press.

Itoh K, Kaneko T, Kudo M & Mizuno N. (1984). The intercollicular region in the cat: a possible relay in the parallel somatosensory pathways from the dorsal column nuclei to the posterior complex of the thalamus. *Brain Research* **308,** 166-171.

Jami L. (1992). Golgi tendon organs in mammalian skeletal muscle: functional properties and central actions. *Physiological Reviews* **72,** 623-666.

Jane JA & Schroeder DM. (1971). A comparison of dorsal column nuclei and spinal afferents in the European hedgehog (Erinaceus europeaus). *Experimental neurology* **30,** 1-17.

Jankowska E, Rastad J & Zarzecki P. (1979). Segmental and supraspinal input to cells of origin of non-primary fibres in the feline dorsal columns. *The Journal of physiology* **290,** 185-200.

Jasmin L, Courville J & Bakker D. (1985). Afferent projections from forelimb muscles to the external and main cuneate nuclei in the cat. *Anatomy and embryology* **171,** 275-284.

Jenkins BA & Lumpkin EA. (2017). Developing a sense of touch. *Development* **144,** 4078-4090.

Johansson H & Silfvenius H. (1977a). Axon-collateral activation by dorsal spinocerebellar tract fibres of group I relay cells of nucleus Z in the cat medulla oblongata. *The Journal of physiology* **265,** 341-369.

Johansson H & Silfvenius H. (1977b). Connexions from large, ipsilateral hind limb muscle and skin afferents to the rostral main cuneate nucleus and to the nucleus X region in the cat. *The Journal of physiology* **265,** 395-428.

Johansson H & Silfvenius H. (1977c). Input from ipsilateral proprio-and exteroceptive hind limb afferents to nucleus Z of the cat medulla oblongata. *The Journal of physiology* **265,** 371-393.

Johansson RS & Flanagan JR. (2009). Coding and use of tactile signals from the fingertips in object manipulation tasks. *Nat Rev Neurosci* **10,** 345-359.

Johansson RS, Landstro¨m U & Lundstro¨m R. (1982). Responses of mechanoreceptive afferent units in the glabrous skin of the human hand to sinusoidal skin displacements. *Brain Research* **244,** 17-25.

Johnson Jr J, Welker W & Pubols Jr B. (1968). Somatotopic organization of raccoon dorsal column nuclei. *Journal of Comparative Neurology* **132,** 1-43.

Johnson KO. (2001). The roles and functions of cutaneous mechanoreceptors. *Current Opinion in Neurobiology* **11,** 455-461.

Jones EG & Friedman DP. (1982). Projection pattern of functional components of thalamic ventrobasal complex on monkey somatosensory cortex. *Journal of Neurophysiology* **48,** 521-544.

Kaas JH. (2004). Somatosensory system. *The human nervous system***,** 1059-1092.

Kaas JH, Nelson RJ, Sur M, Lin C-S & Merzenich MM. (1979). Multiple representations of the body within the primary somatosensory cortex of primates. *Science* **204,** 521-523.

Kaelber WW. (1981). Escape from and avoidance of nociception elicited by intracranial stimulation of the cat subthalamus. *Experimental Neurology* **73,** 397-420.

Kaelber WW & Smith TB. (1979). Projections of the zona incerta in the cat, with stimulation controls. *Experimental Neurology* **63,** 177-200.

Keller J & Hand P. (1970). Dorsal root projections to nucleus cuneatus of the cat. *Brain research* **20,** 1-17.

Kemplay S & Webster K. (1989). A quantitative study of the projections of the gracile, cuneate and trigeminal nuclei and of the medullary reticular formation to the thalamus in the rat. *Neuroscience* **32,** 153-167.

Kitagawa J, Tsuboi Y, Ogawa A, Ren K, Hitomi S, Saitoh K, Takahashi O, Masuda Y, Harada T, Hanzawa N, Kanda K & Iwata K. (2005). Involvement of Dorsal Column Nucleus Neurons in Nociceptive Transmission in Aged Rats. *Journal of Neurophysiology* **94,** 4178-4187.

Knibestöl M. (1973). Stimulus—response functions of rapidly adapting mechanoreceptors in the human glabrous skin area. *The Journal of Physiology* **232,** 427-452.

Knibestöl M. (1975). Stimulus-response functions of slowly adapting mechanoreceptors in the human glabrous skin area. *the Journal of Physiology* **245,** 63-80.

Kosinski R, Azizi S, Border B & Mihailoff B. (1986a). Origin and ultrastructural identification of dorsal column nuclear synaptic terminals in the basilar pontine gray of rats. *Journal of Comparative Neurology* **253,** 92-104.

Kosinski R, Azizi S & Mihailoff G. (1988a). Convergence of cortico-and cuneopontine projections onto components of the pontocerebellar system in the rat: an anatomical and electrophysiological study. *Experimental brain research* **71,** 541-556.

Kosinski R, Lee H & Mihailoff G. (1988b). A double retrograde fluorescent tracing analysis of dorsal column nuclear projections to the basilar pontine nuclei, thalamus, and superior colliculus in the rat. *Neuroscience letters* **85,** 40-46.

Kosinski RJ, Neafsey E & Castro AJ. (1986b). A comparative topographical analysis of dorsal column nuclear and cerebral cortical projections to the basilar pontine gray in rats. *Journal of Comparative Neurology* **244,** 163-173.

Kruger L, Siminoff R & Witkovsky P. (1961). Single neuron analysis of dorsal column nuclei and spinal nucleus of trigeminal in cat. *Journal of neurophysiology* **24,** 333-349.

Kuypers H & Tuerk J. (1964). The distribution of cortical fibres within the nuclei cuneatus and gracilis in the cat. *Journal of anatomy* **98,** 143.

Kuypers HG. (1958). An anatomical analysis of cortico-bulbar connexions to the pons and lower brain stem in the cat. *Journal of anatomy* **92,** 198-218.

Kuypers HG, Hoffman AL & Beasley RM. (1961). Distribution of Cortical "Feedback" Fibers in the Nuclei Cuneatus and Gracilis. *Proceedings of the Society for Experimental Biology and Medicine* **108,** 634-637.

Kuypers HGJM & Maisky VA. (1975). Retrograde axonal transport of horseradish peroxidase from spinal cord to brain stem cell groups in the cat. *Neuroscience Letters* **1,** 9-14.

Kwiat GC & Basbaum AI. (1992). The Origin of Brainstem Noradrenergic and Serotonergic Projections to the Spinal Cord Dorsal Horn in the Rat. *Somatosensory & Motor Research* **9,** 157-173.

Landgren S & Silfvenius H. (1971). Nucleus Z, the medullary relay in the projection path to the cerebral cortex of group I muscle afferents from the cat's hind limb. *The Journal of physiology* **218,** 551-571.

Leem JW, Willis WD & Chung JM. (1993). Cutaneous sensory receptors in the rat foot. *Journal of Neurophysiology* **69,** 1684-1699.

Leong SK, Shieh JY & Wong WC. (1984). Localizing spinal-cord-projecting neurons in adult albino rats. *Journal of Comparative Neurology* **228,** 1-17.

Li CX, Yang Q & Waters RS. (2012). Functional and structural organization of the forelimb representation in cuneate nucleus in rat. *Brain research* **1468,** 11-28.

Li L, Rutlin M, Abraira VE, Cassidy C, Kus L, Gong S, Jankowski MP, Luo W, Heintz N & Koerber HR. (2011). The functional organization of cutaneous low-threshold mechanosensory neurons. *Cell* **147,** 1615-1627.

Liu C-n. (1956). Afferent nerves to Clarke's and the lateral cuneate nuclei in the cat. *AMA Archives of Neurology & Psychiatry* **75,** 67-77.

Löken LS, Wessberg J, McGlone F & Olausson H. (2009). Coding of pleasant touch by unmyelinated afferents in humans. *Nature neuroscience* **12,** 547.

Loutit AJ, Maddess T, Redmond SJ, Morley JW, Stuart GJ & Potas JR. (2017). Characterisation and functional mapping of surface potentials in the rat dorsal column nuclei. *The Journal of Physiology* **595,** 4507-4524.

Loutit AJ, Shivdasani MN, Maddess T, Redmond SJ, Morley JW, Stuart GJ, Birznieks I, Vickery RM & Potas JR. (2019). Peripheral Nerve Activation Evokes Machine-Learnable Signals in the Dorsal Column Nuclei. *Frontiers in Systems Neuroscience* **13**.

Low JST, John LAM-S & Tracey DJ. (1986). Nucleus Z in the rat: Spinal afferents from collaterals of dorsal spinocerebellar tract neurons. *Journal of Comparative Neurology* **243,** 510-526.

Lund RD & Webster KE. (1967). Thalamic afferents from the dorsal column nuclei. An experimental anatomical study in the rat. *Journal of Comparative Neurology* **130,** 301-311.

Luo W, Enomoto H, Rice FL, Milbrandt J & Ginty DD. (2009). Molecular identification of rapidly adapting mechanoreceptors and their developmental dependence on ret signaling. *Neuron* **64,** 841-856.

Macefield VG. (2005). Physiological characteristics of low-threshold mechanoreceptors in joints, muscle and skin in human subjects. *Clin Exp Pharmacol Physiol* **32,** 135-144.

Magherini P, Pompeiano O & Seguin J. (1975). Responses of nucleus z neurons to vibration of hindlimb extensor muscles in the decerebrate cat. *Archives italiennes de biologie* **113,** 150-187.

Magherini PC, Pompeiano O & Sequin JJ. (1974). The response of nucleus z neurons to sinusoidal stretch of hindlimb extensor muscles. *Brain research* **73,** 343-349.

Mantle-St. John LA & Tracey DJ. (1987). Somatosensory nuclei in the brainstem of the rat: independent projections to the thalamus and cerebellum. *Journal of Comparative Neurology* **255,** 259-271.

Mariño J, Martinez L & Canedo A. (1999). Sensorimotor integration at the dorsal column nuclei. *Physiology* **14,** 231-237.

Martinez L, Lamas J & Canedo A. (1995). Pyramidal tract and corticospinal neurons with branching axons to the dorsal column nuclei of the cat. *Neuroscience* **68,** 195-206.

Maslany S, Crockett DP & Egger MD. (1991). Somatotopic organization of the dorsal column nuclei in the rat: transganglionic labelling with B-HRP and WGA-HRP. *Brain Research* **564,** 56-65.

Maslany S, Crockett DP & Egger MD. (1992). The cuneate nucleus in the rat does have an anatomically distinct middle region. *Neuroscience letters* **139,** 130-134.

Massopust LC, Hauge DH, Ferneding JC, Doubek WG & Taylor JJ. (1985). Projection systems and terminal localization of dorsal column afferents: An autoradiographic and horseradish peroxidase study in the rat. *Journal of Comparative Neurology* **237,** 533-544.

May PJ. (2006). The mammalian superior colliculus: laminar structure and connections. In *Progress in Brain Research*, ed. Büttner-Ennever JA, pp. 321-378. Elsevier.

McComas A. (1963). Responses of the rat dorsal column system to mechanical stimulation of the hind paw. *The Journal of physiology* **166,** 435-448.

McCurdy M, Gibson A & Houk JC. (1992). Spatial overlap of rubrospinal and corticospinal terminals with input to the inferior olive. *Neuroimage* **1,** 23-41.

McCurdy M, Houk J & Gibson A. (1998). Organization of ascending pathways to the forelimb area of the dorsal accessory olive in the cat. *Journal of Comparative Neurology* **392,** 115-133.

McHaffie JG, Kruger L, Clemo HR & Stein BE. (1988). Corticothalamic and corticotectal somatosensory projections from the anterior ectosylvian sulcus (SIV cortex) in neonatal cats: An anatomical demonstration with HRP and 3H-leucine. *Journal of Comparative Neurology* **274,** 115-126.

Mihailoff GA, Burne RA, Azizi SA, Norell G & Woodward DJ. (1981a). The pontocerebellar system in the rat: An HRP study. II. Hemispheral components. *Journal of Comparative Neurology* **197,** 559-577.

Mihailoff GA, Watt C & Burne R. (1981b). Evidence suggesting that both the corticopontine and cerebellopontine systems are each composed of two separate neuronal populations: an electron microscopic and horseradish peroxidase study in the rat. *Journal of Comparative Neurology* **195,** 221-242.

Miki K, Fukuoka T, Tokunaga A & Noguchi K. (1997). Calcitonin gene-related peptide increase in the rat spinal dorsal horn and dorsal column nucleus following peripheral nerve injury: Up-regulation in a subpopulation of primary afferent sensory neurons. *Neuroscience* **82,** 1243-1252.

Millar J & Basbaum AI. (1975). Topography of the projection of the body surface of the cat to cuneate and gracile nuclei. *Experimental Neurology* **49,** 281-290.

Mjaatvedt A & Wong-Riley M. (1988). Relationship between synaptogenesis and cytochrome oxidase activity in Purkinje cells of the developing rat cerebellum. *Journal of Comparative Neurology* **277,** 155-182.

Molenaar GJ. (1976). The rhombencephalon of Python reticulatus, a snake possessing infrared receptors. *Netherlands Journal of Zoology* **27,** 133-181.

Molinari HH. (1984). Ascending somatosensory projections to the dorsal accessory olive: an anatomical study in cats. *Journal of Comparative Neurology* **223,** 110-123.

Molinari HH, Schultze KE & Strominger NL. (1996). Gracile, cuneate, and spinal trigeminal projections to inferior olive in rat and monkey. *Journal of Comparative Neurology* **375,** 467-480.

Mountcastle VB. (1984). Central nervous mechanisms in mechanoreceptive sensibility. *Handbook of physiology* **3,** 789-878.

Munger BL, Pubols L & Pubols B. (1971). The Merkel rete papilla—a slowly adapting sensory receptor in mammalian glabrous skin. *Brain research* **29,** 47-61.

Nagata T & Kruger L. (1979). Tactile neurons of the superior colliculus of the cat: Input and physiological properties. *Brain Research* **174,** 19-37.

Naito J & Kawamura K. (1982). Thalamocortical neurons projecting to the areas surrounding the anterior and middle suprasylvian sulci in the cat. *Experimental Brain Research* **45,** 59-70.

Nicolelis MAL, Chapin JK & Lin RCS. (1992). Somatotopic maps within the zona incerta relay parallel GABAergic somatosensory pathways to the neocortex, superior colliculus, and brainstem. *Brain Research* **577,** 134-141.

Nijensohn DE & Kerr FW. (1975). The ascending projections of the dorsolateral funiculus of the spinal cord in the primate. *Journal of Comparative Neurology* **161,** 459-469.

Niu J, Ding L, Li JJ, Kim H, Liu J, Li H, Moberly A, Badea TC, Duncan ID & Son Y-J. (2013). Modality-based organization of ascending somatosensory axons in the direct dorsal column pathway. *The Journal of Neuroscience* **33,** 17691-17709.

Nord SG. (1967). Somatotopic organization in the spinal trigeminal nucleus, the dorsal column nuclei and related structures in the rat. *J Comp Neurol* **130,** 343-356.

Noriega AL & Wall JT. (1991). Parcellated organization in the trigeminal and dorsal column nuclei of primates. *Brain research* **565,** 188-194.

Nyberg G. (1988). Representation of the forepaw in the feline cuneate nucleus: a transganglionic transport study. *Journal of Comparative Neurology* **271,** 143-152.

Nyberg G & Blomqvist A. (1982). The termination of forelimb nerves in the feline cuneate nucleus demonstrated by the transganglionic transport method. *Brain research* **248,** 209-222.

Nyberg G & Blomqvist A. (1984). The central projection of muscle afferent fibres to the lower medulla and upper spinal cord: an anatomical study in the cat with the transganglionic transport method. *Journal of Comparative Neurology* **230,** 99-109.

Ostapoff E-M, Johnson J & Albright B. (1983). Mechanosensory projections to cuneate, gracile, and external cuneate nuclei in a tree squirrel (fox squirrel, Sciurus niger). *neuroscience* **9,** 107-127.

Ostapoff E-M, Johnson JI & Albright BC. (1988). Medullary sources of projections to the kinesthetic thalamus in raccoons: External and basal cuneate nuclei and cell groups x and z. *Journal of Comparative Neurology* **267,** 231-252.

Ostapoff EM & Johnson JI. (1988). Distribution of cells projecting to thalamus vs. those projecting to cerebellum in subdivisions of the dorsal column nuclei in raccoons. *Journal of Comparative Neurology* **267,** 211-230.

Padberg J, Cerkevich C, Engle J, Rajan AT, Recanzone G, Kaas J & Krubitzer L. (2009). Thalamocortical connections of parietal somatosensory cortical fields in macaque monkeys are highly divergent and convergent. *Cerebral Cortex* **19,** 2038-2064.

Paxinos G, Huang X-F, Sengul G & Watson C. (2012). Organization of brainstem nuclei.

Paxinos G & Watson C. (1998). A stereotaxic atlas of the rat brain. *New York: Academic*.

Pearson J & Garfunkel D. (1983). Evidence for thalamic projections from external cuneate nucleus, cell groups Z and X, and the mesencephalic nucleus of the trigeminal nerve in squirrel monkey. *Neuroscience letters* **41,** 41-47.

Perl ER. (1968). Myelinated afferent fibres innervating the primate skin and their response to noxious stimuli. *The Journal of Physiology* **197,** 593-615.

Pompeiano O & Brodal A. (1957). Spino-vestibular fibers in the cat. An experimental study. *Journal of Comparative Neurology* **108,** 353-381.

Proske U & Gandevia SC. (2012). The Proprioceptive Senses: Their Roles in Signaling Body Shape, Body Position and Movement, and Muscle Force. *Physiological Reviews* **92,** 1651-1697.

Qi H-X, Gharbawie OA, Wong P & Kaas JH. (2011). Cell-poor septa separate representations of digits in the ventroposterior nucleus of the thalamus in monkeys and prosimian galagos. *Journal of Comparative Neurology* **519,** 738-758.

Qi HX & Kaas JH. (2006). Organization of primary afferent projections to the gracile nucleus of the dorsal column system of primates. *Journal of Comparative Neurology* **499,** 183-217.

Quy PN, Fujita H, Sakamoto Y, Na J & Sugihara I. (2011). Projection patterns of single mossy fiber axons originating from the dorsal column nuclei mapped on the aldolase C compartments in the rat cerebellar cortex. *Journal of Comparative Neurology* **519,** 874-899.

Ramanathan KR, Ressler RL, Jin J & Maren S. (2018). Nucleus reuniens is required for encoding and retrieving precise, hippocampal-dependent contextual fear memories in rats. *Journal of Neuroscience* **38,** 9925-9933.

 doi:10.20944/preprints201911.0084.v1

Rasmusson DD. (1988). Projections of digit afferents to the cuneate nucleus in the raccoon before and after partial deafferentation. *Journal of Comparative Neurology* **277,** 549-556.

Rasmusson DD. (1989). The projection pattern of forepaw nerves to the cuneate nucleus of the raccoon. *Neuroscience letters* **98,** 129-134.

Ricardo JA. (1981). Efferent connections of the subthalamic region in the rat. II. The zona incerta. *Brain Research* **214,** 43-60.

Rinvik E & Walberg F. (1975). Studies on the cerebellar projections from the main and external cuneate nuclei in the cat by means of retrograde axonal transport of horseradish peroxidase. *Brain Research* **95,** 371-381.

Robards MJ. (1979). Somatic neurons in the brainstem and neocortex projecting to the external nucleus of the inferior colliculus: an anatomical study in the opossum. *Journal of Comparative Neurology* **184,** 547-565.

RoBards MJ, Watkins III DW & Masterton RB. (1976). An anatomical study of some somesthetic afferents to the intercollicular terminal zone of the midbrain of the opossum. *Journal of Comparative Neurology* **170,** 499-524.

Robinson F, Houk J & Gibson A. (1987). Limb specific connections of the cat magnocellular red nucleus. *Journal of Comparative Neurology* **257,** 553-577.

Roda JM & Reinoso-Suárez F. (1983). Topographical organization of the thalamic projections to the cortex of the anterior ectosylvian sulcus in the cat. *Experimental Brain Research* **49,** 131-139.

Roger M & Cadusseau J. (1985). Afferents to the zona incerta in the rat: A combined retrograde and anterograde study. *Journal of Comparative Neurology* **241,** 480-492.

Romanowski CA, Mitchell IJ & Crossman AR. (1985). The organisation of the efferent projections of the zona incerta. *Journal of anatomy* **143,** 75-95.

Rosen I. (1969). Localization in caudal brain stem and cervical spinal cord of neurones activated from forelimb group I afferents in the cat. *Brain research* **16,** 55-71.

Rüegg D, Séguin J & Wiesendanger M. (1977). Effects of electrical stimulation of somatosensory and motor areas of the cerebral cortex on neurones of the pontine nuclei in squirrel monkeys. *Neuroscience* **2,** 923-927.

Rüegg D & Wiesendanger M. (1975). Corticofugal effects from sensorimotor area I and somatosensory area II on neurones of the pontine nuclei in the cat. *The Journal of physiology* **247,** 745-757.

Rustioni A. (1973). Non-primary afferents to the nucleus gracilis from the lumbar cord of the cat. *Brain Research* **51,** 81-95.

Rustioni A & Hayes N. (1981). Corticospinal tract collaterals to the dorsal column nuclei of cats. *Experimental brain research* **43,** 237-245.

Rustioni A, Hayes NL & O'Neill S. (1979). Dorsal Column Nuclei and Ascending Spinal Afferents in Macaques. *Brain* **102,** 95-125.

Rustioni A & Kaufman A. (1977). Identification of cells of origin of non-primary afferents to the dorsal column nuclei of the cat. *Experimental brain research* **27,** 1-14.

Rustioni A, Schmechel D, Cheema S & Fitzpatrick D. (1984). Glutamic acid decarboxylase-containing neurons in the dorsal column nuclei of the cat. *Somatosensory research* **1,** 329-357.

Sadjadpour K & Brodal A. (1968). The vestibular nuclei in man. A morphological study in the light of experimental findings in the cat. *Journal fur Hirnforschung* **10,** 299.

Salas MA, Bashford L, Kellis S, Jafari M, Jo H, Kramer D, Shanfield K, Pejsa K, Lee B & Liu CY. (2018). Proprioceptive and cutaneous sensations in humans elicited by intracortical microstimulation. *Elife* **7,** e32904.

Sanders K & Zimmermann M. (1986). Mechanoreceptors in rat glabrous skin: redevelopment of function after nerve crush. *Journal of neurophysiology* **55,** 644-659.

Sarko DK, Johnson JI, Switzer III RC, Welker WI & Reep RL. (2007). Somatosensory nuclei of the manatee brainstem and thalamus. *The Anatomical Record: Advances in Integrative Anatomy and Evolutionary Biology: Advances in Integrative Anatomy and Evolutionary Biology* **290,** 1138-1165.

Sawyer EK, Turner EC & Kaas JH. (2016). Somatosensory brainstem, thalamus, and cortex of the California sea lion (Zalophus californianus). *Journal of Comparative Neurology* **524,** 1957-1975.

Schroeder DM & Jane JA. (1971). Projection of dorsal column nuclei and spinal cord to brainstem and thalamus in the tree shrew, Tupaia glis. *Journal of Comparative Neurology* **142,** 309-350.

Schroeder DM & Jane JA. (1976). The Intercollicular Area of the Inferior Colliculus. *Brain, Behavior and Evolution* **13,** 125-141.

Schwark HD & Ilyinsky OB. (2001). Inflammatory pain reduces correlated activity in the dorsal column nuclei11Published on the World Wide Web on 6 December 2000. *Brain Research* **889,** 295-302.

Scott J. (1990). Classification of muscle spindle afferents in the peroneus brevis muscle of the cat. *Brain research* **509,** 62-70.

Smith MC & Deacon P. (1984). Topographical anatomy of the posterior columns of the spinal cord in man: The long ascending fibres. *Brain* **107,** 671-698.

Somana R & Walberg F. (1980). A re-examination of the cerebellar projections from the gracile, main and external cuneate nuclei in the cat. *Brain research* **186,** 33-42.

Stein BE, Spencer RF & Edwards SB. (1983). Corticotectal and corticothalamic efferent projections of SIV somatosensory cortex in cat. *Journal of Neurophysiology* **50,** 896-909.

Stein BE, Stanford TR & Rowland BA. (2014). Development of multisensory integration from the perspective of the individual neuron. *Nature Reviews Neuroscience* **15,** 520.

Strata F, Coq J-O & Kaas J. (2003). The chemo-and somatotopic architecture of the Galago cuneate and gracile nuclei. *Neuroscience* **116,** 831-850.

Swenson RS, Kosinski RJ & Castro AJ. (1984). Topography of spinal, dorsal column nuclear, and spinal trigeminal projections to the pontine gray in rats. *Journal of Comparative Neurology* **222,** 301-311.

Tawil RN, Saadé NE, Bitar M & Jabbur SJ. (1983). Polysensory interactions on single neurons of cat inferior colliculus. *Brain Research* **269,** 149-152.

Therman PO. (1941). TRANSMISSION OF IMPULSES THROUGH THE BURDACH NUCLEUS. *Journal of Neurophysiology* **4,** 153-166.

Uddenberg N. (1968). Functional organization of long, second-order afferents in the dorsal funiculus. *Experimental brain research* **4,** 377-382.

Villanueva L, Bernard JF & Le Bars D. (1995). Distribution of spinal cord projections from the medullary subnucleus reticularis dorsalis and the adjacent cuneate nucleus: A phaseolus vulgaris- leucoagglutinin study in the rat. *Journal of Comparative Neurology* **352,** 11-32.

Villanueva L, Desbois C, le Bars D & Bernard JF. (1998). Organization of diencephalic projections from the medullary subnucleus reticularis dorsalis and the adjacent cuneate nucleus: a retrograde and anterograde tracer study in the rat. *Journal of Comparative Neurology* **390,** 133-160.

Walberg F, Nordby T, Hoffmann KP & Holländer H. (1981). Olivary afferents from the pretectal nuclei in the cat. *Anatomy and Embryology* **161,** 291-304.

Wang C-C & Westlund KN. (2001). Responses of rat dorsal column neurons to pancreatic nociceptive stimulation. *NeuroReport* **12,** 2527-2530.

Weber JT & Harting JK. (1980). The efferent projections of the pretectal complex: an autoradiographic and horseradish peroxidase analysis. *Brain Research* **194,** 1-28.

Wei JY, Kripke BR & Burgess P. (1986). Classification of muscle spindle receptors. *Brain research* **370,** 119-126.

Weiss C, Houk JC & Gibson AR. (1990). Inhibition of sensory responses of cat inferior olive neurons produced by stimulation of red nucleus. *Journal of Neurophysiology* **64,** 1170-1185.

Whitsel BL, Petrucelli LM & Sapiro G. (1969). Modality representation in the lumbar and cervical fasciculus gracilis of squirrel monkeys. *Brain Research* **15,** 67-78.

Whitsel BL, Petrucelli LM, Sapiro G & Ha H. (1970). Fiber sorting in the fasciculus gracilis of squirrel monkeys. *Experimental Neurology* **29,** 227-242.

Wiberg M & Blomqvist A. (1984a). The projection to the mesencephalon from the dorsal column nuclei. An anatomical study in the cat. *Brain Research* **311,** 225-244.

Wiberg M & Blomqvist A. (1984b). The spinomesencephalic tract in the cat: Its cells of origin and termination pattern as demonstrated by the intraaxonal transport method. *Brain Research* **291,** 1-18.

Wiberg M, Westman J & Blomqvist A. (1986). The projection to the mesencephalon from the sensory trigeminal nuclei. An anatomical study in the cat. *Brain Research* **399,** 51-68.

Wiberg M, Westman J & Blomqvist A. (1987). Somatosensory projection to the mesencephalon: An anatomical study in the monkey. *Journal of Comparative Neurology* **264,** 92-117.

Wodlinger B, Downey JE, Tyler-Kabara EC, Schwartz AB, Boninger ML & Collinger JL. (2014). Ten-dimensional anthropomorphic arm control in a human brain−machine interface: difficulties, solutions, and limitations. *Journal of Neural Engineering* **12,** 016011.

Wong-Riley MT. (1989). Cytochrome oxidase: an endogenous metabolic marker for neuronal activity. *Trends in neurosciences* **12,** 94-101.

Woudenberg RA. (1970). Projections of mechanoreceptive fields to cuneate-gracile and spinal trigeminal nuclear regions in sheep. *Brain research* **17,** 417-437.

Wree A, Itzev DE, Schmitt O & Usunoff KG. (2005). Neurons in the dorsal column nuclei of the rat emit a moderate projection to the ipsilateral ventrobasal thalamus. *Anatomy and Embryology* **210,** 155-162.

 doi:10.20944/preprints201911.0084.v1

Xu J & Wall J. (1996). Cutaneous representations of the hand and other body parts in the cuneate nucleus of a primate, and some relationships to previously described cortical representations. *Somatosensory & motor research* **13,** 187-197.

Xu J & Wall J. (1999). Functional organization of tactile inputs from the hand in the cuneate nucleus and its relationship to organization in the somatosensory cortex. *Journal of Comparative Neurology* **411,** 369-389.

Zhao F, Welsh D, Williams M, Coimbra A, Urban MO, Hargreaves R, Evelhoch J & Williams DS. (2012). fMRI of pain processing in the brain: A within-animal comparative study of BOLD vs. CBV and noxious electrical vs. noxious mechanical stimulation in rat. *NeuroImage* **59,** 1168-1179.

Zimmerman A, Bai L & Ginty DD. (2014). The gentle touch receptors of mammalian skin. *Science* **346,** 950-954.

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Tables

Table 1. Morphology and neural characteristics of the dorsal column nuclei rostrocaudal zones. Abbreviations: RA, rapidly adapting; SA, slowly adapting, see **Figure 1** for remaining abbreviations.

		General description	Cell types/sizes	Response properties	Receptive fields
Rostral	**GrN**	Appears reticulated and less dense than middle DCN	Mixed cell sizes Many large cells	Mostly RA, driven by a mixture of deep and cutaneous inputs	Mostly large Dominated by representation of proximal and axial body parts
	CuN			Almost exclusively SA, mostly driven by deep inputs	
Clusters	**GrN**	Dense cell clusters, surrounded by cell-poor septa Less defined than in the CuN	Small or medium round cells with dense bushy dendritic arbours	Mostly RA with some SA cutaneous responses	Mostly very small Dominated by representation of distal limbs
	CuN	Dense cell clusters, surrounded by cell-poor septa More defined than in the GrN		Mostly SA with some RA cutaneous responses	
Shell	**GrN**	Thin reticulated shell surrounding the clusters region on the medial, dorsal, and lateral sides	Small or medium round cells, some spindle cells	Mostly RA with some SA cutaneous responses	Larger than cluster region cells Dominated by representation of proximal and axial body parts
	CuN			Mostly SA with some RA cutaneous responses	
Ventral	**GrN**	Reticulated appearance, no obvious clustering	Small or medium round cells, some spindle cells, and cells with large radiating dendritic arbours	Mostly RA with some SA responses, mostly driven by proprioceptive inputs	Larger than cluster region cells Relatively even representation of the body
	CuN	Ventral and lateral to the cluster region, no obvious clustering		Mostly SA with some RA responses, mostly driven by proprioceptive inputs	
Caudal	**GrN**	Appears less dense than middle DCN with relatively uniform cell dispersion	Medium and large, round cells, scattered multipolar and spindle cell bodies	Mostly cutaneous RA responses Higher proportion of Pacinian-like responses	Mostly very large Relatively even representation of the body
	CuN			Mostly cutaneous SA responses Higher proportion of Pacinian-like responses	

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Figures and legends

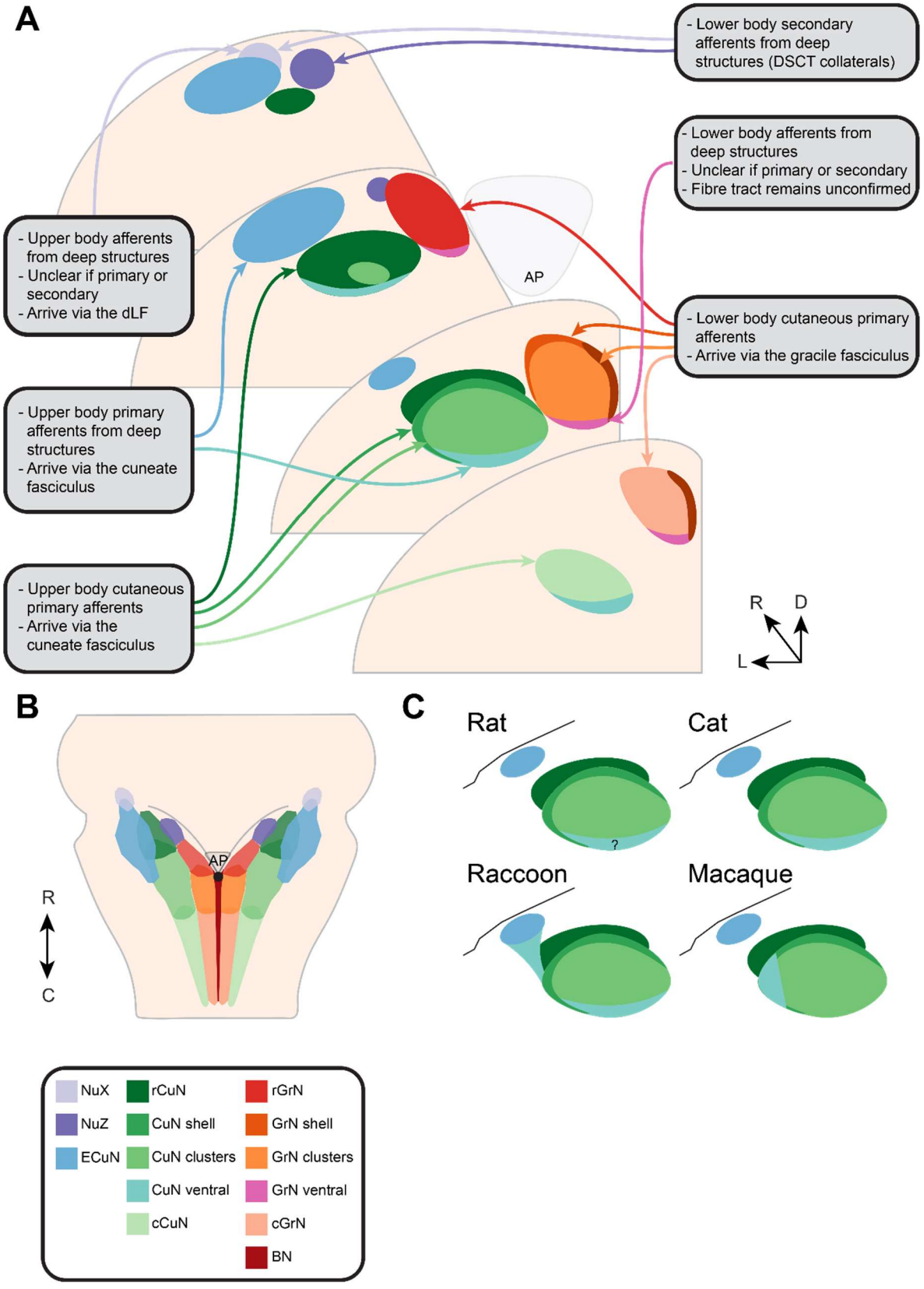

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Figure 1. The organisation of the dorsal column nuclei-complex and their ascending afferent inputs. (A) A schematic representation of the dorsal medulla (left side only) shows the DCN-complex across four rostro-caudal levels. Arrows indicate ascending inputs from spinal cord or dorsal root ganglia neurons to each sub-region of the complex (colour coded according to the figure key). Grey boxes describe body regions and fibre tracts of the ascending afferents. All ascending afferents have receptive fields ipsilateral to their DCN-complex targets. **(B)** Schematic representation of the DCN-complex in the medulla viewed from the dorsal aspect. Translucent shading demonstrates the overlap and dorso-ventral arrangements of nuclei. Obex (black dot) is located at the caudal end of the fourth ventricle, where the rGrN sit more laterally to either side of area postrema (AP). **(C)** Species differences of the CN ventral region is shown. CN ventral appears to extend throughout the rostrocaudal zones in all four species, but changes shape for some species in the middle DCN. This region is defined by a more reticulated appearance which is unclear in rats, however like other species, receives predominantly proprioceptive inputs. In cats, CN ventral is found at the base of the CN. Raccoons have a 'bridge' region of proprioceptive-recipient cells extending from the ECN to the ventral portion of mCuN and rCuN. Macaques and other primates have a triangular-shaped zone at the lateral edge of the mCuN and rCuN, named *pars triangularis*. Pars triangularis is depicted within the mCuN, but in more rostral segments (not shown) where the ECuN is larger, this region would fill the space between the lateral portion of the CuN and the ventral medial portion of the ECuN. Orientations indicated for A and B: C, caudal; D, dorsal; L, lateral; R, rostral. Abbreviations: AP, area postrema; BN, Bischoff's nucleus; cCuN, caudal cuneate nuclei; CuN clusters, cluster regions of the middle cuneate nuclei; CuN shell, shell region of the middle cuneate nuclei; CuN ventral, ventral region of the cuneate nuclei; rCuN, rostral cuneate nuclei; DCN, dorsal column nuclei; ECuN, external cuneate nuclei; cGrN, caudal gracile nuclei; GrN clusters, cluster regions of the middle gracile nuclei; GrN shell, shell region of the middle gracile nuclei; GrN ventral, ventral region of the gracile nuclei; rGrN, rostral gracile nuclei; NuX, nucleus X; NuZ, nucleus Z; dLF, dorsal aspect of the lateral funiculus; DSCT, dorsal spinocerebellar tract.

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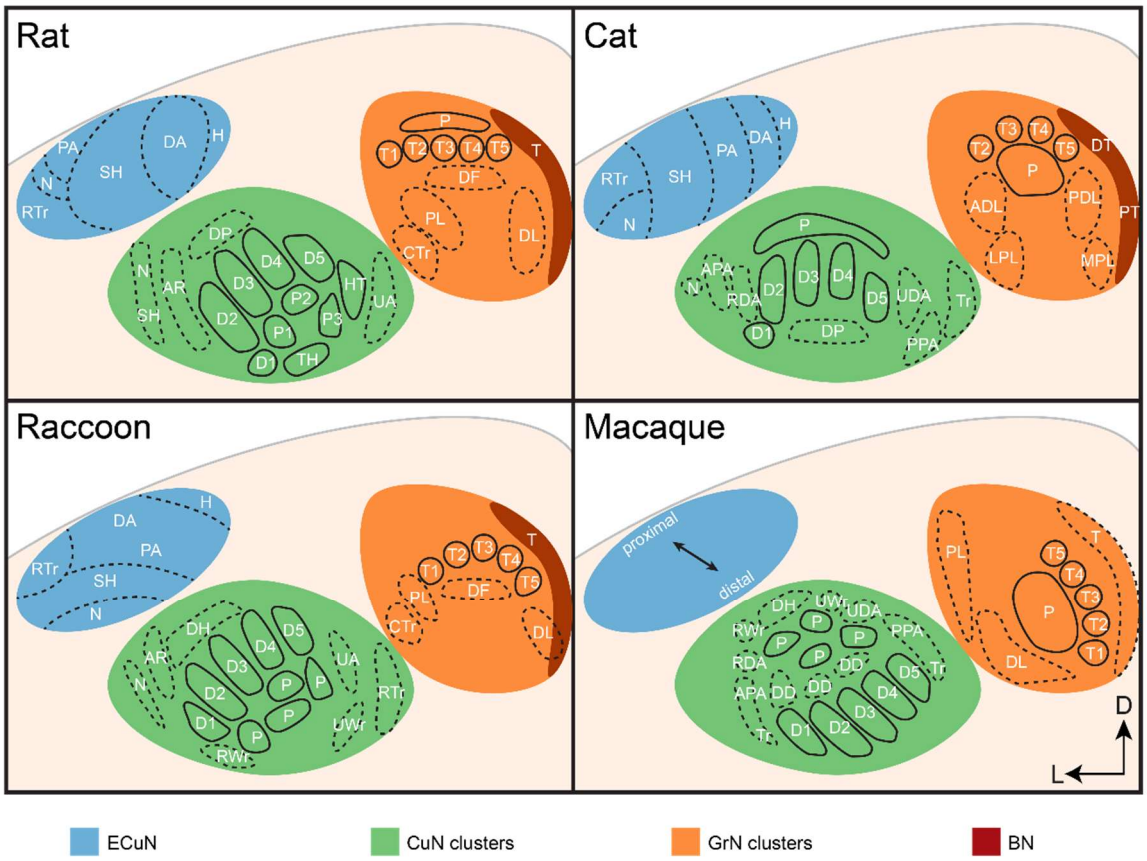

ADL	anterior distal leg	**H**	hand	**RDA**	radial distal arm
APA	anterior proximal arm	**HT**	hypothenar pad	**RTr**	rostral trunk
AR	radial arm	**LPL**	lateral proximal leg	**RWr**	radial wrist
CTr	caudal trunk	**MPL**	medial proximal leg	**SH**	shoulder
D1-D5	digits 1-5	**N**	neck	**T**	tail
DA	distal arm	**P**	palm	**T1-T5**	toes 1-5
DD	dorsal digits	**P1-P3**	palmar pad 1-3	**TH**	thenar pad
DF	dorsal foot	**PDL**	posterior distal leg	**Tr**	trunk
DH	dorsal hand	**PA**	proximal arm	**UA**	ulnar arm
DL	distal leg	**PL**	proximal leg	**UDA**	ulnar distal arm
DP	dorsal paw	**PPA**	posterior proximal arm	**UWr**	ulnar wrist
DT	distal tail	**PT**	proximal tail		

Figure 2. Somatotopy of DCN middle regions and the ECuN of four commonly studied mammalian species. Comparison of rat, cat, raccoon, and macaque somatotopy of the DCN middle region, and the ECuN reveals similarities and differences among species. Solid lines indicate representations of known or suggested clustering patterns, best revealed through CO reactivity, whereas dashed lines indicate cluster regions with poorly defined boundaries. Groups of afferents from different body regions, particularly the glabrous skin of the digits/toes and palmar/plantar pads, terminate on individual CO-dense clusters of the DCN, like those indicated by solid lines. Afferents from other body regions, particularly the lower body and trunk, may terminate in several CO-dense clusters, or in more nebulous CO-dense regions,

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like those indicated by dashed lines. A single CO-dense cluster may receive afferents from several different body regions, but this is unlikely in digit-associated clusters. Rats, raccoons, and macaques (and other primates) all show a characteristic crescent-shaped digit arrangement, with the palmar pads on the concave side of the crescent. Contrastingly, cats show a straighter digit arrangement, with the pad represented on the convex side. The macaque hand representation is flipped upside-down compared to rats and raccoons, which appears to be different, even to other nonhuman primates, but may be similar in humans. For convenience, the ECuN is shown at its largest cross-sectional area to display the somatotopy. However, the largest cross-sectional area would normally be found in more rostral locations compared to the middle DCN (see **Figure 1**). The ECuN does not show clustering, and location mapping is poorly defined compared to the CuN and GrN. ECuN somatotopy in different species generally shows a medial to lateral progression of distal to proximal body regions. The macaque ECuN map has not been well characterised, but has been described to have distal body parts dorsally and medially, and proximal body parts ventrally and laterally. The table below the DCN maps contains abbreviations from the maps. Orientations indicated: L, lateral; D, dorsal. Abbreviations: CO, cytochrome oxidase. See **Figure 1** legend for all other abbreviations.

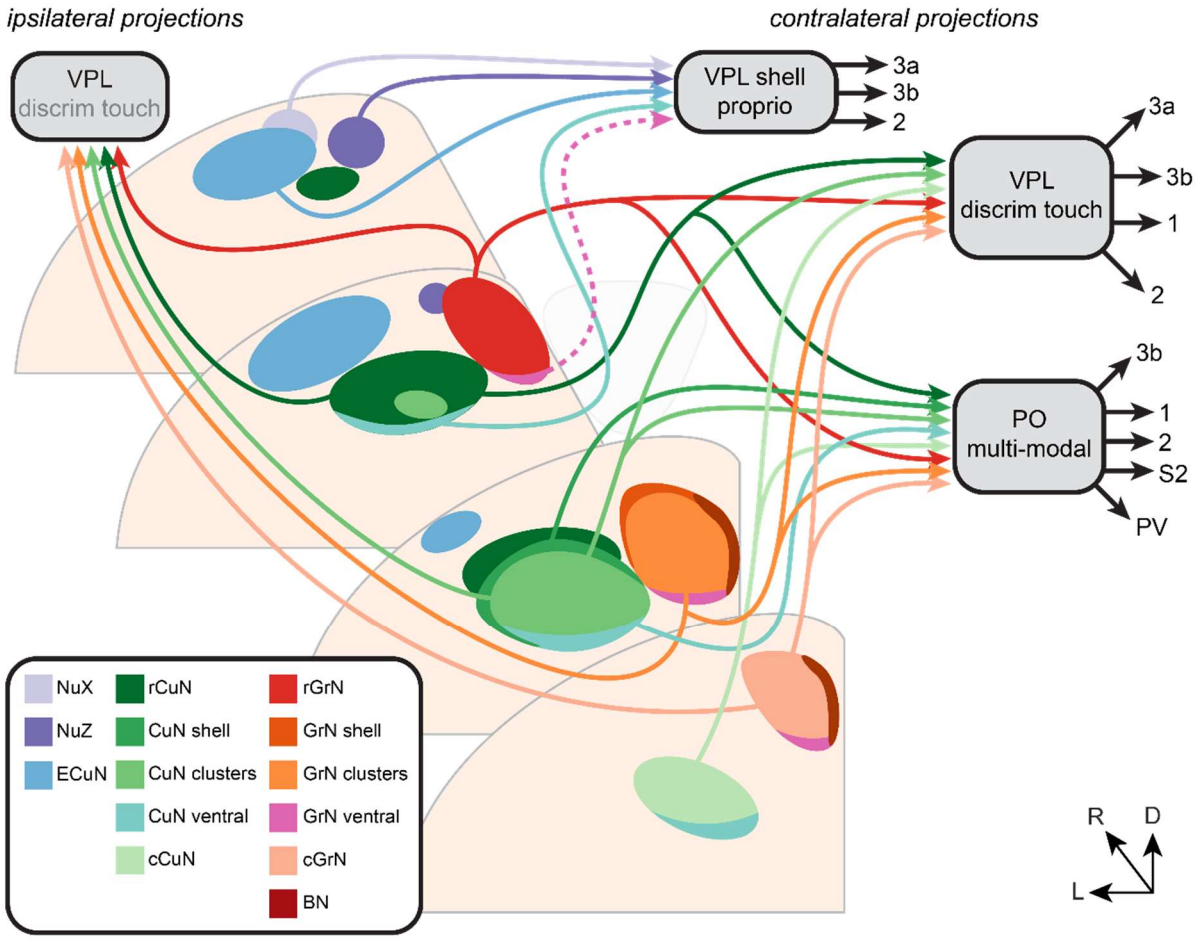

Figure 3. The dorsal column nuclei-complex projection targets in the thalamus. The DCN-complex neurons projecting to the thalamus make up the *cortical system*, which is the dominant DCN-complex output system. The arrows indicate projections from the DCN-complex to thalamic targets. For clarity, arrows are shown for only one rostro-caudal level, but represent the entire rostro-caudal extent of each respective

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region. The first cortical subsystem involves the VPL, which receives the most DCN-complex projections and conveys discriminative touch information to cortical areas 3a, 3b, 1, and 2. The VPL receives almost all its inputs from the DCN clusters regions, with some input from rostral and caudal zones. The second cortical subsystem involves the VPL shell region that is the main target of the DCN-complex that convey proprioceptive information to cortical areas 3a, 3b, and 2. Most of the VPL shell inputs originate from neurons in the ECuN, ventral DCN, and NuX and NuZ. The third cortical subsystem involves thalamic PO, which receives multimodal inputs from most of the DCN, except the ventral zone, and projects to areas 3b, 1, 2, S2, and PV. Almost all thalamic projections from the DCN-complex are contralateral, except for a minor projection to the ipsilateral VPL, which originates from neurons in all the GrN zones, rCuN, and CuN clusters. Orientations indicated: L, lateral; D, dorsal; R, rostral. Abbreviations: PO, posterior group of the thalamus; PV, the parietal ventral area; S2, secondary somatosensory cortex; VPL, ventroposterior lateral nucleus of the thalamus; VPL shell, the anterior shell surrounding the ventroposterior lateral nucleus of the thalamus. See **Figure 1** legend for all other abbreviations and orientations.

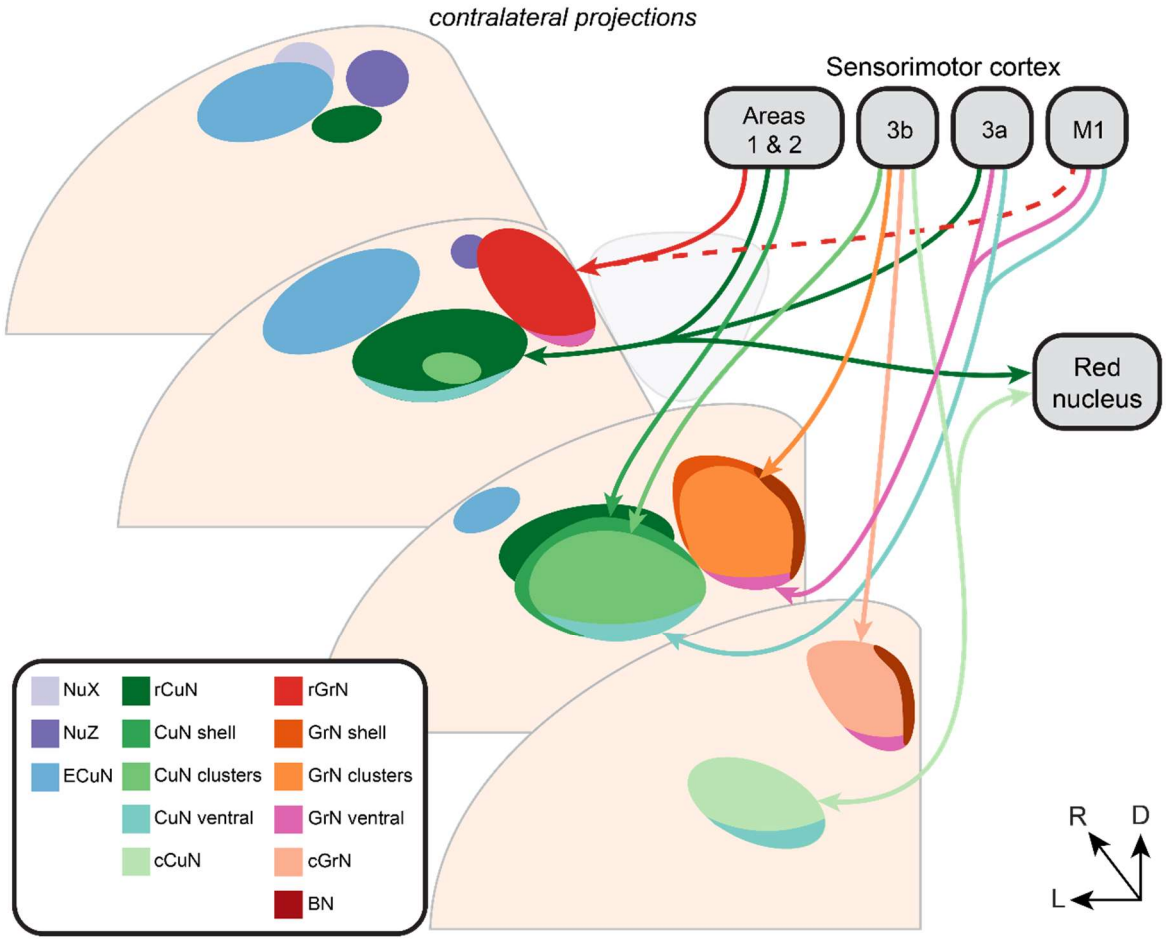

Figure 4. Dorsal column nuclei-complex inputs from the sensorimotor cortex and red nucleus. In addition to receiving peripheral and spinal ascending afferents, the DCN-complex also receives inputs from the sensorimotor cortex and red nucleus. DCN regions that predominantly receive ascending cutaneous inputs, including the DCN clusters and caudal regions, receive corticofugal projections from area 3b. Regions that predominantly receive proprioceptive-related ascending inputs, including ventral and rostral DCN, receive corticofugal projections from areas 3a and 4. The red nucleus sends projections to the rostral and caudal CuN, which are both regions that send reciprocal projections to the red nucleus. See **Figure 1** legend for orientations and abbreviations.

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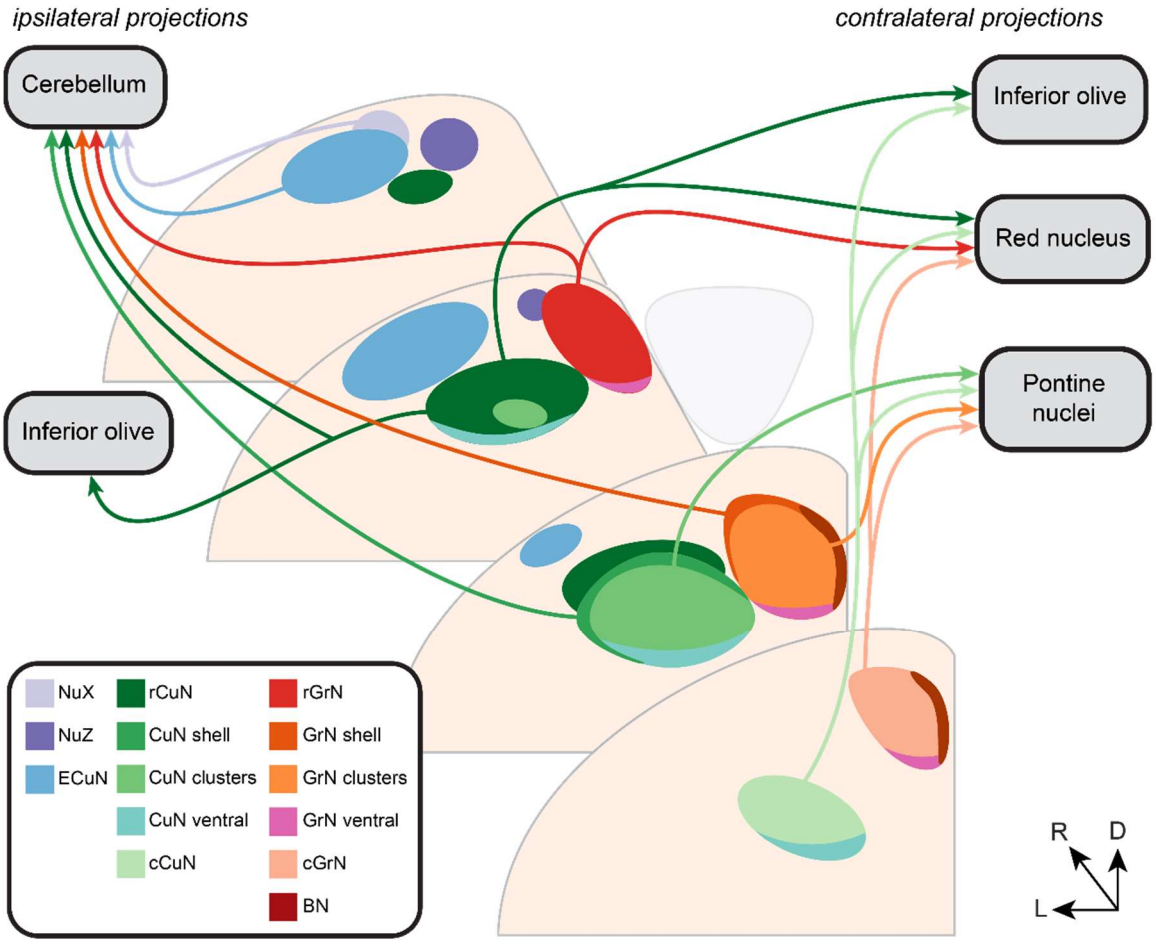

Figure 5. The dorsal column nuclei-complex projection targets of the *cerebellar system*. The dominant population of projections in the *cerebellar system* are to the ipsilateral cerebellum, from the ECuN, rostral DCN, and some inputs from DCN shell regions and nuclei X. The IO and RN receive inputs from neural populations in the rostral and caudal DCN. The pontine nuclei receive inputs from the DCN clusters and caudal regions. Cerebellar, IO, and RN inputs predominantly convey proprioceptive-related information, but interestingly the pontine nuclei appear to receive cutaneous discriminative touch information. Abbreviations: DCN, dorsal column nuclei, ECuN, external cuneate nuclei, IO, inferior olive; RN, red nucleus; See **Figure 1** legend for orientations and all other abbreviations.

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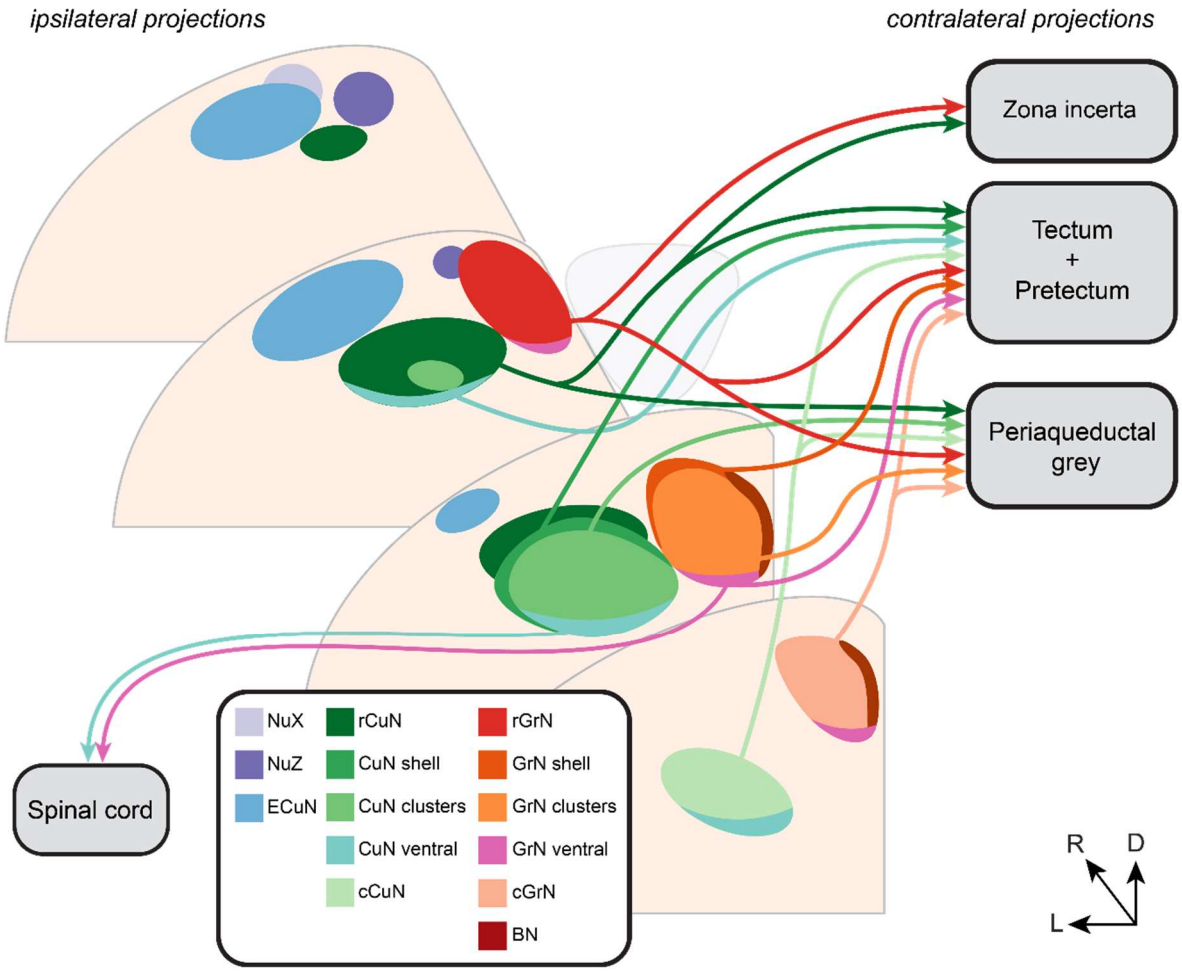

Figure 6. The dorsal column nuclei-complex projections to the tectum, pretectum, zona incerta, periaqueductal grey, and spinal cord. The DCN-complex projections to the tectum and pretectum are considered part of the cerebellar system and originate from DCN regions outside the clusters, conveying multimodal somatosensory information. Zona incerta receives a small amount of multimodal input from the rostral DCN and is also considered part of the DCN-complex cerebellar system. The periaqueductal grey appears to receive inputs from all regions of the DCN, but these have not been properly defined. The spinal cord receives ipsilateral connections from ventral DCN regions, which are the target of primarily proprioceptive-related inputs and receive dense corticofugal inputs from areas 3a and 4. The main target in the spinal cord is lamina IV of the dorsal horn, which is the location of cell bodies with axons that comprise the PSDC. Abbreviations: PSDC, postsynaptic dorsal column. See **Figure 1** legend for all other abbreviations and orientations.