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Clustered and laminar topographic patterns in rat cerebro-pontine pathways

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Abstract Novel neuroanatomic approaches for investigating topographic maps at a systems level include combined use of sensitive neural tracing techniques and computerized methods for three-dimensional reconstruction from serial sections. Application of these methods have allowed discovery of new principles of topographic organization in the rat pontine nuclei. The pontine nuclei are intercalated in the large pathways connecting the cerebral cortex to the cerebellum. In rat, cerebro-pontine projections are characterized by multiple delineated terminal fields. It is generally accepted that these projections are topographically organized. The presence of widespread axonal clusters in the pontine nuclei is typically interpreted to represent a complex scheme of organization. In recent anatomic investigations of somatosensory corticopontine projections in young and adult rats, a somatotopic distribution of axonal clusters, concentrically organized in an inside-out fashion, has been reported. This review summarizes the topographic principles of organization proposed for somatosensory corticopontine projections, and discusses the possibility that widely segregated corticopontine terminal fields are located inside lamellar volumes. This organizational pattern may be explained by mechanisms operative during development, and resembles the patterns of organization previously described in cat and monkey. Possible implications of this architecture are discussed in relation to map transformations from the cerebral cortex to the cerebellum.

Keywords Pontine nuclei · Cerebellum · Neural tracers · 3-D reconstruction · Database

Introduction

The mammalian brain is characterized by orderly topographic arrangement of afferent and efferent projections among its components (see, e.g. Woolsey 1958; Woolsey and Van der Loos 1970; Welker 1971; Killackey et al. 1995; Chklovskii 2000), and knowledge of structural architecture in brain regions and interconnecting pathways is considered to be fundamental for understanding brain function (Leise 1990; Nelson and Bower 1990; Brown 1992; Katz 1996; Kaas 1997). Connectivity patterns are commonly characterized with neural tracing techniques and the spatial distribution of labelled neuronal populations and axonal terminals is investigated in microscopic serial sections (for review, see Köbbert et al. 2000; Van Haften and Wouterlood 2000). New approaches in neuroanatomy include the use of computerized techniques for three-dimensional (3-D) reconstruction of serial section data (Leergaard and Bjaalie 2002a) and the use of local coordinate systems for studying topography in smaller regions of the brain (Brevik et al. 2001; Bjaalie 2002). For example, the combined use of sensitive neural tracing techniques and tools for 3-D visualization and analysis has made it possible to discover new principles of topographic organization in the rat corticopontine projection (for a methodological review, see Leergaard and Bjaalie 2002a). The pontine nuclei represent the first link in the large pathways connecting the cerebral cortex to the cerebellum (for reviews, see Brodal 1982a; Brodal and Bjaalie 1992, 1997; Schmähmann and Pandya 1997), and the communication between the cortex and cerebellum is a central feature in many current theories of cerebellar function (Marr 1969; Albus 1971; Ito 1984; Leiner et al. 1993; Bower 1997; De Schutter and Bjaalie 2001). The computations taking place in the pontine nuclei, and the principle architecture of the pathways from the cerebral cortex via the pontine nuclei to the cerebellum are not well understood.

A substantial number of anatomic investigations of the rat corticopontine system have characterized multi-

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ple, delineated terminal fields in the pontine nuclei that are topographically distributed from medial to lateral (for a review, see Ruigrok and Cella 1995). The projection system has been ascribed a longitudinal columnar organization, in which different cortical regions project to segregated 'private' zones, and to separate overlapping or 'convergent' zones (Wiesendanger and Wiesendanger 1982; Mihailoff et al. 1985; Panto et al. 1995). The segregated and clustered nature of corticopontine projections has also been interpreted to represent a compartmentalized organization, in which functionally relevant signals are brought together (Schwarz and Thier 1995, 1999; Schwarz and Möck 2001). However, beyond a general agreement that corticopontine projections terminate as widespread clusters and display a complex medial-to-lateral topographic distribution pattern, the principles of topographical organization in the pontine nuclei have been debated (Schwarz and Thier 1995, 1999; Bjaalie and Leergaard 2000; Schwarz and Möck 2001).

Use of computerized 3-D analyses of the spatial distribution of corticopontine axonal clusters, labelled in single or dual tracing experiments, has allowed demonstration of somatotopic organization in the projections from the primary somatosensory cortex (SI) to the pontine nuclei in adult rats (Leergaard et al. 2000a, 2000b). In this scheme of organization, labelled corticopontine axonal clusters are distributed within concentric layers with an inside-out organization. The clusters are described as distributed within 'logical' lamellar volumes. This description was influenced by previous findings that corticopontine projection patterns in newborn rats (Leergaard et al. 1995) are congruent with the inside-out settling of neurons migrating into the pontine nuclei (Altman and Bayer 1978, 1987; see also Altman and Bayer 1996).

In contrast to the general notion of complex corticopontine topography, the findings of Leergaard et al. (2000a, 2000b) indicate a more basic pattern of organization, where widely segregated clusters fit into a three-dimensional pontine map in which the neighbouring relationships of the somatosensory cortical map are largely preserved. This would imply that the rat pontine nuclei consist of multiple clusters that are somatotopically distributed within concentric, lamellar volumes. This basic organizational pattern may be explained by simple developmental principles, and resembles the patterns of organization previously described in cat and monkey (for review, see Brodal 1982a; Brodal and Bjaalie 1997; Schmähmann and Pandya 1997).

This review summarizes recently reported principles of topographic organization in projections from the somatosensory cortex to the pontine nuclei in rat, and deals with the establishment of topographic order in corticopontine projections and the concept of a concentric inside-out arrangement of somatosensory, corticopontine terminal fields. Finally, possible functional implications of a clustered and laminar pattern in the pontine nuclei will be discussed.

Establishment of topographic corticopontine projections

In rat, topographically organized projections have been described at early postnatal stages. There is evidence that topographic maps in the pontine nuclei emerge from initially diffuse and abundant projections during development (Mihailoff et al. 1984). While Heffner et al. (1990) demonstrated that pontine neurons attract axons *in vitro* by target-derived diffusible (presumably non-specific) factors, O'Leary and Terashima (1988) described *in vivo* that pontine afferents grow into the pontine nuclei at stereotypic locations (Fig. 1A), a finding suggestive of more specific target acquisition. The finding in newborn rats that newly established corticopontine axons aggregate in distinct curved clusters, that are interconnected by thin rims of fibres, thus forming a semicircular, or lamellar structure (Fig. 1B), gave rise to the notion of corticopontine axons distributed in lamellar subspaces (Leergaard et al. 1995). In that study, a complete mapping of the 3-D distribution of early cortical projections to the pontine nuclei was combined with previous data on: (1) cortical development (Hicks and D'Amato 1968; Smart 1984; Uylings et al. 1990; McCandlish et al. 1993; see also Bishop et al. 2000; O'Leary and Nakagawa 2002); (2) the gradual emergence of subcortical projections (Stanfield and O'Leary 1985; Gribnau et al. 1986; O'Leary and Terashima 1988; De Carlos and O'Leary 1992; Erzurumlu and Jhaveri 1992); (3) data on the orderly migration and settling of pontine neurons (Altman and Bayer 1978, 1987). The correlation between spatial distribution patterns and neurogenetic gradients prompted the hypothesis that the pontine topographical map could be established by interaction of simple temporal and spatial gradients present in source (cerebral cortex) and target (pontine nuclei) regions (Fig. 1C; Leergaard et al. 1995, 2000a, 2000b). Whether the detailed projection pattern is shaped by multiple (specific) chemotropic substances operative in the pontine nuclei, or by one or few (non-specific) substances in combination with other mechanisms remains unresolved. Similar correlations between neurogenetic gradients and the pattern of efferent and afferent connectivity, have also been suggested for the corticostriatal projections (Bayer and Altman 1987, 1991; Leergaard et al. 2000a), corticothalamic (Bolz et al. 1990, 1993; Novak and Bolz 1993), corticospinal (Joosten et al. 1991, 1993, 1994), and thalamocortical (Götz et al. 1992; Bolz et al. 1992) systems (for review, see Lakke 1997). Thus, the correspondence of the observed pontine labelling patterns with developmental gradients described by others, suggests that the organizational blueprint of the large-scale distribution patterns originates from sequential spatial and temporal events during development.

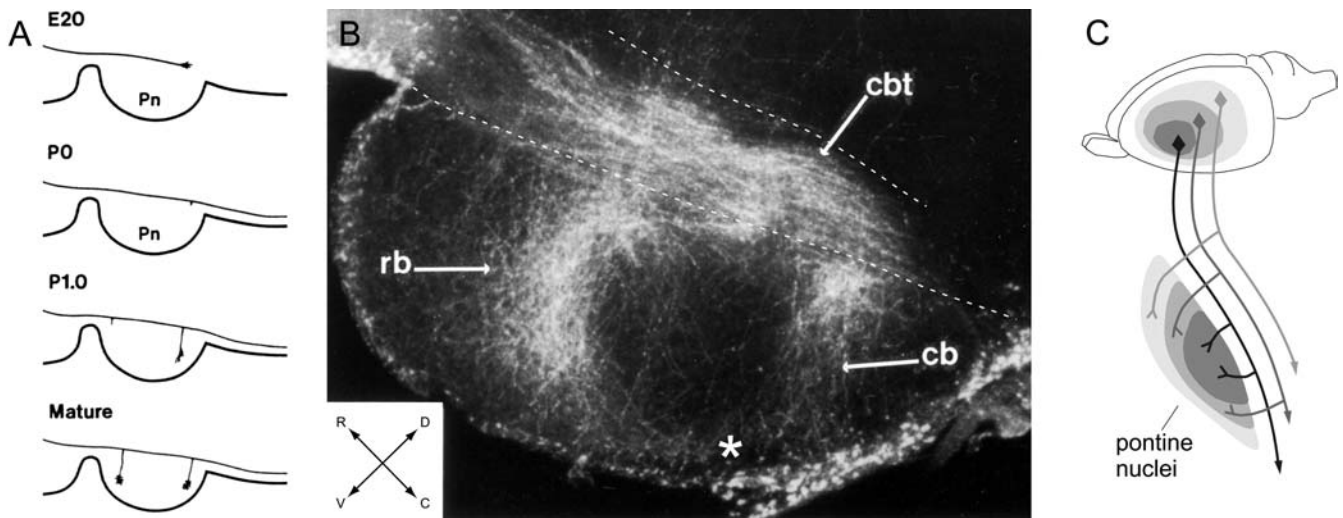


Fig. 1A–C Establishment of topographic corticopontine projections. **A** Diagram showing how corticopontine projections develop as collaterals from primary corticospinal axons at stereotypic rostral and caudal levels (modified from O’Leary and Terashima 1988, with permission). **B** Photomicrograph of a sagittal section through the pontine nuclei of a 6 day old rat (modified from Leergaard et al. 1995, with permission). Crystals of Dil were implanted in the parietal cortex three days earlier. Labelled axons are visible in the corticobulbar tract, and distinct rostrally and caudally located bundles within the pontine nuclei. The rostral and caudal bundles are bridged ventrally by a thin rim of fibres (*asterisk*), and form a semicircular lamella surrounding a central core region. **C** Cartoon of the hypothesis explaining the establishment of general topographic organization in the rat corticopontine system (Leergaard et al. 1995; reproduced from Leergaard et al. 2000b, with permission). The cerebral neurogenetic gradient ripples outward from the anterolateral cortex (Smart 1984; Uylings et al. 1990), and the cerebral axonogenetic gradient is presumed to follow the neurogenetic gradient (Erzurumlu and Jhaveri 1992). Altman and Bayer (1978, 1987) reported that pontocerebellar neurons migrate and form the pontine nuclei inside-out in a pattern of concentric rings (presumably layers in 3-D) in a temporal sequence. Corticopontine fibres bundles grow into the pontine nuclei at rostral and caudal locations around the time of birth (O’Leary and Terashima 1988), attracted by chemotropic cues emanating from neurons in the pontine nuclei (Heffner et al. 1990; O’Leary et al. 1991; Bastmeyer et al. 1998). The distribution of early corticopontine projections (Leergaard et al. 1995) is congruent with the concentric rings described by Altman and Bayer (1978, 1987). Temporal gradients, from early to later, are illustrated by increasingly brighter shades of grey. It is hypothesized that early arriving corticopontine neurons innervate the early established core of pontine nuclei (*dark grey*), whereas later arriving fibres innervate progressively more external volumes (*grey* and *bright grey*) (*c* caudal, *cb* caudal bundle, *cbt* corticobulbar tract, *d* dorsal, *pn* pontine nuclei, *r* rostral, *rb* rostral bundle, *v* ventral)

How may widely dispersed axonal clusters constitute a lamellar scheme of organization?

The presence of multiple segregated clusters in adult rats has typically been regarded as evidence for complex patterns of organization (Mihailoff et al. 1978, 1985; Wiesendanger and Wiesendanger 1982; Panto et al. 1995; Schwarz and Thier 1995, 1999; Schwarz and Möck 2001), different from the simple, lamellar pattern

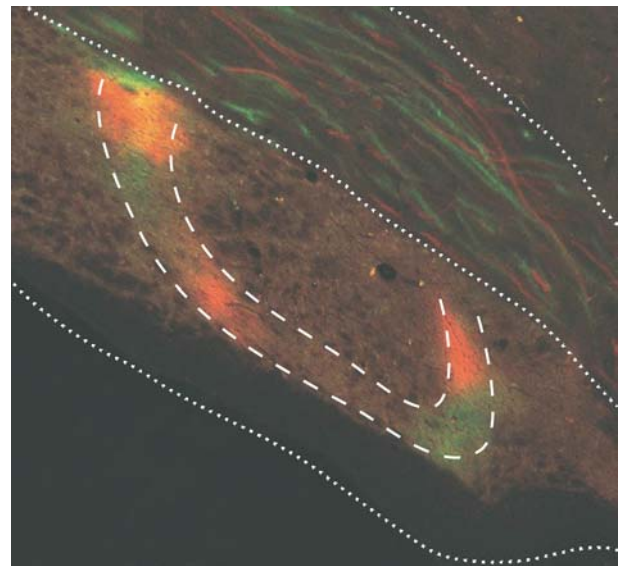


Fig. 2 Photomicrograph of a sagittal section through the pontine nuclei showing anterogradely double labelled segregated axonal clusters that together make up a semicircular lamellar volume (mirrored and modified from Schwarz and Möck 2001, with permission; original version shown in Fig. 3E). Segregated injections in the whisker barrel field of the primary somatosensory cortex (see Fig. 3C) label adjacent axonal clusters. The shape and distribution of the red and green labelled clusters is readily interpreted as a lamella (*dashed lines*). The original photomicrograph was mirrored to facilitate comparison with Fig. 1B

observed in young animals (Leergaard et al. 1995). However, several investigators have documented anterogradely labelled clusters in adult animals with shapes reminiscent of the curved lamellar or semicircular patterns seen in young animals, without specifically reporting this finding (see e.g. Fig. 2, Fig. 3A, 3B; levels 5 and 6; Fig. 4E, level 60 and 70; Fig. 4D, level 80). Furthermore, the resemblance of young and adult projection patterns is readily seen when comparing the distribution of pontine plexuses labelled by injection of fluorescent tracer in the parietal cortex in two independent studies

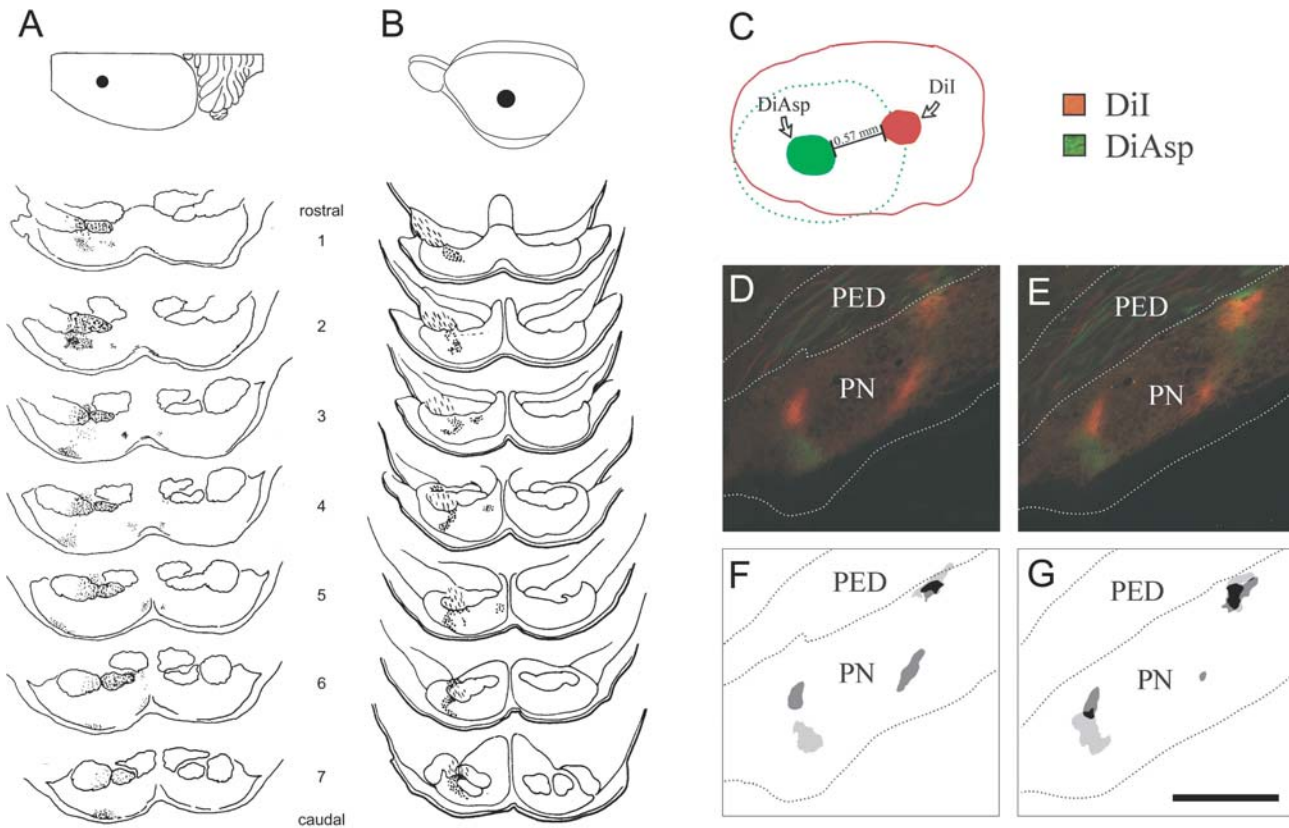


Fig. 3A–G Presentation of anterograde corticopontine tracing data in drawings and photomicrographs of microscopic sections. **A, B** Pontine axonal plexuses are labelled by injection of neural tracer into the primary somatosensory cortex, and coded as dot in drawings of a seven selected transverse sections through the pontine nuclei. **A** Modified from Mihailoff et al. (1978), with permission. **B** Modified from Wiesendanger and Wiesendanger (1982) with permission. **C** Drawing of two tracer injection sites (DiI and DiAsp) in the whisker barrel field of the primary somatosensory cortex, which gave rise to labelled axonal clusters in the pontine nuclei. **D, E** Show photomicrographs of two sagittal sections through the pontine nuclei, containing adjacent red (DiI) and green (DiAsp) axonal clusters. **F, G** Show interpretations of the labelled zones based on image analysis. **D–G** reproduced from Schwarz and Möck (2001) with permission. The labelling patterns obtained in these three different studies of somatosensory corticopontine projections appear different and are difficult to compare (*Ped* peduncle, *pn* pontine nuclei) Bar 500 μm

(Figs. 1B and 2; Leergaard et al. 1995; Schwarz and Möck 2001). In young animals, two dense rostral and caudal axonal clusters are bridged ventrally by a thin bridge of fibres and together form a lamellar subspace (Fig. 1B). In adult animals, axonal clusters are generally more restricted and segregated, however, in some sections it is clearly visible that several segregated clusters together form a semicircular shape, which may be interpreted as a ‘logical’ lamella (Fig. 2). Thus, widely separated axonal clusters may be confined within the same lamellar subspace. When investigating serial sections, such phenomena are typically only observed in a few sections, while remaining sections reveal more obscure patterns. In this context, it is important to analyze complete series of sections and consider the 3-D nature of

the distribution patterns (Fig. 4; see also discussion below).

The concept of concentrically arranged corticopontine projections

Several anatomic investigations have pointed out that corticopontine projections are orderly distributed, and regional differences in the location of projections from motor, somatosensory, visual and auditory cortical regions have been described (for review, see Ruigrok and Cella 1995). Leergaard et al. (2000b) found that the perioral representations of SI project to a central core in the pontine nuclei (Fig. 5B, 5C), whereas extremity and trunk representations are located more externally (Fig. 5B, D–G). The somatotopic order of the cortical map is largely preserved among the pontine representations, i.e. both rostrally and caudally located clusters retain the neighbouring relationships of the SI somatotopic map (Fig. 5A, B). The presence of multiple projection clusters from each body representation indicates that the pontine nuclei contain several representations of the SI map. The complementary shapes and distribution of the projections from major SI body surface representations (Fig. 5C–G) supported the notion that segregated clusters are incomplete parts of ‘logical’ lamellar volumes. Further investigations at a higher resolution, involving simultaneous injection of two anterograde tracers into different SI whisker barrels, demonstrated narrow, partly overlapping, paired clusters of labelling in the pontine nuclei (Leergaard et al. 2000a). 3-D reconstructions re-

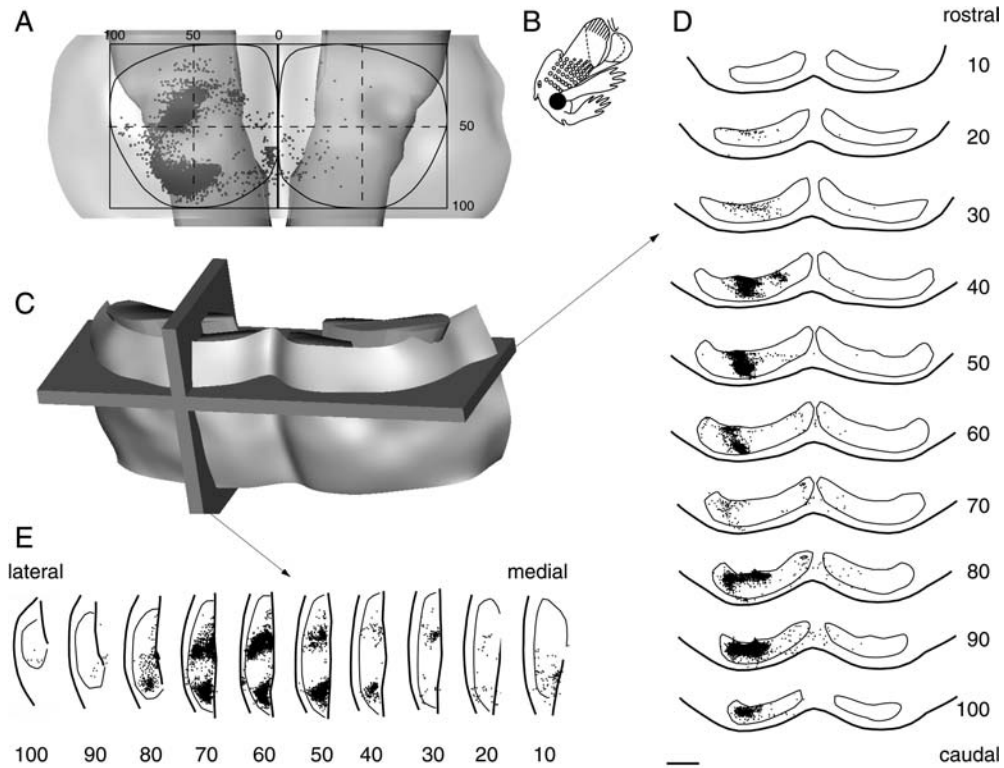


Fig. 4 Computer-generated 3-D reconstruction of the rat pontine nuclei subdivided into consecutive series of sagittal and transverse slices (Leergaard et al. 2000b; reproduced from Leergaard and Bjaalie 2002; with permission), showing the distribution of pontine terminal fields after injection of BDA into the trunk representation of the primary somatosensory cortex (**B**). **A** 3-D reconstruction of the pontine nuclei in view from ventral. The ventral surface of the pons is represented as a transparent surface, and the dorsally located descending peduncles are visible as solid surfaces. The dots represent the distribution of BDA labelled fibres within the

pontine nuclei. The local coordinate system for the pontine nuclei is shown as a rectangular frame. Curved solid lines represent nuclear boundaries. Coordinate systems of relative values from 0 to 100% are used. The halfway (50%) reference lines are shown as dotted lines. The rectangular boxes in **C** illustrate 200 µm thick transverse and sagittal slices (shown in **D** and **E**, respectively) from the computer reconstruction. The numbers assigned to each slice refer to the internal pontine coordinate system. Depending on the chosen plane of sectioning, the shapes of the terminal fields appear different. Compare also with Fig. 1. *Bar* 500 µm

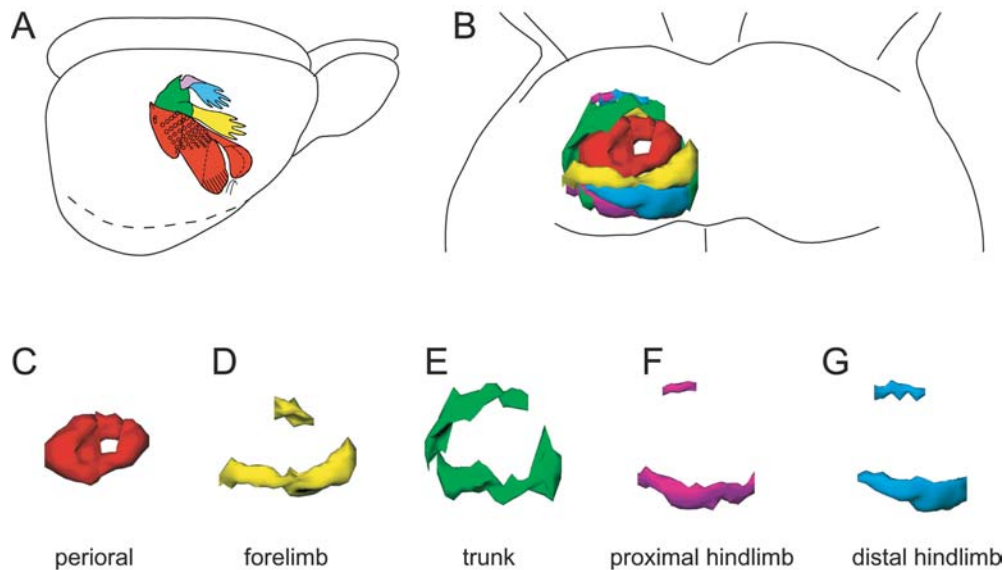
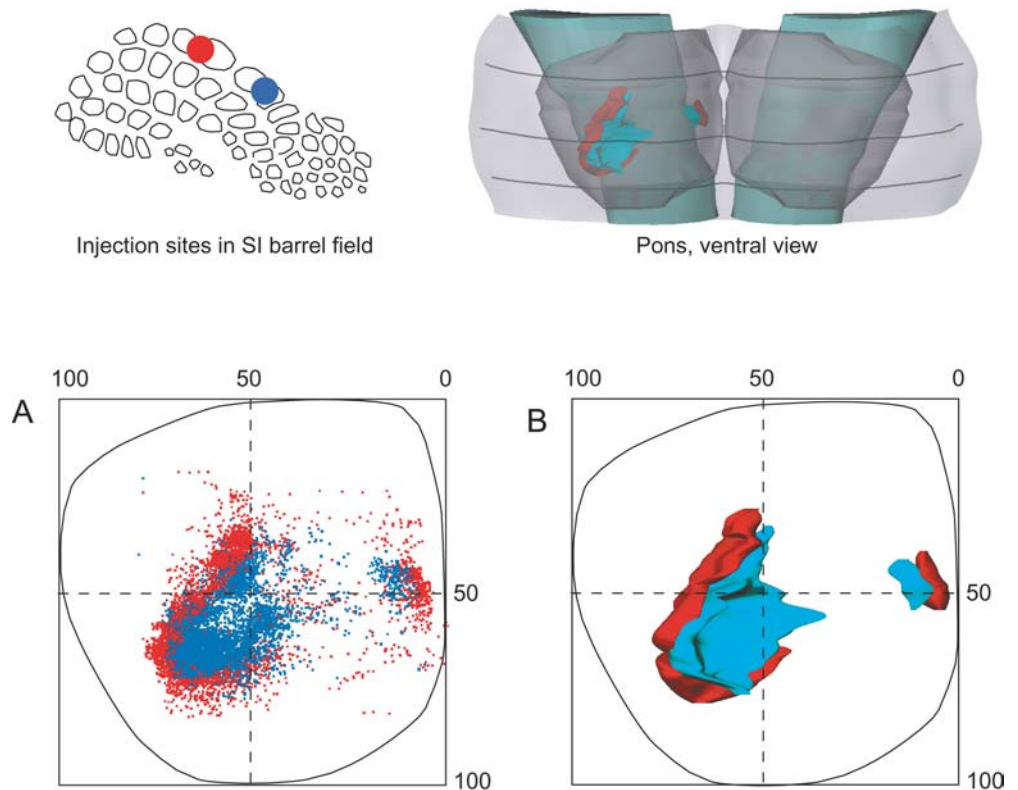


Fig. 5A–G Three-dimensional surface models showing somatotopic organization of pontine projections from major body surface representations in the primary somatosensory cortex (SI) (data from Leergaard et al. 2000b). **A** Colour-coded cartoon of the SI somatotopic map (modified from Welker 1971, with permission). **B** Line drawing of the pontine nuclei showing computer-generated surface representations of pontine projections from the perioral

(red), forelimb (yellow), trunk (green), proximal hindlimb (pink), and distal hindlimb (blue) somatosensory representations of SI. The concentric internal-to-external arrangement of the clusters is apparent, and both rostrally and caudally located clusters largely preserve the somatotopic neighbouring relationships of the SI map. The individual computerized surface models are shown separately in **C–G**

Fig. 6A, B 3-D reconstruction showing the topography of pontine terminal fields arising in the rat SI whisker barrel field (Leergaard et al. 2000a; modified from Leergaard and Bjaalie, 2002a, with permission). The anterograde tracers BDA (blue) and FR (red) were injected into electrophysiologically defined individual whisker representations in SI (shown in the upper left inset) and the distribution of labelling was computer reconstructed in 3-D (upper right inset). **A** Computer-generated dot map showing the distribution of BDA (blue) and FR (red) labeled fibers within the ipsilateral pontine nuclei. The clusters of blue dots surround the clusters of red dots externally. **B** The outer boundaries of labelled clusters are demonstrated by solid surfaces. The labelled clusters arising from the same row of SI barrels are located in dual lamellae that are shifted from internal to external



vealed that these clusters are somatotopically organized components of concentrically organized lamellar subspaces (Fig. 6; see also, <http://www.nesys.uio.no>).

Three main distribution gradients can be observed in the adult rat corticopontine projection. First, the frontal to occipital axis of the cerebral hemisphere is represented from medial to lateral in the pontine nuclei (Wiesendanger and Wiesendanger 1982; Mihailoff et al. 1985; Leergaard et al. 1995; 2000a, 2000b). Second, cortical sites at increasing distance from the anterolateral cortex project to progressively more external subspaces in the pontine nuclei (Figs. 5 and 6; Leergaard et al. 1995, 2000a, 2000b). Third, at increasing distance from the anterolateral cortex (which projects centrally in the pontine nuclei), cortical sites of origin close to the anterolateral cortex have a stronger projection to caudal parts of the pontine nuclei, and a weaker projection to rostral parts (this concerns in particular projections from the limb representations in SI; Fig. 5; Leergaard et al. 1995, 2000b), while the most medially located cortical regions predominantly project to rostral parts of the pontine nuclei, and have minor caudal projections (Leergaard et al. 1995; Leergaard and Bjaalie 1998, 2002b). Thus, in rat, corticopontine terminal fields are organized inside-out in a concentric fashion, and a given cortical location gives rise to multiple, elongated clustered terminal fields that are distributed in accordance with the principles above. Recent electrophysiological investigations (Eycken et al. 2000) demonstrated restricted receptive fields in the pontine nuclei in agreement with the somatotopic map presented by Leergaard et al. (2000b).

The general topological rule that cortical sites of origin distributed from frontal to occipital give rise to terminal fields in the pontine nuclei distributed from medial to lateral, is seen already in the corticofugal pathways (Glickstein et al. 1992; Coleman et al. 1997). It is likely that the mediolateral spatial gradient in the pontine nuclei is directly derived from the mediolateral organization of fibres in the descending peduncle. This mediolateral distribution is clearly present in primates (Nyby and Jansen 1952; Dhanarajan et al. 1977; Brodal 1978; Wiesendanger et al. 1979; for review, see Schmahmann and Pandya 1997), and rats (Wiesendanger and Wiesendanger 1982; Mihailoff et al. 1985), but not in cats, where corticopontine projections are widely distributed in the mediolateral dimension (Brodal 1968, 1983; Enger and Brodal 1985; Bjaalie 1989; Bjaalie and Brodal 1989).

An inside-out organization of sharply defined lamellar zones in the pontine nuclei was first emphasized in primates (Nyby and Jansen 1952; Dhanarajan et al. 1977; Brodal 1978; Wiesendanger et al. 1979; Hartmann-von Monakow et al. 1981). Brodal (1978) characterized corticopontine terminal fields in the monkey as resembling the skins of an onion. In cat, Brodal (1968) emphasized the rostrocaudal continuity of labelled patches, and described somatosensory corticopontine terminal fields as rostrocaudally oriented columns. Later work, mapping the pontine projections from other regions of the cat cerebral cortex, visualized numerous patchy terminal fields distributed within lamellar zones (Brodal 1983, 1987; Enger and Brodal 1985; Bjaalie 1989; Bjaalie and Brodal

1989). Although the corticopontine labelling pattern was primarily characterized as a complex mosaic, Bjaalie and Brodal (1989) also recognized a concentric lamellar inside-out organization. By combined use of retrograde tracing and 3-D reconstructions techniques, Nikundiwe et al. (1994) showed that pontocerebellar neurons are distributed in gradually shifting lamellae. Similarly, Bjaalie et al. (1997) demonstrated that corticopontine terminal fibres in cat form small-scale clusters and large-scale lamellae, thereby supporting the notion that the cerebro-ponto-cerebellar system is organized according to relatively simple topographic rules. In rat, however, most authors adopted the early terminology of Brodal (1968) and described the projections to the pontine nuclei as located in multiple rostrocaudally oriented columns (Fig. 1A,B; Mihailoff et al. 1978, 1984, 1985; Wiesendanger and Wiesendanger 1982; Lee and Mihailoff 1990; Panto et al. 1995). This tendency to emphasize the rostrocaudal continuity of the labelling patterns probably relates to the use of a transverse section plane. When a sagittal section plane is used, however, different labelling patterns appear (Figs. 2 and 3D–G; Schwarz and Thier 1995; Schwarz and Möck 2001). This was shown to advantage with the use of 3-D reconstruction and digital slicing of the same data set into both transverse and sagittal section planes (Fig. 4; Leergaard et al. 2000b).

In summary, the terminal fields of rat corticopontine projections are typically topographically distributed at segregated locations in the pontine nuclei. The clusters are located within a pattern of concentrically organized volumes, and their internal-to-external position is related to the distance of the cortical site of origin from the anterolateral part of the parietal cortex. Thus, anterolateral parts of SI project centrally in the pontine nuclei, while medial parts of SI have predominant caudal projections (Wiesendanger and Wiesendanger 1982; Panto et al. 1995; Leergaard et al. 2000b). Projections from cortical areas located further away from the anterolateral cortex (i.e. more frontally, medially, or posteriorly) have a rostral preponderance of fibre distribution in the pontine nuclei (Leergaard and Bjaalie 1998, 2002b). This is in accordance with previous findings that pontine projections from the occipital hemispheres (visual and auditory areas) in rodents are predominantly located in the rostro-lateral regions of the pontine nuclei in rats (for review, see Ruigrok and Cella 1995). From a comparative anatomic perspective, it is apparent that the global topographic layout of corticopontine organization in the rat largely resembles the one found in primates.

Architectural features of corticopontine brain maps

The topographic organization of brain maps are generally thought to reflect specific computational properties (Nelson and Bower 1990). It follows from the discussion above that the architecture of the somatosensory cortical projections onto the pontine may be characterized as small-scale clusters that are distributed within large-

scale, topographically organized, logical lamellar subspaces. Possible implications of these topographic patterns are briefly discussed below.

Clusters

Clustering is a common architectonic phenomenon in the brain. Grouping of neural elements is apparently advantageous in terms of wiring economy, by allowing localized connectivity patterns (Mitchison 1992). Complex clustered patterns, resembling those found in the pontine nuclei, have been described in the basal ganglia, thalamus, tectum, ventral complex of the lateral lemniscus, and trigeminal nuclei, among others (see, e.g., Huerta et al. 1983; Gerfen 1992; Cox et al. 1996; Mize et al. 1998; Malmierca et al. 1998; Alloway et al. 1999; Groenewegen et al. 1999). The functional consequence of a clustered organization is debated. Malach (1994) proposed that the segregation and clustering of axonal terminals in the cerebral cortex should be viewed as devices for maximizing neuronal diversity, rather than devices for segregation of information in separate processing streams. The modular, or clustered, organization in the neostriatum has also been viewed as suitable for specific integration, or combination of sensory signals (Graybiel 1990; Brown 1992; Brown et al. ; Alloway et al. 1999). In line with this, the sharply delineated clusters in the pontine nuclei might facilitate integration of signals. The close spatial relationship between the narrow, partially overlapping clusters in the pontine nuclei (Figs. 6 and 7B–D; Leergaard et al. 2000a), provides large interfaces between clusters, and appears to create specific somatotopic gradients of cortical influence on pontine neurons. The 3-D geometry of clusters (Figs. 5 and 6) might also contribute to integrative processing. The transformation from an essentially 2-D cortical map to a widespread 3-D clustered map in the pontine nuclei creates enlarged interfaces towards neighbouring clusters and opportunities for new neighbouring relationships (Leergaard and Bjaalie 1998; Schwarz and Thier 1999; Leergaard et al. 2000b). The 3-D map of major SI body representations in the pontine nuclei largely preserves the neighbouring relationships of the cerebral cortical map and to some extent also new neighbouring relationships are formed (Leergaard et al. 2000b). Thus, somatosensory signals from adjacent body representations remain in close spatial proximity within the pontine nuclei and have large interfaces. Furthermore, the widespread distribution of clusters in the pontine nuclei seems to provide considerable divergence. The presence of several somatosensory maps in the pontine nuclei (Leergaard et al. 2000a, 2000b) could indicate that signals are dispersed to different functional units. Clustering of labelling is not necessarily equivalent to a modular organization, such as described in the cerebral cortex. Cortical modules (Lorente de Nó 1938; Mountcastle 1957) are based on identifiable basic units that are defined by several criteria (Mountcastle 1979; Leise 1990). From recent tracing studies of

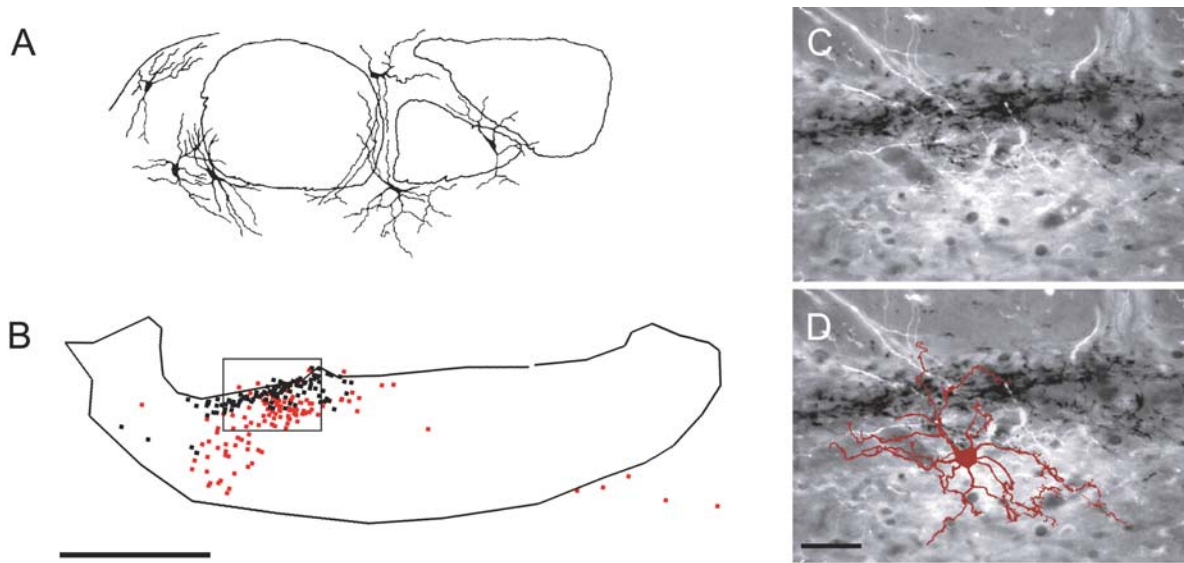


Fig. 7A–D The relationship between pontocerebellar neurons and corticopontine axonal clusters in the pontine nuclei. **A** Golgi-stained neurons close to the descending corticobulbar and corticospinal tract (reproduced from Mihailoff et al. 1981, with permission). **B** Original digital plot of a transverse section through the pontine nuclei, containing two axonal clusters labeled by dual tracer injection into separate whisker barrels in the primary somatosensory cortex (data from Leergaard et al. 2000a). BDA-labelled axons are represented as black dots, FR-labelled axons as red dots. **C** Photomicrograph of BDA (black) and FR (white) labelled axons from the same transverse section as shown in **B** (position indicated by rectangle in **B**). **D** Composite illustration of labeled corticopontine axons (data from Leergaard et al. 2000a) superimposed with a typical Golgi labeled neuron, shown to the same scale (modified from Mihailoff et al. 1981, with permission). The extent of dendritic arbors of typical pontine cells combined with narrow corticopontine axonal clusters illustrates the potential for pontocerebellar neurons to sample information from several narrow axonal clusters. *Bar* in **B** 500 μ m; *Bar* in **C**, **D** 50 μ m

the corticopontine system, it is evident that a slight displacement of the cortical site of injection corresponds to a gradual shift in the localization of labelled clusters in the pontine nuclei, rather than labelling of ‘new’ clusters (Leergaard et al. 1995, 2000a, 2000b). The somatotopic organization of major SI body representations (Leergaard et al. 2000b), and the partially overlapping and smoothly shifting whisker representations in the pontine nuclei (Leergaard et al. 2000a), indicate a continuous (non-modular) organization of corticopontine afferents. In this respect, the clustered appearance of the labelling is merely a product of the sharply delineated tracer deposits. Schwarz and Thier (1995, 1999) proposed a modular organization of the pontine nuclei, based on the argument that dendritic trees of pontine neurons respect the boundaries of terminal fields of axons originating from an arbitrary site in the cerebral cortex. Neurons located within the boundaries of a given terminal field, are thought to share the same input, different from that of neighbouring fields. It is difficult to conceive how the proposed pontine modules relate to narrow and partly

overlapping terminal fields (Fig. 7; Bjaalie and Brodal 1989; Bjaalie et al. 1997; Leergaard et al. 2000b). A central issue in this respect is how dendritic arbors relate to the clustered axonal terminal fields (Fig. 7; see also discussion below). If dendrites extend into multiple clusters, then convergence and integration of signals is likely. Otherwise, if dendrites remain confined within putative compartmental borders, a certain degree of convergence would still follow from overlap of terminal fields (Leergaard et al. 2000a).

Lamellae

Laminar distribution of neural components is also a fundamental organizing principle in the mammalian brain. The loose lamellar organization described in the pontine nuclei is notably different from the sharply defined laminae found in e.g. the cerebral cortex (Zilles and Wree 1995) or the inferior colliculus (Malmierca et al. 1995). The hodologically defined lamellar subspaces in the pontine nuclei are logical compartments, and not cytoarchitecturally defined structures. The identification of such logical lamellar subspaces facilitate the description of global topographic distribution principles, and are therefore helpful for understanding the overall spatial relationship of labelled axonal clusters. The lamellar subspaces described in the pontine nuclei represent higher order organizational patterns that preserve topographic order at a global scale, while the interdigitating, possibly divergent, clustered pattern introduces a potential for convergence, integration, and diversity of neuronal properties

Transformation from continuous cerebral to fractured cerebellar maps

The corticopontine projection is the first link in the projection from the cerebral cortex onto the cerebellum. It

is notable that the two brain regions connected by these pathways have very different patterns of topographic organization. SI contains a relatively continuous map of the body surface (Woolsey 1958; Welker 1971; for review, see Chapin and Lin 1990). By contrast, the tactile responses in the cerebellar granule cell layer form a highly discontinuous, or fractured, map (Shambes et al. 1978; Bower et al. 1981; Bower and Kassel 1990; for review, see Welker 1987). From physiological data, it is evident that the tactile-related cerebro-cerebellar circuit exhibits precise projection patterns (Bower et al. 1981). The nature of the map transformation from the continuous cerebral to the discontinuous cerebellar map remains obscure. The clustered aspect of the corticopontine projections may be interpreted to represent an interface between the different cerebral and cerebellar maps (Schwarz and Thier 1995, 1999; Schwarz and Möck 2001); however, the finding of preserved spatial relationships among somatosensory corticopontine projections at several locations in the pontine nuclei, would rather suggest the presence of several organized somatosensory representations in the pontine nuclei (Leergaard et al. 2000b). This interpretation is further supported by dual-tracing evidence of co-located, partially overlapping and systematically displaced pontine projections from SI whisker barrels (Leergaard et al. 2000a). Thus, at least the somatosensory maps in the pontine nuclei appear to possess a smooth and continuous organization. Orderly somatotopic shifts are found among major body representations (Leergaard et al. 2000b) as well as among individual whisker representations (Leergaard et al. 2000a). While the neighbouring relationships of the SI map are largely preserved, some additional new neighbouring relationships are introduced by interdigitation of clusters, and the transformation from 2-D to 3-D maps (Leergaard and Bjaalie 1998; Schwartz and Thier 1999; Leergaard et al. 2000b). Further detailed investigations of the projections from the pontine nuclei onto the cerebellum are needed to elucidate the organizational principles underlying the transformation from continuous (SI) to fractured (cerebellar) somatosensory representations.

Integration versus segregation of information

While pontine projections from different regions of the cerebral cortex generally have a segregated nature (Wiesendanger and Wiesendanger 1982; Mihailoff et al. 1985; Panto et al. 1995), several anatomic and physiologic investigations have proposed the presence of zones of overlap, or convergence, of projections from separate cortical sites (Rüegg et al. 1977; Potter et al. 1978; Mihailoff et al. 1978, 1981, 1985; Wiesendanger and Wiesendanger 1982; Panto et al. 1995). From a functional point of view, it is important to determine to what extent topographic specificity is preserved or integrated among pontine projections from neighbouring and more separated cortical locations.

Evidence of maintained specificity (recognized as distinct clustering of neuronal elements) at several stages in the reciprocal pathways connecting the cerebral cortex with the basal ganglia, thalamus, and cerebellum, has given rise to theories of discrete parallel circuits, or 'closed loops', in which the influences from different cortical regions remain largely segregated throughout the pathways (Alexander et al. 1986, 1990; Alexander and Crutcher 1990; Goldman-Rakic and Selemon 1990; Middleton and Strick 1998, 2000, 2001). The idea of parallel pathways through the basal ganglia was initially postulated by Heimer and Wilson (1975) and supported by subsequent experimental findings (for a review, see Groenewegen et al. 1990). Alexander and co-workers proposed that structural convergence and functional integration occurs within rather than between circuits coursing through the basal ganglia (Alexander et al. 1986, 1990; Alexander and Crutcher 1990). Other investigators have argued that the large degree of structural convergence in the projections to the basal ganglia provides evidence against the concept of parallel circuits (Chevalier and Deniau 1990; Percheron and Fillion 1991). The controversy with regard to parallelism in basal ganglia circuitry relates to the precision of the somatotopic organization and the degree of functional convergence. The important question concerning the theories of parallel circuits through the basal ganglia and the cerebellum is whether the presumed parallel pathways are functionally segregated or interact at their interfaces (Parent and Hazrati 1995; Mink 1999). The finding of partial overlap among corticopontine projections from neighbouring cortical locations (Leergaard et al. 2000a) suggests convergence of (functionally related) afferent pathways onto single pontine neurons ('open loops'), while the finding of decreasing overlap with increasing distance between the cortical sites of origin is associated with segregated pathways ('closed loops'). The degree of functional overlap among different terminal fields and convergence onto single pontine neurons depends on the relationship between the dendritic arbors of pontine neurons and corticopontine axonal terminal fields. Ultra-structural analysis is required to finally confirm synaptic convergence anatomically. Nevertheless, there is evidence indicating structural convergence in the pontine nuclei. Although Schwarz and Thier (1995) emphasized a compartmental organization with dendritic trees of pontocerebellar neurons largely respecting individual terminal fields of corticopontine axons, Mihailoff et al. (1981) demonstrated pontine neurons with long dendrites, probably extending into more than one afferent projection area (Fig. 7A). Corticopontine synapses are mainly established distally on thin dendrites (Holländer et al. 1968; Mihailoff and McArdle 1981), and, thus pick up signals from a relatively large zone outside the soma. In cat, dendritic trees average $187 (\pm 73) \times 339 (\pm 81) \mu\text{m}$ (Brodal and Steen 1983). Dendritic trees in monkey appear to be within the same range (Copper and Fox 1976; Brodal 1982b). In rat, roughly judged from illustrations of Golgi stained cells (Mihailoff et al. 1981) and cells visualized by intra-

cellular fills (Schwarz and Thier 1995), dendritic arbors extend between 50 to 300 μm from the soma. Pontine neurons tend to be elongated and asymmetric, in parallel to the long axes of pontine terminal fields (Brodal 1982b; Brodal and Steen 1983; Schwarz and Thier 1995). It seems that pontine neurons have the potential to integrate afferent signals from multiple clusters distributed both within and across several lamellar subspaces (Leergaard et al. 2000a). A comparison of Golgi stained neurons (Mihailoff et al. 1981, their Fig. 46) with our results (Leergaard et al. 2000a) shows to advantage the potential for local integration (Fig. 7). This notion is apparently opposed to the modular pattern with strict boundaries proposed as a general principle of organization in the pontine nuclei (Schwarz and Thier 1995, 1999; for a discussion of this topic, see Brodal and Bjaalie 1997; Schwarz and Thier 1999, 2000; Bjaalie and Leergaard 2000). The combined evidence of partly overlapping terminal fields of corticopontine projections from individual whisker barrels (Leergaard et al. 2000a), and relatively large pontine neurons (Mihailoff et al. 1981) strongly indicates convergence among projections from individual SI-whisker barrels. It is, however, less clear whether sensory projections representing other body parts, or different modalities, are segregated or converge in the pontine nuclei. In a recent study, Schwarz and Möck (2001) made dual tracer injections into functionally related, segregated somatosensory and motor regions in the cerebral cortex, and reported largely non-overlapping, but often co-located labelled clusters in the pontine nuclei (Figs. 2 and 3C–G). Thus, it appears that functionally related signals from segregated cortical locations are brought together in close spatial proximity in the pontine nuclei.

The orderly mapping, combined with the widespread distribution of pontine terminal fields, may also serve to integrate somatosensory signals from adjacent body representations, and possibly, also to combine these with information of a different modality from other regions of the cerebral cortex and from subcortical sources of afferents to the pontine nuclei. Specific convergences in the pontine nuclei among projections from different cortical sites and among cortical and subcortical projections have been described (Mihailoff et al. 1985, 1989; Kosinski et al. 1986, 1988; Aas 1989; Aas and Brodal 1989; Bjaalie and Brodal 1989; Lee and Mihailoff 1990; Mihailoff 1995; see also Mihailoff et al. 1992). Close spatial relationship among pontine terminal fields originating in different parts of the cerebral cortex may partly represent the substrate for large receptive fields of pontine neurons (Rüegg and Wiesendanger 1975; Baker et al. 1976; Rüegg et al. 1977; Potter et al. 1978; Thier et al. 1988; Suzuki et al. 1990; Mihailoff et al. 1992).

Conclusions

The use of computerized anatomic tools for 3-D reconstruction and analysis has introduced a new perspective

on the architecture of the rat pontine nuclei. The rat somatosensory corticopontine system displays an inside-out arrangement of clustered terminal fields, with a complex array of widespread but orderly distributed corticopontine axonal terminal fields (Leergaard et al. 2000a, 2000b). This pattern resembles the organization previously described in cat and monkey (for reviews, see Brodal 1982a; Brodal and Bjaalie 1997; Schmähmann and Pandya 1997). The large-scale pattern of organization may be explained developmentally by a simple topographic relationship between cortical site of origin and the location of pontine terminal fields. In rat, as in cat and monkey, widely separated axonal clusters are located within logical lamellar subspaces that are organized from the inside and out. Within the somatosensory system, the somatotopic order of the 2-D cerebral map in SI is largely preserved in a 3-D clustered pontine map (Leergaard et al. 2000a, 2000b). Thus, the fractured somatotopy described in the cerebellum is most likely associated with the second link in the cerebro-cerebellar pathways, the pontocerebellar projections. The lamellar subspaces described in the pontine nuclei represent a higher order topographic organization, while the segregated and interdigitating pattern of axonal clusters represents a potential for convergence and integration. The 3-D geometry of narrow and partly overlapping axonal clusters in the pontine nuclei may serve to increase pontine neuronal diversity, by providing differentially weighted convergence of cortical signals onto single pontine neurons.

Topographically specific pathways and domains represent a basis for theories of segregated, parallel circuitry (Alexander et al. 1986; Middleton and Strick 2000). The high degree of global segregation revealed in the topographic maps of the pontine nuclei is apparently consistent with such theories. There is, however, also evidence of overlap in the pontine nuclei of projections from adjacent cortical sites (Leergaard et al. 2000a), and more remote areas (Bjaalie and Brodal 1989), indicating integration of functionally related information. Thus, to what degree single pontine neurons receive convergent signals from the remote cerebral cortex remains an unresolved issue, and in this respect it is important to accurately determine how pontine dendritic arbors relate to narrow clustered axonal terminal fields, as well as characterizing the input and output relations of individual pontine neurons. The global understanding of the topographical mapping of corticopontine projections summarized here may represent a basis for further experimental investigations of how cerebral signals are integrated and / or relayed to the cerebellum. To this end, application of a local coordinate system for the pontine nuclei (Brevik et al. 2001) and accumulation of 3-D spatial distribution data in data repositories (Bjaalie 2002; Leergaard and Bjaalie 2002a) may represent important methodological innovations for comparison of multimodal localization data, and ultimately for gaining new knowledge about the cerebro-cerebellar system.

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