Organizing Principles of Cortical Integration in the Rat Neostriatum: Corticostriate Map of the Body Surface Is an Ordered Lattice of Curved Laminae and Radial Points

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ABSTRACT

The neuroanatomic organizing principles underlying integrative functions in the striatum are only partially understood. Within the three major subdivisions of the striatum—sensorimotor, associative, and limbic—longitudinal zones of axonal plexuses from the cerebral cortex end in bands and clusters that innervate cell groups. To identify organizing principles of the corticostriate bands and clusters, we localized somatosensory cortical cells receptive to light touch on the hindlimb, forelimb, or vibrissae by extracellular recording, and we labeled their projections by iontophoretic application of dextran anterograde tracers. The results show that cortical cells in columnar groups project to the striatum in the form of successive strips, or laminae, that parallel the curve of the external capsule. The vibrissae somatosensory cortex projects to the most lateral lamina, just medial to the vibrissae projection, the major axonal arborizations arising from hindlimb and forelimb somatosensory cortex are organized within a common lamina, where they interdigitate and overlap as well as remain separate. In addition, the hindlimb and forelimb cortices send small projections to the vibrissae lamina, and vice versa, forming broken, radially oriented lines of points across the laminar strips. The major somatosensory projections are in the dorsolateral, calbindin-poor sensorimotor striatum, whereas the radially oriented projection points extend into the medial, calbindin-rich associative striatum. Extending previous studies of corticostriate projections, this report shows a grid translation of columnar somatosensory cortical inputs into striatum and a detailed map for the rat sensorimotor zone. The lattice-like grid is a novel functional/neuroanatomic organization that is ideal for distributing, combining, and integrating information for sensorimotor and cognitive processing. J. Comp. Neurol. 392:468–488, 1998.

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The mammalian neostriatum plays a critical role in voluntary movement and normal cognition (Brown et al., 1997). One of its functional hallmarks is the higher order integration of sensory and motor activity, such as proprioceptive and visual tracking movements (Schneider et al., 1986, 1987; Mink and Thach, 1991). In the rat, lesions of the neostriatum affect the sequencing of grooming behavior (Berridge and Whishaw, 1992; Cromwell and Berridge, 1996). However, the somatotopic map necessary for such sensorimotor integration has been poorly understood in the rat. Although it has long been known that sensorimotor cortex projects to a dorsolateral region of neostriatum, commonly referred to as the sensorimotor zone, the intrinsic organization of this sensorimotor zone in the rat is unknown. Across species, unresolved issues for striatal organization are the amount of segregation and convergence of corticostriate pathways within a subregion, such as the sensorimotor zone, and the identification of an overall rule or organizing principle for the corticostriate...
CORTICOSTRIATE ORGANIZATION

Deoxyglucose autoradiography also show a rough striatal somatotopy (Alexander et al., 1994). Metabolic mapping studies using mixed in rats (Kunzle, 1977; Crutcher and DeLong, 1984; striatal somatotopy, but it is particularly complex and mosaic formed by corticostriatal input. Maximum diversity of input is provided by axonal arborizations from cortex that terminate in small, concentrated clusters that appear "patchy" or as points or puffs; they have been referred to as matrisomes that reflect striatal modules (Flaherty and Graybiel, 1991; Graybiel et al., 1993; Parthasarathy and Graybiel, 1997). Functional metabolic mapping studies have also demonstrated small concentrations of activity (Brown, 1992; Brown and Sharp, 1995; Brown et al., 1996), confirming the physiologic significance of these anatomic formations. But a single organizing scheme has not yet emerged that gives coherence to the anatomic arrangement allows significant integration from separated cortical regions. Maximum diversity of input is provided by axonal arborizations from cortex that terminate in small, concentrated clusters that appear "patchy" or as points or puffs; they have been referred to as matrisomes that reflect striatal modules (Flaherty and Graybiel, 1991; Graybiel et al., 1993; Parthasarathy and Graybiel, 1997). Functional metabolic mapping studies have also demonstrated small concentrations of activity (Brown, 1992; Brown and Sharp, 1995; Brown et al., 1996), confirming the physiologic significance of these anatomic formations. But a single organizing scheme has not yet emerged that gives coherence to the anatomic arrangement allows significant integration from separated cortical regions.

Electrophysiological and anatomic studies find a rough striatal somatotopy, but it is particularly complex and mixed in rats (Kunzle, 1977; Crutcher and DeLong, 1984; Malach and Graybiel, 1986; Carell and West, 1991; Mittler et al., 1994). Metabolic mapping studies using [14C]deoxyglucose autoradiography also show a rough striatal somatotopy (Brown et al., 1987; Brown, 1992; Brown and Sharp, 1995). However, the discrete zones of peak metabolism in the metabolic mapping studies demonstrated a striking anisotropic, orderly pattern that may be arranged to make possible all of the permutations and combinations of striatal somatosensory afferents necessary for complex movements (Brown, 1992). The present study was undertaken to seek the anatomical substrate of the metabolic mapping studies and to understand more fully the existence of an anisotropic pattern of representation within a dorsoventral somatotopic plane.

Unlike the cerebral and cerebellar cortices, the neostriatum is not composed of layers of distinct cell types. Studies of its organization have emphasized chemoarchitectural rather than morphologic findings. Specifically, two major neostriatal compartments have been described: cholinesterase-poor, opioid receptor-rich islands, called striosomes or patches, that are embedded in a much larger surrounding matrix (Pert et al., 1976; Graybiel and Ragsdale, 1978; Graybiel, 1990; Gerfen, 1992). In addition, the matrix in medial striatum is rich in calbindin compared with the lateral striatum, which is almost devoid of calbindin (Gerfen et al., 1985). This calcium-binding protein, which may be critically important in some cells for calcium transport and as an intracellular buffer, is distributed heterogeneously throughout the brain and may be associated with specific neural pathways and systems, for example, taste (Celio, 1990; Baimbridge et al., 1992). Calbindin distribution in the striatum is especially interesting for the functional division it may reveal. The medial, calbindin-rich domain correlates with the associative subdivision of the striatum, whereas the lateral, calbindin-poor zone correlates with the dorsolateral sensorimotor subdivision (Frobalos et al., 1994). One goal of the present study was to examine the somatotopic organization of primary somatosensory cortex (SI) in striatum and its relationship to the distribution of calbindin.

To compare anatomical arrangements as closely as possible with function, we studied the neostriatal projections of somatosensory cortical cells within a columnar-shaped group. In somatosensory cortex, cells with similar receptive fields are arranged in columns (Mountcastle, 1957; Kossut et al., 1988). In several species, macrow columns in somatosensory cortex have been estimated to be 200–1,000 µm in diameter (for review, see Swindale, 1990). In our previous studies with [14C]deoxyglucose in rats, somatosensory stimulation of the forelimb (FL) or hindlimb (HL) activated a columnar region in cortex 300–600 µm (Brown, 1992). In the anatomic studies of the corticostriate system reported here, we injected tracers into HL, FL, and vibrissae (VIB) somatosensory regions 300–600 µm in diameter, approximating a macrocolumn in rat somatosensory cortex. These are relatively small cortical injections, which were guided by electrophysiological confirmation. In addition, the tracers used, FluoroRuby (FR) and biotinylated dextran amine (BDA), made it possible to visualize individual axons and to distinguish axons of passage from terminal arborizations. The studies have revealed a new principle of anatomical organization for the translation of neocortical global somatotopy into a functional neostriatal schema.

MATERIALS AND METHODS

Subjects, tracers, and groups

Seventy-two male Sprague-Dawley rats (250–350 g; Taconic Farms, Germantown, NY) received iontophoretic injections of the anterograde tracers FR (dextran, tetramethylrhodamine; D-1817; Molecular Probes, Eugene, OR) or FR and BDA (dextran, biotin; D-1956, Molecular Probes). Phaselinesus vulgaris-leucocagglutinin (PHA-L; L-1110; Vector Laboratories, Burlingame, CA) was used in four cases. FR and BDA were used because they fill axons and terminal plexuses robustly and show individual axons (Schmued et al., 1990; Veeman et al., 1992). Also, these two tracers allow the handling of serial sections and double labeling with relative ease. Furthermore, it was important to this investigation to label functionally specific cell groups in the cortex, and both tracers can be ejected iontophoretically from the same electrode used for multiunit recording. We used PHA-L to control for retrograde-anterograde effects that might be present for FR and BDA (Chen and Aston-Jones, 1996).

The injection sites were in electrophysiologically identified somatosensory cortex corresponding to HL (n = 18), FL (n = 24), or VIB (n = 15). In 12 rats, both FR and BDA were each injected into a separate somatosensory cortical region (i.e., HL/VIB, FL/VIB, or HL/FL). In three additional rats, the size of the injection site was measured 15–25 minutes after the injection, before most of the tracer had been transported or had flowed away. The mapping results are based on nine HL, 12 FL, seven VIB, three FL/VIB, three HL/VIB, and three FL/HL rats that received 250–600 µm wide injections into coronal sections. This area was large enough to observe transport and similar to...
that activated by stimulation of a single vibrissa (Kossut et al., 1988), the HL, or the FL (Brown, 1992).

Electrophysiological recording and tracer injections

Glass capillary microelectrodes with tips 30–60 µm in diameter that were created with a Narishige electrode puller (Tokyo, Japan) were front loaded with FR, BDA, or PHA-L (10% FR or 10% BDA in 0.01 M phosphate-buffered saline [PBS], pH 7.2–7.4; 2.5% PHA-L in 0.01 M PBS, pH 8.0). The impedance of the microelectrodes was 0.5–2.0 megohms. To monitor cell activity, a silver wire inside the microelectrode was attached to an amplifier, oscilloscope, and audio monitor.

Stereotaxic surgery was performed under pentobarbital anesthesia (50–60 mg/kg; supplements, 10–15 mg/kg). Anesthesia level was monitored by using muscle tension and withdrawal reflex responses. Before surgery, the HL or FL to be stimulated was closely shaved; the VIB remained undisturbed. The cortical map of Chapin and Lin (1984) was used as an initial guide to determine the injection coordinates. The microelectrode was lowered with a micro-manipulator to a depth of 700 µm into the cortex. Region-specific activity was monitored at 25-µm intervals from 700 µm to 1,000 µm deep. If no site-specific activity was found, then the electrode was relocated at 100–200 µm intervals anteroposteriorly. The stimulus was applied contralateral to the injection site with a hand-held bristle, similar to a von Frey hair, that bent at 2.5g of pressure. HL and FL were taped or brushed. The entire VIB field contralateral to the injection was brushed from posterior to anterior, causing each vibrissa to bend; individual vibrissae were bent to further define the responsive field. To confirm site-specific responses, ipsilateral and contralateral stimulations were applied to HL, FL, VIB, face, and trunk. All animal protocols were approved by the Animal Institute Committee at Albert Einstein College of Medicine.

Once a site-specific receptive field was confirmed, a constant-current source was attached to the microelectrode, and the tracer was applied iontophoretically. A positive-pulse current alternating on for 7 seconds then off for 7 seconds was applied at 5–7 µamps for 12–30 minutes (FR, 15 minutes at 6–7 µamps; BDA, 30 minutes at 5 µamps; PHA-L, 12–15 minutes at 6 µamps).

Histological procedures

After 7–16 days, the rats were anesthetized with pentobarbital (60 mg/kg) and perfused transcardially with 0.9% saline followed by 10% neutral buffered formalin. The brains were removed, postfixed with 20% sucrose in formalin for at least 24 hours, and cut with a cryostat into 30-µm-thick coronal sections. In all rats, serial sections were saved in 0.01 M PBS with 0.05% sodium azide, pH 7.4, and incubated overnight with fluorescein avidin D; A-2001, Vector Laboratories). Alternate sections were mounted on uncoated slides for fluorescence microscopy or were processed to visualize calbindin. The FR- and BDA- fluorescent slides were thoroughly air dried, cleared in xylene for 10 min-
utes, and coverslipped with glycerol/phosphate buffer solution containing p-phenylenediamine (Sigma Chemical Co., St. Louis, MO), a fluorescent-fade retardant. The fluorescence lasted over 12 months.

For PHA-L and calbindin immunocytochemistry, standard avidin-biotin-peroxidase complex (ABC) methods (Vectorstain kit; Vector Laboratories) were used. The floating sections were exposed to the primary antibody overnight, to the secondary antibody for 30–60 minutes, and to ABC for 30–60 minutes, and sections were then developed with diaminobenzidine tetrahydrochloride. For PHA-L, anti-PHA-L (AS-2300; Vector Laboratories) was the primary antibody, and biotinylated anti-rabbit immunoglobulin (IgG; BA-1000; Vector Laboratories) was the secondary antibody. For calbindin, the primary antibody was mouse monoclonal anticalbindin-D (C-8666; Sigma), and the secondary antibody was biotinylated anti-mouse immunoglobulin (Ig; RPN-1001; Amersham, Arlington Heights, IL).

Anatomical analysis

The single-tracer FR sections were examined with a Nikon microscope (Tokyo, Japan), an ultraviolet (UV) light source, and a rhodamine filter. The double-tracer sections were examined with an Olympus microscope (Tokyo, Japan), a UV light source, and a mixed rhodamine/fluorescein filter to view FR and BDA simultaneously. Confocal microscopy (RCM8000; Nikon) was used to confirm overlapping projections and to look for special patterns within a field of intermingling HL and FL axons in three animals. There were 70–75 fluorescent sections to map from each FR or FR/BDA rat. Fluorescent terminal regions were drawn onto a projection of each thionin-stained section. For the FR/BDA double-label sections, the alternate section stained for calbindin was projected to map the fluorescence. To confirm the localization in the drawings, the fluorescent axon terminals in the striatum were photographed, and montages were constructed. The montages and the stained sections were digitized. We aligned a montage and its alternate stained section by using computer software (Photoshop 3.0; Adobe Systems, Mountain View, CA). These digitized alignments produced the most accurate localization of the patterns observed (see, e.g., Fig. 10). The PHA-L injections were photographed and compared with the FR-based maps.

The anteroposterior (AP) level was estimated by using the atlas of Paxinos and Watson (1986). In each case, all histological sections were used; a match was made for the first section and the atlas; then, at ten sections away, the match was checked for agreement with the atlas. In five rats, 26-gauge, stainless steel tubing was lowered stereotaxically and perpendicularly into the brain 3.0 mm posterior to Bregma as a histological alignment marker to help define the AP level. Based on findings from this group, the estimated error for matching two animals and pooling their data is 200–400 µm.

RESULTS

Cortical injection sites and extrastriatal projections

Electrophysiological recording at the cortical injection site revealed cells around the electrode with either large or small receptive fields for the tapping or brushing stimulus (Fig. 1). In four rats, the receptive field included the whole...
dorsal FL. Other FL cases had a smaller receptive field (Fig. 1A). Receptive fields for HL sites were digits, parts of digits, regions of the dorsal paw, or footpad (Fig. 1B). For VIB, the receptive fields included the lower two rows of the vibrissae or specific responses to individual vibrissae (Fig. 1C).

The injection sites sampled cortex 1–2 mm anteroposteriorly (Fig. 1D). Inspection of the thionin-stained sections showed that the injection sites were in granular cortex (Welker et al., 1984; Fig. 2). Fluorescence microscopy revealed labeled cells predominantly in layers III–VI (Fig. 3). The area of labeled cells ranged from approximately 300 µm to 600 µm wide (Fig. 3). If the width of the injection site was less than 200 µm, then only a few corticostriate axons were visible. If it was greater than 600 µm, then two or more corticocortical transport sites to the other side were seen as well as a wide corticostriate projection field. For the cases studied in detail, the pattern of the labeled...
cells in SI was a single vertical array from which a discrete bundle of axons clearly projected to innervate the striatum (Fig. 3).

Contralateral to the injection, HL and FL anterograde corticocortical projections were highly localized to a single band. For VIB, contralateral cortical projections were very sparse. Ipsilateral to the injection, the secondary somatosensory cortex (SII) showed sparse-to-heavy anterograde, columnar labeling in all cases. The ventrobasal complex of the thalamus was also labeled: The ventrolateral thalamus was labeled in the HL-injected animals. Labeling in both the thalamus and SII was somatotopically distinct. Furthermore, retrograde labeling was clear in the cortex and thalamus. It was greatest in SII in the FR-injected rats. However, far fewer retrogradely labeled cells were present in SII than were seen at the injection site.

Patterns of cortical axon terminal arborizations in striatum

Overview. From 2 mm posterior to 2 mm anterior to Bregma, the pattern of cortical axon terminal arborization in striatum changed every 120–260 µm. The predominant patterns in one HL, one FL, and one VIB case are shown in Figures 4–6. The laminar arrangement is summarized in Figure 7. In successive coronal sections through the main body of the striatum, axon terminal arborizations from a single body part appear as strips, layers, or laminae and as small, dense zones of patchy points medial and lateral to the major laminae. The configurations were remarkably similar across animals. Each pattern shown was seen in each case of the group represented. The major axon terminal fields were in the dorsolateral striatum, but some sparse medial projections were also seen in the calbindin-rich zone. Posteriorly, the HL and FL axonal arborization laminae were particularly patchy and were seen in compact strips, whereas, anteriorly, they were less dense and wider. For VIB projections, the lamina was wider posteriorly than the anteriorly. Finally, the laminae maintained an angle of orientation roughly parallel to the edge of the calbindin-rich zone and the external capsule (Fig. 7).

Specific patterns. In all animals, a striking posterior arrangement of axons and terminal arborizations consisted of two or three dense clusters along a 1.0–1.4 mm dorsoventral strip ending in a loose, ventral cluster. In the HL and FL group, the centers of the clusters were 500 µm from the external capsule (Fig. 8A,B). In the VIB group, the clusters were 0–400 µm from the external capsule (Fig. 8C,D). The ventral pattern of axon terminals was extraordinarily similar for HL, FL, and VIB (Figs. 4–7, top left section; Fig. 8B,D).
More anteriorly, from AP – 1.9 to –0.8, dense clusters of terminals had remarkably round, wedge- or strip-like shapes for HL and FL (Fig. 9). The bands or strip-like shapes forming the laminae were 200–400 µm long and 100–150 µm wide. The HL and FL projections overlapped completely for 360 µm at one point within this region (Fig. 7, AP – 1.7; Fig. 10). Along this 1.0-mm-long AP area, the clusters and plexuses changed their dorsoventral position, but kept their mediolateral position at 500 µm from the external capsule. Also, the density of the plexuses changed every 200–300 µm anteroposteriorly. The lamina of VIB varicose axons was lateral to HL and FL at this and all AP levels.

Farther anteriorly, from AP – 0.3 to –0.7, a new plan of two distinct plexuses emerged: The major plexus lamina for the HL and FL was joined by a second, smaller axon terminal cluster that was 500–800 µm medial to it (Fig. 11). In FL cases, a third axon plexus was often visible in the medial calbindin-rich zone near the globus pallidus (Fig. 5, AP – 0.4). These most medial clusters were smaller than the lateral ones and were extremely sparse. Furthermore, small points of terminal plexuses were seen for HL and FL far laterally against the external capsule and within the VIB lamina region (Fig. 7, AP – 0.4). Finally, VIB projection zones surrounded the major HL projection strip (Fig. 7, AP – 0.4). The major HL and FL laminae were 200–300 µm from the external capsule.

Near Bregma, HL and FL axons intermingled significantly within a widened lamina (Fig. 7, AP – 0.2). Sparse medial terminal fields in the calbindin-rich matrix were visible at these levels (Figs. 4–7); some of these medial fields were on the edge of the calbindin-rich zone (Fig. 7, AP – 0.2).

Anterior to Bregma (AP + 0.4), another pattern was present that was remarkable for the interdigitation and overlap of the HL and FL projections (Fig. 7, AP + 0.4). For the FL, the field of terminals was large (1.0 × 0.7 mm) with a sparsely innervated core, and its lateral edge was offset from the external capsule by only 100 µm. In the double-label experiments, the sparse core contained a dense axon plexus from the HL cortex (Fig. 12).

Throughout the rest of the anterior striatum, the lateral laminae and small medial zones of terminals varied in density and exact position (Figs. 4–6). The VIB projection was very sparse to nonexistent. At AP levels –0.2 and +0.6, axons were very sparse for the FL and were dense for the HL. At AP +0.8, a large extent of the dorsolateral striatum was covered by HL projections. At AP +1.0, the axon plexus field for FL was relatively ventrolateral; at AP +1.2, it again extended dorsally; and, at +1.6, it was at its most ventrolateral (Fig. 5), whereas HL remained relatively dorsal (Figs. 4, 7).

Contralateral projections

Contralateral corticostriate projections were sparse compared with ipsilateral projections and were not as extensive anteroposteriorly. They were most dense in HL cases and least dense in VIB cases. In the HL cases, they were anterior to Bregma, slightly medial to the ipsilateral projections. In the FL cases, contralateral projections were seen from AP – 0.6 to +1.22 and were far less dense than their ipsilateral counterparts. Within 0.2 mm of Bregma, the FL projections were symmetric, but, at AP +0.4, contralateral was dorsal to ipsilateral.

Confocal analysis

Confocal microscopy was used to confirm and analyze in detail the overlapping projections at AP – 1.7. The confocal imaging showed that the projections clearly occupied the same region (Fig. 10) but revealed no patterns that were not observed with traditional microscopy. Analysis of other sections showed clusters of terminals from HL cortex as small as 10 µm in diameter.

PHA-L and short-term injections

Compared with FR and BDA injections, PHA-L injections labeled only a few cells in cortex. The distribution of labeled axons was similar to that of FR and BDA, but the terminal fields were far less dense and were not quite as extensive anteroposteriorly. The area of extracellular space containing FR 15–20 minutes after the injection was up to twice as large as the area of labeled cells visible 7–14 days later.

DISCUSSION

This study found a laminar and lattice-like organization of cortical inputs to the sensorimotor striatum in rat that is consistent with a dorsoventral somatotopic and anisotropic plan. For the first time in any species, the data show the translation of vertical arrays of cells in cortex to the striatum and that the translation forms a lattice-like, or grid, structure. For the first time in rat, the data show a detailed functional/neuroanatomic map of the striatal sensorimotor zone. Furthermore, the data show a consistent axis of orientation of the cortical projections and chemoarchitecture.

The procedures that labeled cells in a discrete vertical array in the cortex revealed in striatum an ordered pattern of successive axonal arbors forming laminae in the calbindin-poor, peripheral region of the neostriatum in parallel with the external capsule and the border of the calbindin-rich zone. In coronal sections, these laminae were seen as strips, or fingers, for VIB, HL, and FL. Projections from different cortical representations overlapped, interdigitated, or remained separate in different parts of the laminae, depending on AP position. Importantly, the axonal plexuses associated with each body representation were extraordinarily similar in size and shape and were predictably located from animal to animal. This new body map of the skin surface in rat striatum will facilitate further functional studies of highly localized neuronal activity and transmitter and molecular events. The locations of the ordered laminae, their widths and lengths, their parallel relationship to the calbindin-rich matrix, and their satellite radial points may be important keys to the overall organization of sensorimotor, limbic, and associative cortical inputs.

Goldman and Nauta (1977) saw alternating strips of terminal fields from the prefrontal cortex and suggested that the corticostriate axonal plexus pattern was similar to the columnar distribution of thalamic afferents in the cerebral cortex. The present findings extend that view by associating strips of terminal fields in the striatum with columnar cortical regions representing specific regions of the skin surface. The strips and patchy somatosensory
cortical projections in rat were similar to matrisomes and strips described as "fingers" in primates (Selemon and Goldman-Rakic, 1985; Flaherty and Graybiel, 1991). The predominance of this organization across species underscores its importance for integrative mechanisms of the striatum.

Fig. 4. Hindlimb (HL) sensorimotor corticostriate projection map of a single case (Fig. 1A, case 2). Shown in this and the following two figures are tracings of thionin-stained, right coronal hemisections and drawings of the fluorescent varicose axon plexuses in striatum observed in alternate sections. Numbers indicate the approximate anteroposterior location in mm relative to Bregma. The drawings show the major, high-density projection fields and span nearly the entire anteroposterior projection observed. The drawings show findings at 120–600 µm intervals. For the HL projection, varicose axon fields were small and infrequent posterior to Bregma and were 400–500 µm medial to the external capsule. Anterior to Bregma, the plexuses were larger and more lateral within 200 µm of the external capsule. Axon plexuses were most dense and largest from anteroposterior (AP) +0.62 to +1.40. From AP –0.40 to +1.40, small axon plexuses were seen medially. AC, anterior commissure; EC, external capsule; F, fimbria; GP, globus pallidus; IC, internal capsule; OT, optic tract; S, septum; STR, striatum; V, ventricle.
Comparison of the present somatotopic map with physiological and lesion studies in the rat

Somatotopy in the dorsolateral striatum of rat has been suggested by electrophysiological studies of somatosensory and motor responses (Carelli and West, 1991; Mittler et al., 1994). In those studies, the limbs tended to be represented dorsal to the head and face. However, there was also considerable intermingling of body-part representation along the electrode paths studied, which would be predicted from the present anatomic results. Slightly...
curved, parallel, alternating strips of inputs related to different body parts, patchy innervation across strips, and dorsoventral intermingling within strips would produce maps like those presented in previous electrophysiological studies that used electrodes perpendicular to the skull surface (Carelli and West, 1991; Mittler et al., 1994). In addition, striatal lesions disrupt FL reaching movements when the lesion is in the FL area mapped in this study (Pisa and Schranz, 1988). The lesion that interrupts the grooming sequence in rats (Cromwell and Berriidge, 1996) impinges on a region where the HL and VIB somatosensory inputs are especially prevalent and interdigitate, but other, unknown, inputs to this region may be important to the sequence of grooming behavior.

Fig. 6. Vibrissae (VIB) somatosensory corticostriate projection map of a single case (Fig. 1C, case 6). The drawings show findings at 200–700 µm intervals. Narrow varicose axon plexus fields were most dense posterior to Bregma. Anterior to Bregma, they were sparse and formed a narrow band in the most dorsolateral striatum (AP +0.55 formed to +1.50). AC, anterior commissure; EC, external capsule; F, fimbria; GP, globus pallidus; IC, internal capsule; OT, optic tract; S, septum; STR, striatum; V, ventricle.
Fig. 7. Composite diagrams of coronal sections through the striatum show the hallmarks of the organization of inputs from the cortical representation of the three body regions studied. Grays indicate the hindlimb (HL) and forelimb (FL), stippling indicates the vibrissae, and black indicates the HL-FL overlap regions. The double-headed arrow (center) indicates a region of HL-FL overlap. Single-headed arrows indicate regions where vibrissae overlaps with HL and FL projections. The calbindin-rich region is indicated by slanted hatching. White zones in the calbindin-rich region are striosomes. The corticostriate body representation is distributed into strips and “patchy” zones that form laminae throughout the anteroposterior extent of the striatum. The dashed lines emphasize the lamina divisions. The vibrissae (VIB) lamina (stippled) is the most lateral, or peripheral, against the external capsule. However, at AP −0.4, small, patchy axonplexuses are seen in this VIB strip from HL and FL cortex (arrows). The lamina containing HL and FL axon terminal arborizations is just medial to the vibrissae strip. At some AP levels (e.g., −2.0), overlapping of HL and FL projection fields is minimal in this lamina; however, at AP −1.7, there is a distinct, small zone of complete overlap of projection fields, and at AP −0.2, the axon terminal fields from HL and FL cortex overlap considerably (double-headed arrow). At AP +0.4, the HL field is surrounded by the FL field, and they are partially overlapping (black), whereas the vibrissae cortex also sends a projection to the FL field (arrow). At other AP levels, the three body-region fields are relatively distinct. The third lamina, in the calbindin-poor zone, contains projections predominantly from the vibrissae cortex (AP −0.8 to +0.4). The calbindin-rich zone contains small projections from all three somatosensory cortex regions. EC, external capsule; F, fimbria; GP, globus pallidus; IC, internal capsule; STR, striatum; V, ventricle.
Characteristics of the cortical injection site

The mediolateral and anteroposterior distribution of the recording/injection sites in the cortex confirmed the global somatotopic maps shown by others in rat (Hall and Lindholm, 1974; Chapin and Lin, 1984; Welker et al., 1984; Sievert and Neafsey, 1986). The cells at the injection sites had cutaneous receptive fields, like those described by Welker et al. (1984), Simons (1978), and Chapin (1986), who also confirmed a globally somatotopic and columnar organization of functionally related cells in rat somatosensory cortex. Like Chapin (1986), we found relatively large receptive fields in infragranular layers, and, in several animals, the receptive field included many vibrissae oriented along rows. Furthermore, the injection sites formed a vertical array of cells from 300 µm to 600 µm in diameter that were oriented perpendicular to the cortical surface regardless of the electrode orientation (Fig. 3A). Corticocortical transport to the other side formed a single column in most cases. However, some injections may have included cells without the same receptive field as that of the cells recorded. Therefore, the injections were selective for the body region under study but not necessarily for the same receptive field.

Fig. 8. A complex strip of axons and plexuses in the posterior striatum (AP −2.5 to −2.2) that was remarkably similar within and across groups of animals. A: A montage of fluorescence photomicrographs in a forelimb (FL) case. Axons and plexuses are found on a relatively long dorsoventral strip (thick arrows). Arrowheads indicate the external capsule. Thin arrow at left indicates the internal capsule. B: The overall striatal location of the FL projection plexuses seen in A. The digitized fluorescence photomicrograph montage is superimposed on a digitized alternate thionin-stained section. C: Montage of fluorescence photomicrographs in a vibrissae (VIB) case. Heavily labeled axons from the cortex enter the striatum and internal capsule (top arrow). Axons and plexuses are visible in a strip (center arrow) and open cluster (bottom arrow) next to the external capsule. Arrowheads indicate the external capsule. D: The overall striatal location of the VIB projection plexuses seen in C. Arrows parallel those in C. Compare the area of the bottom rectangle in B with that in D. They both show an open plexus. The top rectangles in B and D indicate a dense plexus in each case. AM, amygdala; EC, external capsule; IC, internal capsule; OT, optic tract; T, thalamus. Scale bars = 0.250 mm in A, 0.500 mm in C, 1.00 mm in D (also applies to B).
The laminae of corticostriate projections appeared to be the major planks of a lattice-work with cross pieces that were formed by smaller, patchy zones of axon terminal plexuses (Fig. 13). Striosomes, seen in three dimensions, also form a lattice, confirming the importance of this structural arrangement in striatum. The mediolateral somatotopy (HL/FL/VIB) of the major laminae, or planks, reflects the mediolateral somatotopy of the cortex. The crossing, discrete, and patchy zones may reflect some corticocortical connections. For example, sensory projections to the motor cortex may be paralleled by patchy projections of the somatosensory cortex to a motor lamina in striatum. However, the patchy projections also appear to allow further integration for granular cortex, for example, between HL and vibrissae.

**Relationship of the lattice to striosomes**

Based on findings from other studies (Donoghue and Herkenham, 1986; Malach and Graybiel, 1986; Flaherty...
and Graybiel, 1991; Kincaid and Wilson, 1996), it is likely that the curved laminae of terminals we describe are predominantly within the matrix compartment. We did not see any innervation of the medial striosomes marked by calbindin, consistent with previous findings (Kincaid and Wilson, 1996). We do not know how the somatosensory cortex innervates lateral striosomes, because the calbindin immunocytochemistry we used does not demarcate them. However, deep layers of somatosensory cortex do project to striosomes (Gerfen, 1989). In \(^{3}H\)naloxone autoradiograms that define both medial and lateral striosomes in rats, the laminae of cortical inputs closely parallel the orientation of lines of striosomes: This implies a plan of

Fig. 10. Overlapping varicose arborizations in a narrow strip in posterior striatum in a hindlimb/forelimb (HL/FL) injection case (Fluoro-Ruby/iodinated dextran amine). Left: Montage of confocal images illustrates HL (red) and FL (green) somatosensory corticostriate varicosities and fibers. The zone of innervation by each cortical region is specific and similar. The image is a single 0.33-µm-deep scan from a coronal section. Arrows indicate segments of HL axons that are seen more extensively in the reconstruction on the right. Right:

Confocal reconstruction of the entire 30-µm section thickness from the image on the left shows numerous HL (red) varicosities intermingling with a high density of FL (green) varicose fibers. Smooth HL (red) fibers and varicose fibers are oriented mediolaterally, whereas FL fibers are oriented dorsoventrally. This plexus zone is at the level of approximately AP \(-1.3\) mm. Arrows indicate the same points in each image. Scale bars \(= 50 \mu m\).

and

Fig. 11. Fluorescence photomicrographs of dorsolateral striatum show lateral axon plexus laminae and associated medial plexuses at AP \(-0.4\) to \(-0.8\) mm in coronal sections. A: In a hindlimb (HL) case, plexuses (arrows) are approximately 750 µm apart. The lateral field (top arrow) is approximately 250 µm from the external capsule (arrowheads). B: In a forelimb (FL) case, large plexuses are approximately 500 µm apart (large arrows). The lateral field (line of small arrows) is 350 µm from the external capsule (arrowheads). The lateral field shows a characteristic strip pattern: a narrow dorsal plexus and axons (small arrows) ending in a larger ventral plexus (left large arrow). C: In a vibrissae (VIB) case, plexuses (arrows) are approximately 500 µm apart. The lateral field (right arrow) is within 200 µm of the external capsule (arrowheads). The medial fields were larger in the vibrissae cases than in the HL or FL cases. Scale bar \(= 300 \mu m\) (applies to all).
Figure 11
Fig. 12. A montage of fluorescence photomicrographs shows overlap and interdigitation of hindlimb (HL) and forelimb (FL) axonal terminal plexuses. **Top:** The green FL axons (small arrows) surround the orange HL plexus (large arrow). **Bottom:** Shown is a wider view of the area shown in the top image. The specificity of the innervation zone is especially apparent. Arrowheads indicate the external capsule. Large arrows to the left indicate patchy zones of HL and FL in the major vibrissae lamina region. Large arrows to the right indicate the major HL strip. Small arrows indicate the FL axons and terminals that surround the HL projection. In this digitized image, several fluorescent pericytes were removed. Scale bar = 300 µm.
the injection sites have been greater than 1,000 µm in
topy to study the striatum in primates, cats, and rats, but
studies of striatum and its chemoarchitecture.
and striosomes is an important new concept for functional
organizational scheme. This common orientation of inputs
sensory cortical inputs to the striatum may reflect a larger
al., 1981). Thus, the orientation of the laminae of somato-
tion, i.e., from ventrolateral to dorsomedial (Fentress et
1993). Third, during pre- and postnatal development of the
input laminae and striosomal orientation is a key to the
overall organization of the striatum. First, the laminae
parallel the axis of orientation of striosomes (Fig. 13;
Desban et al., 1993) and the calbindin-rich zone (Fig. 7).
Second, dendritic fields of medium spiny cells correspond
to the axis of orientation of striosomes (Walker et al.,
1993). Third, during pre- and postnatal development of the
striatum, dividing cells follow this same axis of orienta-
tion, i.e., from ventrolateral to dorsomedial (Fentress et
al., 1981). Thus, the orientation of the laminae of somato-
sensory cortical inputs to the striatum may reflect a larger
organizational scheme. This common orientation of inputs
and striosomes is an important new concept for functional
studies of striatum and its chemoarchitecture.

**Distributed, anisotropic body maps in striatum**

Several studies have used sensorimotor cortex somato-
topy to study the striatum in primates, cats, and rats, but
the injection sites have been greater than 1,000 µm in
diameter in most cases (Kunzle, 1977; Malach and Gray-
briel, 1986; Flaherty and Graybiel, 1991; Ebrahimi et al.,
1992). When anterograde tracers are injected into large
areas of different body representations in the cortex, the
projections are arranged in a rough foot-up, head-down
topography in striatum, apparently reproducing the foot-
up, head-down topography of the cortex. However, as we
have found in this study, there is not a simple point-to-
point somatotopic relationship between cortex and stria-
tum. Instead, one region of cortex projects to multipro-
point anteroposterior and medially running strips in the
striatum (Malach and Graybiel, 1986; Flaherty and Gray-
briel, 1991; Ebrahimi et al., 1992). The function of a widely
distributed body surface map in the striatum is not known,
but the anteroposterior distribution is extensive in all
mammals studied (Kunzle, 1975, 1977; Goldman and
Nauta, 1977; Jones et al., 1977; Sellem and Goldman-
Rakic, 1985; Malach and Graybiel, 1986; Flaherty and
Graybiel, 1991, 1993; Ebrahimi et al., 1992; Lopez-
Figuerola et al., 1995). In addition, the projections of
individual SI1 cells to striatum are organized into longitudi-
nal bands, with discrete foci of terminations along the
bands (Levesque et al., 1996). The wide distribution may
be needed to inform the multiple functional regions of the
striatum and/or to provide opportunities for combinations
of inputs.

An anisotropic somatotopic organization in striatum
was first described in cat (Malach and Graybiel, 1986).
Somatotopic anisotropy is characterized by variable rather
than consistent distances among the somatosensory corti-
projection fields for HL, FL, and trunk in cats (Malach
and Graybiel, 1986). This anisotropy was also true for the
somatotopic organization found in the present study. HL
and FL changed their positions relative to each other and
to the VIB throughout the AP extent of the striatum. They
overlapped or interdigitated with each other and the VIB
at specific AP levels. Based on metabolic mapping data, we
previously suggested that the striatum contains a combina-
tional map of the body that provides all possible permuta-
tions of combinations of body regions (Brown, 1992). This
is still a viable hypothesis, but it is now apparent that the
extensive overlapping and interdigitation of patchy zones
from each body representation provide a much more
extensive network than that needed for simple global
body-part combinations: The FL and HL projections over-
lap more than the HL and VIB projections and, thus, are
involved in processes in addition to global body-part
combinations. Furthermore, all of the global body-part
projections include medial regions that are within the
associative domain of the rat striatum (Divac, 1971; Divac
et al., 1978; Divac and Diemer, 1980; McGee and Faull,
1989; Francois et al., 1994).

**HL/FL lamina**

The existence of HL and FL representations within one
strip and VIB within another suggests that body parts that
naturally move together, such as the HL and the FL during
stepping and the VIB during whisking, project to a single
lamina. This predicts that eye and eyelid sensorimotor
cortex would project to a single lamina, as would jaw, lips,
and tongue. Although HL and FL did not overlap in cats as
they did in rats, they were along the same medially run-
ning strip (Malach and Graybiel, 1986). Data from
primates are insufficient to say whether the body-part

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**Fig. 13.** Schematic drawing of the right striatum with striosomes (solid black, patchy areas), the granular cortex projection field, and proposed projection fields from other cortical areas. The image was traced from an actual autoradiogram of a histological section with labeled striosomes ([3H]naloxone). The drawing illustrates the pro-
posed arrangement of corticostriate projections relative to the strio-
somes. In this scheme, granular cortex projects to the most lateral
channel between striosomes. Agranular lateral, medial, and allocorti-
cal regions project to succeeding channels (unlabeled arrows). The
major corticostriate axon arborizations are crossed by smaller, patchy
corticostriate zones (dashed lines), resulting in an overall lattice-like
or grid organization. Striosomes may be where cortical inputs inner-
vate laminae that are associated primarily with neighboring cortical
sites. EC, external capsule.
association in the strips in those species is similar to that in rats. Further studies are needed of this heuristic, function-based hypothesis for a striatal organizational scheme.

**Predicted projection laminae from other cortical regions**

Based on our data and data from other studies, we propose that, in rats, a corticostriate map of principal laminae projections reflects both cortical organization and functional groupings. Thus, the most lateral strip in the posterior half of the striatum would be composed of primary visual, VIB, and head/neck sensory inputs. The visual cortical strips along the edge of the striatum were shown by Lopez-Figueroa et al. (1995). The VIB sensory inputs that we describe here are an extension of that visual strip. Following the cortical and functional organization, head/neck sensory inputs rather than jaw/lips/tongue would be expected ventrally, along the same strip next to the external capsule. According to our predicted scheme, lateral agranular inputs also form a lamina (Fig. 13), and projections from eye/eyelid cortex would be found dorsally, adjacent to primary visual inputs; VIB motor inputs at the midpoint, adjacent to VIB sensory inputs; and head and neck motor inputs ventrally. Patchy inputs from primary visual cortex would then project to the eye/eyelid motor lamina. Further studies of the projections from head, neck, mouth, and trunk and from motor and association cortex are needed to complete the functional mosaic of strips and patchy zones of the striatum.

**Functional implications of a lattice organization**

The functional implications of a lattice-like or grid network are for integrative and combinational operations. A grid is useful for the complete distribution of inputs, and the intersecting points on a grid can both locate in space and combine information. For example, within the granular corticostriate projection, a combinational striatal map may be used to assist detection of body position and to plan future movements based on how body parts are currently positioned. A special set of locations for tactile inputs for HL+FL, another for HL+VIB, another for HL+trunk, etc., is a network that could accommodate all possibilities of body-part-to-body-part relationships. Information about body position is essential to complex sequences of movement, such as grooming. In addition, lack of kinesthetic and cutaneous feedback can cause chorea-like movements, a major symptom of basal ganglia disease (Sharp et al., 1994). Furthermore, with an extensive grid that includes all of cortex, integration is anatomically possible across major cortical sources for events that are polysensory, sensory associative, and sensory limbic. It is a context-sensitive organization. Indeed, the striatum has cognitive as well as sensory and sensorimotor functions (Brown et al., 1997).

**Technical considerations**

One important technical consideration for these findings is that, although the injections were into SI cortex, the tracer was sparsely transported retrogradely into SII and may have been sparsely transported anterogradely from SII to the striatum (Chen and Aston-Jones, 1996). Indeed, the posterior ventral plexus shown in Figure 8A and part of the plexus in the lateral striatum in Figure 11 may have their origin in SII (Levesque et al., 1996). In addition, there may have been sparse retrograde transport into other somatosensory cortical areas (Fabri and Burton, 1991) and agranular motor regions, which were then transported to the striatum. The cortical labeling with FR and BDA was so sparse in these other regions, however, that it would not have produced any visible transport, even from a directly injected site. Although the use of PHA-L partially controls for the problem, the issue of SI-SII–striatal transport is not resolved, and some of the ventral and lateral plexuses we observed may be composed of SI projections (Levesque et al., 1996). However, these projections are functionally related to the injection site and are still of interest for somatosensory representation in the striatum.

**CONCLUSIONS**

The new and most important findings of this study are, first, that the global body representation in the rat striatum is organized into discrete laminae that also overlap and interdigitate with projections from other body sites to form a coherent, lattice-like pattern. This organization provides an anatomic grid for a complex integrating mechanism that includes medial as well as dorsolateral striatum. Second, the axis of orientation of the laminae parallels the striosomes and border of the calbindin-rich zone, a new organizing concept for striosomes and matrix as strips. The findings suggest a new parcellation of the sensorimotor, dorsolateral striatum based on cortical inputs: Parallel laminae form principal body surface zones; but also, cortical projections form patchy inputs to neighboring or distal body-region laminae. It is likely that motor cortex and association cortex also send patchy inputs to these principal body surface laminae. This organizing principle of curved laminae crossed by radial points from neighboring cortical sites may apply to the entire cortico-striate system across species.

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We dedicate this report to the memory of Harvey Etra. We thank Dr. Konstatin Dobrenis for his excellent assistance with the confocal microscope.

**LITERATURE CITED**


Brown et al., 1997).


