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Cortical Connections to Single Digit Representations in Area 3b of Somatosensory Cortex in Squirrel Monkeys and Prosimian Galagos

Chia-Chi Liao, Omar A. Gharbawie, Huixin Qi, and Jon H. Kaas*

Department of Psychology, Vanderbilt University, Nashville, Tennessee

Abstract

The ventral posterior nucleus of thalamus sends highly segregated inputs into each digit representation in area 3b of primary somatosensory cortex. However, the spatial organization of the connections that link digit representations of areas 3b with other somatosensory areas is less understood. Here we examined the cortical inputs to individual digit representations of area 3b in four squirrel monkeys and one prosimian galago. Retrograde tracers were injected into neurophysiologically defined representations of individual digits of area 3b. Cortical tissues were cut parallel to the surface in some cases and showed that feedback projections to individual digits overlapped extensively in the hand representations of areas 3b, 1, and parietal ventral (PV) and second somatosensory (S2) areas. Other regions with overlapping populations of labeled cells included area 3a and primary motor cortex (M1). The results were confirmed in other cases in which the cortical tissues were cut in the coronal plane. The same cases also showed that cells were primarily labeled in the infragranular and supragranular layers. Thus, feedback projections to individual digit representations in area 3b mainly originate from multiple digits and other portions of hand representations of areas 3b, 1, PV, and S2. This organization is in stark contrast to the segregated thalamocortical inputs, which originate in single digit representations and terminate in the matching digit representation in the cortex. The organization of feedback connections could provide a substrate for the integration of information across the representations of adjacent digits in area 3b.

Keywords

spatial integration; hand representation; intrinsic connections; corticocortical connections

In order for humans and other primates to skillfully use their hands in dexterous tasks, information from receptors across the hand must be integrated to provide the necessary sensory guidance. Neurons involved in the early stages of sensory processing up to primary somatosensory cortex (area 3b) tend to have small receptive fields that are specific to a

limited part of the hand, such as part of a single phalange of a digit (Merzenich et al., 1978; Nelson et al., 1980; Sur et al., 1980, 1985; Pons et al., 1987b; DiCarlo et al., 1998; Xu and Wall, 1999; Zhang et al., 2001). These excitatory receptive fields are mediated by orderly and restricted feedforward connections so that a precise somatotopy exists in the cuneate nucleus of the lower brainstem, the ventroposterior nucleus (VP) of the thalamus, and primary somatosensory area 3b (Merzenich et al., 1978; Kaas et al., 1979, 1984; Jones et al., 1982; Culbertson and Brushart, 1989; Florence et al., 1989; Kaas, 1993; Jones, 2007). In monkeys, groups of cells that represent a single digit, or part of a digit, are isolated from each other by surrounding or separating cell-poor septa (Jain et al., 1998b; Rausell and Jones, 1991; Qi and Kaas, 2004; Qi et al., 2011). Although neurons in area 3b are best activated by stimuli on a single digit, their activities are modulated by concurrent stimuli within the same hand or even on the contralateral hand (Burton et al., 1998; Braun et al., 2005; Tommerdahl et al., 2006; Reed et al., 2011). This influence has been shown to reduce neuronal activities in some neurons, but can also have the opposite effect on other neurons (Shimegi et al., 1999, 2000; Moore et al., 1999; Greek et al., 2003; Melzer et al., 2006; Friedman et al., 2008; Reed et al., 2010). Such modulations likely depend on intrinsic connections within area 3b, or feedback connections from higher-order somatosensory fields because feedforward projections primarily connect somatotopically matched representations. Although the connections of area 3b in monkeys has been extensively studied (Jones et al., 1978; Cusick et al., 1985b; Krubitzer and Kaas, 1990; Burton and Fabri, 1995; Burton et al., 1995; Wu and Kaas, 2003; Coq et al., 2004), we still know little about how cortical feedback connections are distributed with the somatotopic representations of the hand within area 3b. This is largely because injections of tracers in area 3b typically involved more than one body part representation, or there has been no attempt to relate patterns of connections to the somatotopy of area 3b in the same cortex.

In the present study we investigated the extent of intrinsic and feedback connections of the area 3b hand representation in four squirrel monkeys and one galago. We identified the representations of the digits in area 3b with receptive field mapping. Those maps guided our tracer injections, which were limited to individual digit representations. We purposely injected different tracers into separate digit representation in order to compare the results within the same case. This allowed us to quantitatively evaluate the distributions of retrogradely labeled neurons in area 3b, other somatosensory areas (3a, 1, 2, PV/S2), and motor cortex (M1) from different injection sites in area 3b. We also evaluated the effectiveness of our attempts to restrict injection uptake zones to the representations of single digits by examining the locations of labeled neurons in the VP as a result of the cortical injections. This measure exploits the inherent organization of VP where contiguous representations of digits are separated from one another by narrow, cell-poor septa that are visible in histological preparations (Qi et al., 2011). Thus, distributions of labeled neurons in area 3b and other regions of cortex could be related to injection sites that only labeled neurons in the representations of single digits in VP. The results indicate that each digit representation in area 3b receives inputs from most other parts of the hand representation in area 3b, and from other digit representations in areas 3a, 1, and PV/S2. These intrinsic and feedback connections provide a basis for the integration of information across representations of digits in area 3b.

MATERIALS AND METHODS

We studied the organization of intrinsic and feedback connections for individual digit representations in area 3b in four squirrel monkeys (*Saimiri bolivian*) and one galago (*Otolemur garnetti*). All surgical procedures and animal care were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* established by National Institutes of Health and approved by the Animal Care and Use Committee of Vanderbilt University.

Surgical procedures

In all surgeries, intramuscular injections of ketamine hydrochloride (10–25 mg/kg) were initially used to induce anesthesia. Animals were placed in a stereotaxic headholder and transitioned to an inhalation anesthetic, isoflurane (1–2%) in oxygen. Surgery was carried out under aseptic conditions, and vital signs including heart rate, respiration rate, blood pressure, expiration CO₂, arterial O₂ saturation, and body temperature were monitored throughout the procedures. Unilateral craniotomies were made over parietal cortex to expose the hand representation of area 3b, which is directly lateral to the tip of the central sulcus in squirrel monkeys. After the dura was removed the exposed brain surface was protected with a thin layer of silicon fluid and digitally photographed. A print of the enlarged image was used for guiding microelectrode penetrations and tracer injections.

Microelectrode multiunit mapping and tracer injections

Hand representations, especially digits, in area 3b were systematically mapped using microelectrode multiunit recordings. A low impedance tungsten microelectrode (1 MΩ) at a 25° angle from vertical was lowered perpendicularly through the cortical surface to depths of 650–1,000 μm where the middle layers of cortex are located. This electrode placement strategy was repeated at 400–500 μm intervals to comprehensively map the hand representation. Standard-mapping methods such as lightly touching with fine probes, brushing, and tapping were used to determine receptive fields and identify responsive modalities. For microelectrode penetrations into the banks of the shallow central sulcus, receptive fields were determined every 200–300 μm until no neuronal activity was detected. Somatotopic organizations of areas 3a, 3b, and 1 determined in previous studies (Sur et al., 1982; Wu and Kaas, 2003) guided our mapping. The hand representations of areas 3b, 3a, and 1 were arranged in parallel with a lateral to medial sequence of digits 1 to 5, and as roughly mirror image representations. Thus, area 3b borders area 3a rostrally with reverted digit representations and adjoins area 1 caudally with adjoining palm representations. To determine the areal border between areas 3b and 3a, neural responsiveness was also considered since neurons in area 3b have small receptive fields and are sensitive to low threshold, cutaneous stimulation such as lightly touching or brushing the skin. In contrast, neurons in area 3a are activated by hand tapping and muscle and joint manipulations.

To confine tracer spread within the boundary of each digit representation in area 3b, small amounts of tracers were injected in the center of electrophysiologically defined digit representations (Qi et al., 2011). Five different tracers were used across the five cases. The tracers included 0.02 μl of a solution of 1% cholera toxin subunit B (CTB; Sigma, St. Louis,

MO) in distilled water, or 0.4 μ L of either fluoro-ruby (FR, MW 3,000 and 10,000; Invitrogen, Carlsbad, CA), biotinylated dextran amine (BDA, MW 3,000 and 10,000; Invitrogen), or fluoro-emerald (FE, MW 3,000 and 10,000; Invitrogen) mixtures of 10% in pH 7.4 phosphate buffer. Lastly, 0.02 μ L of 1% CTB-conjugated with fluoro-emerald (CTB-alexa 488 or CTBG) in distilled water was used in some injections. BDA and FR are often used as bidirectional tracers to label anterograde terminations and retrograde cell bodies (Schmued et al., 1990; Kultas-Ilinsky et al., 2003; Imura and Rockland, 2007). All injections were made with 1- μ L or 2- μ L Hamilton syringes outfitted with glass pipettes drawn to fine tips (~25–50 μ m). To ensure that tracers included supragranular cortical layers, which receive feedback connections, tracer depositions in each location were made at two depths from the pia surface, at 600 and 800 μ m. After injections, the micropipette was kept in position for 2–5 minutes in order to reduce backflow. After the micropipette was withdrawn, the dura was repositioned over cortex and covered with a piece of Gelfilm trimmed to the appropriate size. The opening in the skull was covered with dental cement. The animal was closely monitored as it recovered from anesthesia, and analgesics and prophylactic antibiotics were administered every 12 hours for 3 consecutive days.

After 2–3 weeks, terminal microelectrode mapping in each of the four squirrel monkeys was used to obtain a detailed map of the hand representation in area 3b. Procedures were similar to the microelectrode multiunit mapping used in the survival surgery. Special care was taken to identify rostral and caudal borders of area 3b with areas 3a and 1, which were then marked by small electrolytic lesions that were later identified in cortical sections.

Perfusion and histology

Perfusion was carried out at the end of the mapping session. Animals were deeply anesthetized with a lethal dose of sodium pentobarbital (120 mg/kg) and, when areflexive, perfused transcardially with phosphate-buffered saline (PBS, pH 7.4). In one squirrel monkey and one galago, the perfusion with PBS was followed by 4% paraformaldehyde and 10% sucrose for cutting in the coronal plane. Brains were extracted from the skull and immersed overnight in 30% sucrose containing PBS at 4° C for cryoprotection. In three squirrel monkeys, the PBS perfusion was followed by 2% paraformaldehyde and 10% sucrose-containing fixative. In those cases, the cortical hemispheres were carefully separated from the sub-cortical tissue, manually flattened, postfixed in the same sucrose-containing fix overnight and cut in parallel to the cortical surface. The thalamus was stored in 30% sucrose-containing PBS and cut in the coronal plane. All tissues were sectioned at a thickness of 40 μ m on a freezing microtome and saved in series.

Sections with expected fluorescence label were directly mounted, air-dried, coverslipped, and kept in the dark at 4° C. In order to visualize CTB labeling profiles, tissues were processed according to the protocol of Angelucci et al. (1996), with moderate modifications. In brief, sections were first rinsed in 0.5% Triton-containing 0.05M Tris buffer saline (TBS, pH 7.0; washing solution) and then immersed in a blocking solution of 0.5% Triton, 5% normal rabbit serum (NRS) in 0.05M TBS for 1 hour. A 1:4,000 dilution of the primary antibody (goat anti-CTB; ListBiological Labs, Campbell, CA) in the blocking solution was used to incubate the sections for 4 nights at 4° C. Sections were then repeatedly washed and

immersed in a secondary antibody solution of biotinylated rabbit antigoat IgG (PK-4005; Vector Laboratories, Burlingame, CA) diluted at 1:200 in the same blocking solution for 1.5 hours at room temperature. After 5 washes, the sections were processed with a standard avidin-biotin complex (ABC) reaction. Sections were incubated in the ABC solution (PK-6100; Vector Laboratories) that was made at a ratio of 1 drop of A and 1 drop of B for every 7 ml 0.05M TBS for 1.5 hours. The sections were then washed and incubated in a 3,3'-diaminobenzidine tetrahydrochloride (DAB) solution (50 µg DAB in 100 ml 0.05 M TBS) containing a 0.01% nickel ammonium sulfate for 10 minutes. Finally, an H₂O₂ solution was added into the DAB solution at a 1:10,000 ratio in order to visualize the CTB labeling profiles, which were black in color. In cases with both CTB and BDA injections, the tissue was processed in two stages to visualize labeling from both tracers. Thus, after incubation in the solution containing CTB primary antibody for 4 nights, sections were processed with standard ABC reaction, which revealed BDA-labeled cells and axonal terminals as a brown color. The final stage involved resuming the CTB protocol as described above from the point of the secondary antibody immersion.

Cytochrome oxidase (CO) and Nissl staining were used to reveal cortical and thalamic architecture in separate series of coronal sections. A third series of coronal sections was reacted to reveal the vesicular glutamate transporter 2 (VGLUT2) immunoreactivity using a mouse monoclonal anti-VGLUT2 primary antibody (Millipore, Billerica, MA). Lastly, one series of flattened cortical sections was processed to stain myelinated fiber to reveal areal borders of cortical regions (Jain et al., 1998a, 2001).

Antibody characterization, VGLUT2

Monoclonal anti-VGLUT2 (MAB5504) is a mouse IgG1 antibody with clone 8G9.2, which was developed against recombinant protein from rat VGLUT2. According to the manufacturer's technical information, the antibody detects a band at a molecular weight of 56 kDa on western blots of mouse brain lysates tissue. Species cross-relativities were mainly observed in mice and rats, but the antibody is expected to react positively with human tissue based on sequence homology. Previous studies have revealed that immunoreactivity of anti-VGLUT2 revealed thalamocortical terminations in cortical layer 4 in rats (Kaneko and Fujiyama, 2002), galagos (Wong and Kaas, 2010), and macaque monkeys (Hackett and de la Mothe, 2009). Additionally, subdivisions in the thalamus, especially in VP, were clearly shown by VGLUT2 immunoreactivity in galagos squirrel monkeys, owl monkeys, and macaque monkeys (Qi et al., 2011).

Data analysis

The organizations of retrogradely labeled cells in the thalamus were examined to ascertain that each tracer injection was confined to an individual digit representation in area 3b. The hand representation in VP was determined from successive sections stained for CO and VGLUT2. Results from previous studies revealed that subdivisions containing neurons with dense somatosensory inputs from cuneate nucleus in the hand representation of VP are separated by cell-poor septa (Qi et al., 2011). These ovals represent digits 1 to 5 of the hand in a mediolateral sequence. Only injections that labeled patches of cells corresponding to dark ovals defined by VGLUT2 staining were included in the present study. A

representative example is shown in Figure 1. An upright fluorescent/brightfield microscope was used to examine labeling profiles that were resulted from the FR, FE, CTBG, BDA, or CTB injections. By using Neurolucida software (MBF Bioscience, Williston, VT), labeled cells were systematically plotted and the terminal fields of labeled axons were marked as outlined. Plotting and architecture results were imported into Adobe Illustrator CS5 (Adobe Systems, San Jose, CA). Blood vessels, landmarks, and electrolytic lesions were used to align plots and architecture. Profiles of labeled cells and terminals were digitally captured using a Nikon E800 microscope outfitted with a Nikon DXM1200 camera. Images were imported to Adobe Photoshop CS5 and adjusted for brightness and contrast.

We aligned the electrophysiologically defined somatotopic maps and distributions of labeled cells using Adobe Illustrator. This approach allowed us to quantify the densities of feedback connections to individual digit representations in area 3b. Receptive fields of area 1 were not mapped in this study. Nevertheless, we estimated the borders of its digit representations from widely accepted somatotopic maps of squirrel monkeys (Sur et al., 1982) and from three cases that we recently mapped for a different study (unpubl. obs.). Accordingly, we estimated the representations of the digits and the palm representations in area 1 as mirror images with a slight medial offset to the same representations that we mapped in area 3b. The distributions and densities of cells labeled in area 1 were also used to estimate the borders of individual digit representations in area 1 such that the connections of area 3b with area 1 were primarily with matching representations (Negyessy et al., 2013). We counted the number of cells labeled in each digit representation. The densities of the respective connections were calculated from the ratio of cells labeled in individual digit representations to the total number of labeled cells. Cells labeled within the cores and halos of the injection sites were excluded from quantification.

RESULTS

The two objectives of the study were to determine whether the digit representations in area 3b are connected to one another via 1) intrinsic connections in area 3b, and 2) the feedback connections from areas 1, 3a, M1, and secondary somatosensory cortex (PV/S2) in the upper bank of the lateral sulcus. The results are presented in two parts. First, the profiles of labeling from tracer injections are shown in surface views of cortex to show the organizations of cortical connections of individual digit representations in area 3b. Second, the laminar distributions of labeled neurons, especially in PV/S2 and area 1, are described from cortical sections cut in the coronal plane.

Surface views of distributions of neurons projecting to area 3b

In order to reveal the overall distribution of labeled neurons that project to individual digit representations of area 3b, the cortex of three squirrel monkeys was flattened and cut parallel to the surface. This strategy facilitated aligning neurophysiological maps and connection results in the same plane.

Case 11-53 SqM—Patterns of cortical connections of the representations of individual digits in area 3b of squirrel monkey 11-53 were determined by placing small injections of FR in the representations of digits 1 and 3, and CTB in the representations of digits 2 and 4.

Injection cores and dense uptake zones were completely, or near completely, confined to the representations of the target digits (Fig. 2). The injections primarily labeled neurons in areas 3b, 3a, 1, 2, PV/S2, and M1 (Fig. 3). The evidence for the considerable convergences of projections from various cortical areas onto individual digit representations in area 3b is apparent in Figures 3 and 4. The populations of CTB (blue dots) and FR (red dots) labeled neurons overlapped throughout their distributions.

Intrinsic connections within area 3b: CTB-labeled neurons from injections in digits 2 and 4 overlapped extensively in the territory of digit 3. This population of labeled cells extended medially into the representations of digit 5, palm and wrist, and extended laterally into the representation of digit 1. Likewise, FR-labeled neurons from injections in digits 1 and 3 overlapped in the representations of digits 2 and 4, and extended into the representations of digit 5 and wrist at reduced densities. Neurons were labeled throughout the rostrocaudal extent of the digits and palm representations in area 3b. Labeled neurons extended as far medially as the forearm representation, but did not encroach into the trunk, hind-limb, and tail in the most medial aspects. Few labeled neurons were in the most lateral part of the hand representations, and only an occasional neuron was labeled across the hand face border, which was identified as a narrow, cell-poor septum (see Jain et al., 2001).

Feedback projections from area 1: Neurons were also labeled throughout most of the territory of the hand representation in area 1. CTB-labeled neurons overlapped with FR-labeled neurons in the medial portion of the hand representation of area 1, and to a lesser extent in the lateral portion. The overlap in the boxed region of area 1 is shown at higher magnification in Figure 4A, where it is apparent that tracer injections in single digit representations in area 3b labeled neurons in the representations of more than one digit in area 1. Labeled neurons in area 1 did not extend laterally into representations of the face and mouth or medially into representations of the forearm, trunk, hindlimb, or tail (except for an occasional neuron).

Feedback projections from area 2: Just caudal to area 1, a parallel representation of the body is well established in area 2 of macaque monkeys (Pons and Kaas, 1986), but the existence of an area 2 in New World squirrel monkeys and other New World monkeys remains in question (Padberg et al., 2005). The number of labeled cells in the expected territory of area 2 was smaller than for other somatosensory areas. Nevertheless, cells labeled in area 2 were largely confined to the same mediolateral extent as the cells labeled in areas 3b and 1.

Feedback projections from area 3a: In contrast, CTB-labeled neurons were distributed throughout the hand representation in area 3a and overlapped with FR-labeled neurons (Fig. 4C). Those cells extended medially into wrist and forearm representations, but not laterally into the face representation.

Feedback projections from PV/S2: CTB- and FR-labeled neurons also extensively overlapped in the cortex of the upper bank of the lateral sulcus, where PV and S2 are located. In the present study, without detailed microelectrode maps of the region, labeled neurons could not be assigned to hand representations, other parts of PV and S2, or even

specifically to PV or S2. In primates, PV and S2 have mirroring representations of the contralateral body surface with adjoining hand representations in the lateral sulcus and both areas have dense and reciprocal connection with area 3b (Krubitzer et al., 1995; Qi et al., 2002; Coq et al., 2004). Our results show that the anterogradely labeled terminations from FR injections in area 3b form a rostrocaudal distribution in the upper bank of lateral sulcus, where FR- and CTB-labeled neurons were identified (Figs. 3, 4B). Based on the reciprocal connection pattern, we suggest that the labeled fields identify the adjoining hand representations in PV and S2, respectively. The area with overlapping labeled neurons and terminations extended deeply into the lateral sulcus, in the expected representations of the ventral somatosensory area, VS, which may be two adjoining areas, VSr and VSc (Cusick et al., 1989; Coq et al., 2004). The FR-labeled terminations were much more focused than the distributions of FR- and CTB-labeled neurons (light red shading vs. blue dots in Fig. 4B). The scattering of labeled neurons that was more dorsal in Figure 4B (near area 3b) likely included portions of S2 and PV representing the face. Finally, a scattering of labeled neurons just caudal to the PV/S2 region suggests the location of another, yet unidentified somatosensory area with feedback projections to area 3b.

Feedback projections from frontal cortex motor regions: Labeled neurons were distributed across most of the hand representation in M1. Previously described motor maps of M1, revealed by micro-stimulation, indicate that digit movements can be evoked from sites throughout the hand territory, and are intermixed with sites that evoked wrist, elbow, and even shoulder movements (Gould et al., 1986). Thus, it seems unlikely that the feedback projections to area 3b that originate in M1 would be digit-specific. Indeed, the CTB-labeled and FR-labeled populations overlapped in M1 (Fig. 4C). The most medial of those labeled neurons were near the expected medial border of the forelimb representation. Labeled cells were not located laterally in the face representation of M1. A few labeled neurons were located more rostrally in frontal cortex, near the border of M1 with the dorsal premotor area, PMd (Gharbawie et al., 2011). These neurons were likely in PMd, providing evidence that PMd sends feedback to area 3b, albeit sparse.

Case 12-17 SqM—In this squirrel monkey, CTB, FR, and BDA were injected into the digits 2, 3, and 4 representations, respectively (Figs. 5–7). Each injection core was confined to the representation of a single digit (Fig. 5). The CTB injection labeled more cells than the other injections.

Intrinsic connections within area 3b: The distribution of CTB-labeled neurons was most dense within or near the digit 2 representation, but it also extended laterally into the digit 1 representation, caudally into the representation of the palm, and medially into the representations of digits 3, 4, and 5 (Figs. 6, 7B). The BDA injection in the digit 4 representation labeled far fewer neurons, which were primarily localized within the digit 4 representation, and also included the representations of digits 2, 3, 5, and the palm (Fig. 7D). Although FR was the least effective tracer in this case, it labeled neurons throughout the digit 3 representation, the representations of all the other digits and the palm in the caudal area 3b (Fig. 7C). Overall, the most medial of the labeled neurons from all of the injections likely overlapped the representation of the wrist and the most lateral overlapped the hand–

face border. Thus, labeled neurons were mostly distributed within the hand territory, and avoided face, trunk, and hindlimb representations.

Labeled cells were primarily concentrated within the injected digit representation. Smaller concentrations of this population of labeled cells extended into adjacent representations of the digits and palm (Table 1). For example, 49.9% of CTB-labeled cells were located within the digit 2 representation, which was the target zone of the injection. Smaller concentrations of CTB-labeled cells were present in the representations of digits 1 (10%), 3 (21.8%), 4 (1.1%), and 5 (0.3%). Similar distributions of labeled cells were observed in area 3b for the FR and BDA injections (Table 1).

Feedback projections from area 1: CTB injection in the representation of digit 2 in area 3b labeled fewer cells in area 1 as compared to area 3b. The largest proportion of cells labeled in area 1 (34.6%, see Table 2) was concentrated slightly medial to the injection site, which overlapped the expected representation of digit 2 (Fig. 7B). The distribution of labeled neurons extended medially into the expected representations of digits 3 (21.1%), 4 (10.5%), and 5 (1.4%), and laterally into the representation of digit 1 (4.3%). Similar distributions of labeled cells were observed in area 1 for the FR and BDA injections (Fig. 7C,D).

Feedback projections from 3a, M1, S2, and PV: All three injections labeled neurons in the expected hand representation in areas 3a, M1, and PV/S2. Although with smaller concentrations, BDA- and FR-labeled neurons overlapped the CTB-labeled neurons in these areas (insets C, D in Fig. 6).

Case 12-38 SqM—In this squirrel monkey, the hand representation of area 3b was mapped more extensively with microelectrode recordings than the previous two cases (Figs. 8–10). CTB, FR, BDA, and FE injections were placed in the representations of digits 2, 3, 4, and 5, respectively (Fig. 8). The CTB injection labeled more cells than any of the other injections. The FE injection labeled only a few neurons around the injection site, which warranted exclusion from the present analysis.

Intrinsic connections within area 3b: The CTB injection was in the center of the digit 2 representation in area 3b (Fig. 10A). CTB-labeled neurons were primarily concentrated in the digit 2 representation in area 3b (44.4%). Smaller concentrations of this population of cells extended medially and laterally into adjacent representations of the digits and palm (Table 1). Only a few labeled neurons were lateral to the hand–face border. The FR and BDA injections in the representations of digits 3 and 4 of areas 3b, respectively, labeled similar distributions of neurons as the CTB injection in area 3b (Fig. 10B,C).

Feedback projections from areas 1, 3a, M1, S2, and PV: Large numbers of CTB-labeled neurons were located in areas 1, 3a, M1, 1, and PV/S2. In area 1, the distributions of labeled cells were denser in the expected representations of digits 2 and 3, with a scattering of labeled neurons in other parts of the hand representation (Table 2). The distribution patterns of FR- and BDA-labeled neurons were not apparent in area 1 due to their low densities in this area. Although in small numbers for the BDA- and FR-labeled neurons, the three populations of labeled cells overlapped extensively in area 1 (inset B in Fig. 9). A few

labeled neurons were sufficiently caudal to overlap area 2. The few BDA- and FR-labeled neurons overlapped the with widely scattered CTB-labeled neurons across the hand representation in area 3a (inset C in Fig. 9). Labeled cells were less widely distributed within M1 and were perhaps confined to narrow aspects of the hand representation. Almost all of the CTB-labeled neurons in the PV/S2 regions were concentrated in the expected representations of the hand. Only a few FR- and BDA-labeled neurons and BDA-labeled terminals were observed in the vicinity of CTB-labeled neurons (inset D in Fig. 9). Nevertheless, a small proportion of cells were labeled in the upper bank of the lateral sulcus beyond the expected hand representations, potentially in a separate somatosensory area.

Laminar patterns of neurons projecting to area 3b

We investigated the laminar distributions of feedback connections for the representations of individual digits in area 3b in a squirrel monkey and a prosimian galago.

Case 09-37 SqM—In this squirrel monkey, FR was injected into the representations of digits 1, 3, and 5 of area 3b, and CTB was injected into the representations of digits 2 and 4 (Fig. 11). The injections were near completely confined to the electrophysiologically defined boundaries of individual digit representations. Two separate ovals of CTB-labeled cells in VP (Fig. 1) confirm the confinement of the injections into the representation of digits 2 and 4 in area 3b. The distributions of labeled neurons were related to supragranular and infragranular layers, which were determined from adjacent sections stained for Nissl, VGLUT2, and CO.

Laminar distribution of intrinsic connections within area 3b: CTB- and FR-labeled neurons were densely packed in and around the injection sites throughout the supragranular and infragranular layers and in layer 4 (Fig. 12). Beyond the injection sites, neurons labeled in area 3b were observed in both supragranular and infragranular layers. Although the CTB injection labeled more neurons than the FR injection, the two populations of labeled neurons overlapped extensively.

Laminar distribution of feedback connections from areas 1, 3a, M1, S2, and PV:

Similarly, both populations of labeled neurons were present in the supragranular and infragranular layers of areas 3a, 1, M1, and PV/S2 (Figs. 12, 13). CTB injections labeled a higher proportion of neurons in the infragranular layers than the FR injections. The discrepancy between the distributions of the two populations may be related to the CTB injections involving more layers of cortex than the FR injections (Fig. 10B–D). Lastly, anterogradely labeled terminals from the CTB injections were observed in layer 4 of PV/S2 region. The distributions of CTB-labeled terminals were more focused than the FR- and CTB-labeled feedback connections (light blue shading vs. blue dots in Fig. 13A).

Case 10-16 galago—In this galago, CTBG was injected in the representations of digits 1 and 3, and FR was injected in the representations of digits 2 and 4 (Fig. 14). The CTBG injections labeled two separate patches of neurons in VPL (Fig. 14D), which confirm the confinement of the injection to the target digit representations. As in squirrel monkeys, the injections in area 3b labeled neurons in both supragranular and infragranular layers across

most of the hand representation in area 3b and the two populations of labeled cells overlapped extensively (Fig. 15). Although area 1 was not mapped here, neurons labeled caudal to area 3b were in the expected location of area 1 and were present in both supragranular and infragranular layers. In contrast, the greater population of labeled neurons in the PV/S2 region was mainly in the infragranular layers. Similar laminar distribution pattern of labeled neurons was also shown in the cortex of the lower bank of the lateral sulcus, possibly in VS.

DISCUSSION

Neurons in the hand representation of area 3b in primary somatosensory cortex of monkeys have small excitatory receptive fields confined to a small region of skin within a single digit, a pad, or the palm (Merzenich et al., 1978; Sur et al., 1980, 1982; Pons et al., 1987b; Stryker et al., 1987). However, more recent primate studies showed that neuronal responses due to stimulation of the excitatory receptive field is modulated with stimulation elsewhere on the hand (Friedman et al., 2008; Reed et al., 2008, 2010, 2011, 2012; Thakur et al., 2012). The point-to-point precision of the multisynaptic connections that link cutaneous receptors in the hand with neurons in the hand representation of area 3b (Jones et al., 1982; Culbertson and Brushart, 1989; Florence et al., 1989, 1991; Qi et al., 2011) precludes the possibility that this pathway is involved in such widespread activation. We hypothesized that cortical connections to area 3b may reconcile the seemingly contradictory neurophysiological and neuroanatomical observations. Here we investigated the organization of intrinsic connections and feedback projections to the representations of individual digits in area 3b. We conducted our study in squirrel monkeys and galagos, where digit representations are accessible on the cortical surface.

The results indicate that individual digit representations of area 3b are broadly connected to nearly all of the hand representation, but very sparsely or not at all to other parts of area 3b. In addition, overlapping parts of areas 3a, 1, 2, S2/PV, and M1 send projections that converge onto single digit representations of area 3b. Both findings suggest that feedback connections to area 3b do not conform to the narrow organization of the feedforward pathway that links cutaneous receptors to area 3b. A schematic diagram illustrating such connectional organization is shown in Figure 16. Lastly, the results showed that feedback connections outside of area 3b originated primarily in infragranular layers and in supragranular layers, which corresponds to the laminar pattern typical of cortical feedback projections (Rockland and Pandya, 1979; Maunsell and van Essen, 1983; Felleman and Van Essen, 1991). Below, we consider the present results further in relation to previous findings.

Do thalamocortical projections contribute to information spread in area 3b?

Our tracer injections were confined to the representations of single digits in area 3b. Neurons labeled in VP were organized in clusters that overlapped the representations of matching digits, which were identified with VGLUT2 staining. Qi et al. (2011) reported similar digit-to-digit patterns of thalamocortical connections. Although injections of tracers in area 3b of monkeys have been reported to label broader distributions of projecting neurons in VP (Lin and Kaas, 1979; Nelson and Kaas, 1981; Cusick et al., 1985a; Cusick

and Gould, 1990; Darian-Smith et al., 1990; Krubitzer and Kaas, 1992; Padberg et al., 2009), those results likely reflect injections that involved large parts of area 3b, and possibly even white matter. Smaller injections in the hand representation of area 3b tend to label clusters of neurons in VP that are organized in vertically elongated clusters, which could correspond to one or two digit representations. In the smaller brains of owl monkeys, axon arbors from VP that terminate in layer 4 of area 3b tend to be less than 350 μm wide (Garraghty et al., 1989). The same axon arbors may be twice that size in the larger brains of macaque monkeys (Garraghty and Sur, 1990; Rausell and Jones, 1991). Nevertheless, the dimensions of the VP axon arbors approximate the rostrocaudal dimensions of individual digit representations in area 3b in the respective species. Although more divergent VP projections may exist, those connections appear to be sparse. Their influence is likely outweighed by dense thalamocortical projections that are very precise (Qi et al., 2011). It is therefore unlikely that thalamocortical projections are directly involved in the widespread modulation of individual digit representation in area 3b.

Intrinsic connections within area 3b

Previous anatomical studies revealed the existence of intrinsic connections within the hand representation of area 3b (Cusick et al., 1985b; Burton and Fabri, 1995; Wu and Kaas, 2003). We built on this work in the present study by mapping the representations of individual digits in area 3b and tracing their connections. Each digit representation of area 3b was intrinsically connected within that representation as well as with the representations of adjacent digits, palm, and wrist. We quantified the numbers of labeled cells in area 3b in two squirrel monkeys to determine the relative densities of the intrinsic connections within area 3b. The results showed that the intrinsic connections of a digit representation originated primarily from within that same representation. Adjacent representations, including digits and/or palm, were the next richest source of connections. Connection strength with more distant representations within the hand was noticeably weaker. The connections of digits 2, 3, and 4 tended to be stronger within the representation of digits 2 to 4. In contrast, connections with digits 1 and 5 were noticeably weaker. This finding was particularly surprising for the connections of digits 2 and 4, where we expected dense connections from digits 1 and 5, respectively. This organization may reflect adaptive specializations within the hand representation to subserve functional use in New World squirrel monkeys (Bortoff and Strick, 1993; Maier et al., 1997). For example, integration of inputs from digits 2, 3, and 4 may be critical for dexterity and hapsis, whereas digits 1 and 5 are typically less involved in those functions.

There was no evidence for connections from more medial representations of area 3b such as trunk, hind-limb, or tail. Connections from the face representation were very sparse (Fang et al., 2002). Our observations suggest that the widespread modulation of neurons in individual digit representations of area 3b could be mediated via intrinsic connections within the hand representation of area 3b.

Feedback projections from area 1

In squirrel monkeys (Sur et al., 1982) and presumably in all primates, area 1 forms a systematic representation of the contralateral body surface that shares the same somatotopic

organization of area 3b, albeit with somewhat larger receptive fields (Sur, 1980; Nelson et al., 1980; Sur et al., 1982; Merzenich et al., 1987; Pons et al., 1987b; Kaas, 1993, 2004; Wu and Kaas, 2003). VP projects to layer 3 of area 1 (Jones and Powell, 1970; Jones, 1975; Jones and Burton, 1976), but sensory evoked activity in area 1 appears to depend on feedforward projections to layer 4 from area 3b (Vogt and Pandya, 1978; Garraghty et al., 1990a). Tracer injections in the present study labeled feedback connections in the hand representation of area 1. Based on the estimated hand representation in area 1 in the present squirrel monkeys, feedback connections from area 1 to a digit representation in area 3b originated primarily from the matching digit representation in area 1 and to a lesser extent from other aspects of the hand representation. This observation is consistent with one recent study using anatomical tracing methods and an optical imaging approach. The authors reported that neurons in individual digits representations in area 3b are mainly connected with the corresponding digits representations in area 1 (Negyessy et al., 2013).

Similarly, injections confined to more than one digit representation of area 3b labeled overlapping distributions of neurons in area 1. Thus, neurons in single digit representations of area 3b received feedback projections exclusively from the hand representation in area 1 that included the representations of matched and unmatched digits. A body surface representation in area 1 of galagos has not yet been derived with microelectrode mapping, possibly because neuronal responses are depressed by anesthetics in these primates. However, the organization of connections between area 3b and a putative area 1 provided evidence for a somatotopic representation of the body surface in area 1 of galagos (Wu and Kaas, 2003). Results from the single galago in the present study showed that feedback connections of different digit representations of area 3b originated from overlapping territories within area 1. In addition, those cells overlapped in supragranular and infragranular layers of area 1. Thus, feedback connections from area 1 to the digit representations of area 3b in galagos shared the organizing principles revealed in squirrel monkeys.

Feedback projections from area 2

In macaque monkeys, area 2 exists as a third cortical representation of the contralateral body surface and parallels the representation in area 1 (Pons et al., 1985). Microelectrode mapping studies have provided less evidence for an area 2 representation in New World monkeys (Merzenich et al., 1978), and the existence of an area 2 in some New World species has been questioned (Padberg et al., 2005). However, connections that link area 3b with the expected location of area 2 in squirrel monkeys provide evidence for the presence of an area 2 in this primate. In the present study, injections into separate digit representations of area 3b labeled connections that largely overlapped in the expected location of area 2. The density of the area 2 connections with area 3b were weaker than the area 1 counterpart, but they constituted a population that could provide feedback information to single digit representations in area 3b about other digits and parts of the hand.

Projections from area 3a

Injections in area 3b in the present cases also labeled neurons in area 3a. In a range of other mammals, a strip of dysgranular cortex along the rostral border of granular 3b separates it

from agranular motor cortex (M1). In primates, this cortex is recognized as area 3a, and it forms a representation primarily of deep receptors for proprioception and closely parallels the somatotopic organization of area 3b (Merzenich et al., 1978; Kaas et al., 1979; Nelson et al., 1980; Huffman and Krubitzer, 2001). Neurons in area 3a receive proprioceptive information from ventroposterior superior nucleus (VPS) (Cusick et al., 1985b), also identified as part of the “shell” of VP (Jones and Friedman, 1982).

Reciprocal connections between areas 3a and 3b have been demonstrated in a number of primate species (Jones et al., 1978; DeFelipe et al., 1986; Krubitzer and Kaas, 1990; Coq et al., 2004). Our results extend previous work by showing that individual digit representations of area 3b receive feedback connections from overlapping territories of area 3a in squirrel monkeys. As expected for feedback connections, the projecting neurons in area 3a were distributed in both the supragranular and infragranular layers. We did not illustrate the overlap of labeled cells in area 3a of the galago in the present study, as the boundaries of area 3a are less clear in coronal sections. However, an overlap of labeled neurons in area 3a was previously illustrated in a surface view after injections of different tracers into the representations of digits 3 and 1 in area 3b of a galago (Wu and Kaas, 2003). Thus, our results and previous results suggest that overlapping populations of cells in area 3a send feedback projections to separate digits representations in area 3b. Thus, area 3a likely contributes to the widespread modulation of individual digit representations in area 3b.

Projections from PV/S2 and other regions of the lateral sulcus

PV and S2 are separate somatotopic representations, which are mirror reversals of each other with adjoining representations of the hand (Friedman et al., 1980; Krubitzer and Kaas, 1990; Krubitzer et al., 1995; Disbrow et al., 2000, 2003; Qi et al., 2002; Wu and Kaas, 2003; Coq et al., 2004). Excitatory activity of neurons in PV and S2 are largely dependent on projections from area 3b (Pons et al., 1987a; Burton et al., 1990; Garrahy et al., 1990b).

Since receptive fields were not mapped for the lateral sulcus in the present study, we cannot assert if connections were labeled in PV, S2 or, as expected, both. Nevertheless, in case 11-53, injections in individual representations of digits in area 3b labeled connections that overlapped in the upper bank of the lateral sulcus. The origins of those feedback connections in PV/S2 also overlapped clusters of axonal terminals, which were anterogradely labeled from the same injections in area 3b. This labeling pattern is consistent with the dense and reciprocal connections between area 3b and PV/S2 (Friedman et al., 1980; Friedman et al., 1986; Burton et al., 1995; Coq et al., 2004). Accordingly, we propose that the cortex in the lateral sulcus that is reciprocally connected with digit representations of area 3b includes the hand representations of PV/S2. Feedback connections from PV/S2 originated in both the supragranular and infragranular layers, as previously reported (Burton et al., 1995; Wu and Kaas, 2003). The collective evidence suggests that PV/S2 has a moderate influence on the widespread modulation of individual digit representations in area 3b. Feedback connections from PV/S2 may have also included sparse connections from the expected representation of the face. Weak feedback connections also originated in cortex ventral and caudal to PV/S2, corresponding to the expected locations of VS (Cusick et al., 1989; Coq et al., 2004) and Ri (Krubitzer and Kaas, 1990; Wu and Kaas, 2003).

CONCLUSIONS

Our results indicate that neurons in single digit representations of area 3b receive information about the stimulation of other digits and other parts of the hand from widespread feedback connections. These projections primarily originate from other parts of the hand representation of area 3b, as well as from the hand representations of areas 1 and 3a, and PV/S2 of the lateral sulcus. Other areas that also provide projections to area 3b include area 2, M1, and the VS and Ri regions. In consideration of the various neuronal characteristics and responsive modalities across each of these cortical fields, their connections with area 3b could contribute to the widespread modulation of individual digit representations in area 3b. Integration of spatial and modal information across multiple digits is likely important for motor control and dexterity. The present study demonstrated that intrinsic and feedback connections are widespread across digit representations in area 3b, and such integration in area 3b is likely mediated by their connections.

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ROLE OF AUTHORS

Study concept and design: LCC, QHX, JHK. Acquisition of data: LCC, OAG, QHX. Analysis and interpretation of data: LCC, QHX, JHK. Drafting of the article: LCC, OAG, JHK. Obtained funding: OAG, QHX, JHK.

Abbreviations

1	area 1
2	area 2
3a	area 3a
3b	area 3b
BDA	biotinylated dextran amine
CO	cytochrome oxidase
CTB	cholera toxin B subunit
CTBG	cholera toxin B subunit-conjugated with fluoro-emerald
FE	fluoro-emerald
FR	fluoro-ruby
M1	primary motor cortex
PV	parietal ventral
Ri	retroinsular cortex
S1	primary somatosensory cortex

S2	secondary somatosensory cortex
VGLUT2	vesicular glutamate transporter 2
VP	ventroposterior nucleus
VPL	ventroposterior lateral nucleus
VPS	ventroposterior superior nucleus
VS	ventral somatosensory cortex

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Figure 1.

A: Patches of neurons labeled in the ventroposterior lateral nucleus (VPL) after cholera toxin B subunit (CTB) was injected into the representations of digits 2 and 4 in area 3b of a squirrel monkey 09-37. **B:** Adjacent section immunoreacted for vesicular glutamate transporter (VGLUT2) shows architectural subdivisions. In both panels, arrowheads mark the medial-lateral extent of the hand representation, and arrows indicate septa that separate the representations of individual digits. Note that CTB-labeled cells in panel A formed clusters confined to individual digit representations revealed in panel B. Scale bar = 500 μ m in A and B.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 2.

A: The surface of somatosensory cortex in the left hemisphere of a squirrel monkey (11-53 SqM) showing recording sites and the locations of injections in digit representations of area 3b. Yellow symbols mark the locations of microelectrode penetrations. The representations of digits 1 to 5 in area 3b are arranged in a lateral to medial sequence, with tips of the digits located rostrally and palm located caudally. The representations of digits 1–4 are outlined. Neuronal responsiveness was classified as good response (GR; solid circle), weak response (WR; open circle), very weak response (vWR; diamond) or no response (NR; cross). Borders separating areas 3a, 3b, and 1 were marked with electrolytic lesions (stars) during electrophysiological mapping. This facilitated estimation of the border in the present illustration (black dashed lines). Fluoro-ruby (FR) was injected into the representations of digits 1 and 3 (red solid circle) and CTB was injected into the representations of digits 2 and 4 (blue solid circle). Red shadings show the extents of FR injections and dark and light purple shadings depict cores and halos of CTB injections. **B–E:** Photomicrographs of flattened cortex from the same case showing the extents of the two FR and two CTB injection sites. D1–4, digits 1–4; M, medial; R, rostral. Scale bars = 1 mm in A; 250 μ m in B–E. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 3.

Distributions of labeled neurons in the flattened cortex for squirrel monkey 11-53 (see Fig. 2). Inset in top left corner shows the locations of FR injections in the representations of digits 1 and 3 and CTB injections in the representations of digits 2 and 4. FR (red dots) and CTB (blue dots) labeled cells are extensively distributed in areas 3b, 1, 3a, primary motor cortex (M1), and PV/S2. The two populations of labeled cells also overlapped throughout their distributions. The pink-shaded region in the upper bank of the lateral sulcus depicts axon terminals labeled from the FR injections. Enlarged views of labeling patterns in area 1 (inset A), PV/S2 (inset B), and M1 (inset C) are shown in Figure 4A–C. Cortical borders were determined from electrolytic lesions (stars) made during electrophysiological mapping and adjacent cortical sections reacted for myelinated fibers. CS, central sulcus; ovals in area 3b lateral to the hand/face border represent myelin dense subdivisions related to parts of the face (F1–F3) or teeth and tongue (Jain et al., 2001). Scale bar = 2 mm.

Figure 4.

Insets from Figure 3 showing the distributions of cells labeled in area 1 (**A**), PV/S2 (**B**), and M1 (**C**). Note the overlap of CTB-labeled cells (blue dots) and FR-labeled cells (red dots). B: The pink-shaded region in the upper bank of the lateral sulcus depicts axon terminals labeled from the FR injections. Scale bar = 500 μ m in A–C.

Figure 5.

A: Photomicrograph showing the hand representation portion of area 3b with recording sites (yellow symbols) marked in a squirrel monkey (12-17 SqM). The representations of digits 2, 3, and 4 in area 3b are outlined. The borders of area 3b are marked by dashed lines. Three tracers, CTB (blue solid circle), FR (red solid circle), and biotinylated dextran amine (BDA; green solid circle) were respectively injected into the representations of digits 2, 3, and 4 of area 3b. Injection cores for the CTB and the BDA injections are depicted in dark purple and green, respectively. Halos for the same injections are shown in lighter shades of the same colors. The extent of the FR injection site is depicted with red shading. Other conventions as in Figure 2. **B:** Dorsolateral view of the brain showing the location of area 3b and tracer injection sites. **C–E:** Photomicrographs of flattened cortical sections showing CTB, FR, and BDA injection sites in the representations of digits 2, 3, and 4 in area 3b. Scale bars = 1 mm in A; 250 μm in C–E. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 6.

A: Distributions of labeled neurons in flattened cortex for squirrel monkey 12-17. CTB, FR, and BDA were injected into the representations of digits 2, 3, and 4 in area 3b. CTB-labeled neurons (blue dots) are heavily distributed in the areas 3b, 1, 3a, and M1 and PV/S2. FR and BDA injections labeled relatively small numbers of cells and therefore have relatively large dots in the magnified insets. FR-labeled (red dots) and BDA-labeled (green dots) cells overlapped with CTB-labeled cells in areas 1/2 (**B**), M1/area 3a (**C**), and PV/S2 (**D**). Other conventions as in Figure 3. Scale bar = 2 mm in A.

Figure 7.

Distributions of labeled neurons in areas 3b and 1 from injections of CTB, FR, and BDA in the representations of digits 2, 3, and 4 in area 3b of squirrel monkey 12-17. The results are superimposed on receptive fields of the digits that were defined with multi-unit recording in areas 3b (solid lines) and estimated area 1 (dashed lines) (A). The distributions of CTB-, FR-, and BDA-labeled neurons are respectively shown in (B–D). Other conventions as in Figure 2. Scale bar = 1 mm in A–D.

Figure 8.

A: Photomicrograph showing the hand representation portion of area 3b with recording sites (yellow symbols) marked in a squirrel monkey (12-38 SqM). The representations of digits 2, 3, 4, and 5 in area 3b are outlined. The borders of area 3b are marked by dashed lines. CTB (blue solid circle), FR (red solid circle), BDA (brown solid circle), and fluoro-emerald (FE; green solid circle) were respectively injected into the representations of digits 2, 3, 4, and 5. **B–E:** Photomicrographs of flattened cortices showing CTB, FR, BDA, and FE injection sites. Other conventions as in Figure 2. Scale bar = 1 mm in A; 250 μm in B–E. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 9.

A: Distributions of labeled neurons in flattened cortex for squirrel monkey 12-38. CTB, FR, BDA were respectively injected into the representations of digits 2, 3, and 4 in area 3b. CTB-labeled cells (blue dots) are broadly distributed in several cortical regions including areas 3b, 1, 3a, M1, and PV/S2. FR-labeled (red dots) and BDA-labeled (green dots) cells overlapped with CTB-labeled cells in areas 1/2 (**B**), M1/area 3a (**C**), and PV/S2 (**D**). The green-shaded regions in the upper bank of the lateral sulcus depict axon terminals labeled from the BDA injection. Other conventions as in Figure 3. Scale bar = 2 mm in A.

Figure 10.

Distributions of labeled neurons from injections in the representation of single digits in squirrel monkey 12-38. The results are superimposed on a receptive field of the digits that was defined with multi-unit recording. CTB was injected into digit 2 (A), FR was injected into digit 3 (B), and BDA was injected into digit 4 (C) representations of area 3b. Note that each injection labeled cells within and outside the boundaries of the injected digit representation in area 3b. Other conventions as in Figure 2. Scale bar = 1 mm in A–C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 11.

A: Photomicrograph showing the hand representation portion of area 3b with recording sites (yellow symbols) marked in a squirrel monkey (09-37 SqM). The representations of digits 1–5 in area 3b are outlined. The borders of area 3b are marked by dashed lines. CTB was injected into the representations of digits 2 (CTB2; blue solid circles) and 4 (CTB4) and FR was injected into the representations of digits 1 (FR1; solid red circles), 3 (FR3), and 5 (FR5). Dark and light purple shadings depict the cores and halos of CTB injection sites, and red shadings show the extent of FR injections. **B–D:** Photomicrographs of coronal sections showing CTB and FR injection sites in digits 1–5 representations of area 3b. P2, 3, palmar pads 2 and 3; PTH, pad thenar. Other conventions as in Figure 2. Scale bar = 1 mm in A; 1 mm in B–D. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 12.

A rostrocaudal series of coronal sections showing labeling patterns after CTB was injected into digits 2, 4 and FR was injected into digits 1, 3, 5 representations of area 3b (09-37 SqM). Inset shows the microelectrode map and locations of the injection sites. CTB-labeled cells (blue dots) are distributed extensively in area 1 and cortex of the upper bank of lateral sulcus, where PV and S2 are located. Although FR-labeled cells (red dots) are scattered and few in number, CTB- and FR-labeled cells overlap in area 1 (inset A in Fig. 13) and PV/S2 region (inset B in Fig. 13). Note that labeled cells are mainly located in supragranular (I–III) and infragranular layers (V–VI), forming a bilaminar pattern. Terminal fields of axons labeled by CTB injections (blue shade) were primarily located in cortical layer 4 in the PV/S2 region. Dashed lines in the drawings indicate the position of layer 4. Scale bar = 1 mm.

Figure 13.

Coronal sections showing the laminar distributions of labeled cells in area 1 (A) and PV/S2 (B). FR injections were in the representations of digits 1 and 3 in area 3b, whereas CTB injections were in the representations of digits 2 and 4 in area 3b (09-37 SqM, see Fig. 11). CTB-labeled cells are depicted as blue dots. The relatively smaller population of FR labeled cells is depicted with larger red dots for visibility. In the representative coronal section for area 1, the FR-labeled cells occupied the same vicinity as the CTB-labeled cells in the supragranular layer. The PV/S2 section shows less overlap between the two populations. Scale bar = 500 μ m in A and B.

Figure 14.

Photomicrograph showing the hand representation portion of area 3b with recording sites (yellow symbols) marked in a galago (10-16 SqM). Glabrous digits are represented rostrally in area 3b and palm and dorsal surface of hand are represented caudally. The representations of digits 1–5 and palm in area 3b are outlined. The borders of area 3b are marked by dashed lines. CTB-conjugated Alexa 488 (CTBG; blue solid circles) was injected into digits 1 (CTBG1) and 3 (CTBG3) representations and FR was injected into digits 2 (FR2) and 4 (FR4) representations. Dark and light green shadings depict cores and halos of CTB injection sites, and red shadings mark the extent of FR injections. **B:** Receptive fields obtained from microelectrode multiunit mapping in panel A. **C:** Photomicrograph of a coronal section showing CTBG and FR injection sites. **D:** Photomicrograph of coronal section of thalamus. Cells were labeled in VPL after CTBG injections in the representations of digits 1 and 3 in area 3b. **E:** Adjacent section immunoreacted for vesicular glutamate transporter (VGLUT2) shows architectural subdivisions. In panels D and E, arrowheads mark the medial-lateral extent of hand representation, and arrows indicate septa that separate the representations of individual digits. doD2, dorsal digit 2. P1, palmar pads 1. Scale bars = 1 mm in A,D,E; 0.5 mm in C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 15.

A rostrocaudal series of coronal sections showing the distributions of labeled cells from CTBG injections into the representations of digits 1 and 3 and FR injections into the representations of digits 2 and 4 in area 3b (10-16 galago). Inset shows the microelectrode map and locations of the injection sites. Dashed lines in the drawings indicate the position of layer 4.

CTBG (blue dots) and FR (red dots) labeled cells are extensively distributed in area 3b and PV/S2 region where they overlapped. Other labeled cells were in area 1 (section 184) and in the region of VS (section 220). Note that labeled neurons were mostly located in infragranular layers and to a lesser extent in the supragranular layers. Scale bar = 1 mm.

Figure 16.

A summary diagram depicting thalamocortical and cortico-cortical connections of area 3b in primary somatosensory cortex. Digit representations in area 3b receive parallel projections from individual digit representations in the VPL. In contrast, individual digit representations in area 3b are intrinsically connected with other digits in area 3b and are innervated by widespread feedback projections from areas 1, 3a, PV/S2, and M1. Note that intrinsic connections with digits 2, 3, and 4 representations are stronger, whereas connections with the representations of peripheral digits 1 and 5 representations are weaker (dashed lines). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 1

Distribution Ratio (%) of Labeled Cells in the Hand Representation of Area 3b

Representations	12-17 SqM			12-38 SqM		
	CTB (5775)	FR (1296)	BDA (2253)	CTB (16820)	FR (4249)	BDA (1528)
D5	0.3	1.5	8.1	0.0	0.7	4.6
D4	1.1	5.9	54.1	0.4	7.9	84.8
D3	21.8	79.2	20.6	36.9	62.1	9.2
D2	49.9	2.7	0.2	44.4	6.2	0.5
D1	10.0	0.2	0.0	10.7	0.3	0.0
Others	16.9	10.5	17.0	7.6	22.8	0.9

Bold indicates the digits representations in area 3b where tracers were injected.

Numbers below CTB, FR and BDA indicate the numbers of total labeled cells.

TABLE 2

Expected Distribution Ratio (%) of Labeled Cells in the Hand Representation of Area 1

Representations	12-17 SqM			12-38 SqM		
	CTB (1683)	FR (74)	BDA (126)	CTB (5022)	FR (198)	BDA (6)
D5	1.4	0.0	9.5	0.5	4.0	0.0
D4	10.5	6.8	43.7	6.5	9.1	0.0
D3	21.1	17.6	8.7	21.1	24.2	33.3
D2	34.6	9.5	0.8	31.5	13.1	0.0
D1	4.3	1.4	0.8	14.8	4.0	0.0
Others	28.1	64.9	36.8	25.6	45.6	66.7

Bold indicates that tracers were injected in the matching digits representations in area 3b.

Numbers below CTB, FR and BDA indicate the numbers of total labeled cells.