

The Sage Handbook of Cognitive and Systems Neuroscience



Neuroscientific Principles, Systems and Methods

Edited by
Gregory J. Boyle

with
Georg Northoff
Aron K. Barbey
Felipe Fregni
Marjan Jahanshahi
Alvaro Pascual-Leone and
Barbara J. Sahakian

Associate Editors
Nadia Bolognini and
Anja Soldan

 Sage



1 Oliver's Yard
55 City Road
London EC1Y 1SP

2455 Teller Road
Thousand Oaks, California 91320

Unit No 323-333, Third Floor, F-Block
International Trade Tower Nehru Place
New Delhi 110 019

8 Marina View Suite 43-053
Asia Square Tower 1
Singapore 018960

Editor: Janka Romero
Editorial Assistant: Benedict Hegarty
Production Editor: Neelu Sahu
Copyeditor: Martin Noble
Proofreader:
Indexer: KnowledgeWorks Global Ltd
Marketing Manager:
Cover Design: Ginkhan Siam
Typeset by KnowledgeWorks Global Ltd
Printed in the UK

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Somatosensory Processing

Jon H. Kaas, Leah A. Krubitzer, Hui-Xin Qi,
and Jamie L. Reed

INTRODUCTION

This review focuses on somatosensory processing of tactile information from the hand in primates. Much of this review is based on studies in monkeys, and to some extent humans (Figure 23.1). Most of the sensory information from the glabrous hand, which is an especially important tactile organ, comes from two classes of afferents and their receptors, the rapidly adapting type 1 (RA1) and the slowly adapting type 1 (SA1) afferents. Other afferents and their receptors, RA2 and SA2, also subserve the glabrous hand, and receptors around the base of hairs in the hairy skin provide additional tactile information. These afferents from the hand branch as they enter the spinal cord to travel in the dorsal column pathway to the cuneate nucleus or terminate on neurons in the dorsal horn of the spinal cord that provide second-order input to the cuneate nucleus at the brainstem-spinal cord junction. Neurons in the cuneate nucleus have axons that cross to the contralateral side of the brainstem, where they terminate in the ventroposterior nucleus (VP) of the somatosensory thalamus. Neurons in VP then project to the hand representation of the primary somatosensory cortex (S1, Brodmann's Area 3b; see

Garey, 1994) and also project to layer 3 of the hand representation of adjoining Area 1. These two cortical areas then contribute tactile information to an array of higher-order somatosensory areas, including Brodmann's Area 2, the second somatosensory area (S2), the parietal ventral area (PV), and the ventral somatosensory areas (VSr and VSc). This network expands to include areas of insular cortex, posterior parietal cortex, and premotor and motor cortex. Feedback connections at all levels add to this complex network of interconnections.

While tactile afferents from the hand are very important in humans and other primates (Mountcastle, 2005), tactile afferents from other parts of the body form similar projection patterns in parallel with those for the hand to complete the representation of the body surface in multiple subcortical and cortical representations of receptors from the skin of the contralateral body. In addition, at least some of these nuclei and areas contain representations of both the contralateral and ipsilateral tongue and teeth. The pathways from face and oral structures are somewhat different than those described for the body. The processed information from peripheral receptors allows humans and other primates to identify objects by touch and use

this information to guide and control sensorimotor behavior. Other mammals have similar somatosensory systems, but often with somewhat different specializations related to specific behaviors and peripheral morphologies. In addition, the number of cortical areas and the complexity of cortical networks is often less elaborate compared to primates. Our review also briefly considers the systems for other types of receptor-afferent inputs, such as those for proprioception, pain, and temperature.

TACTILE RECEPTORS AND AFFERENTS FROM THE GLABROUS SKIN AND HAIRY SKIN

For all mammals, sensory inputs from the face, lips, tongue, and teeth are highly important as most mammals grasp food and prey directly with the mouth and pre-process food by chewing. Primates also use their hands to explore the environment, and grasp food and bring it directly to the mouth. Sensory hairs around the mouth are less important in primates, and missing in humans. Early studies of afferents from the hand in primates and humans have identified four types of low-threshold mechanosensory receptors and afferents (Johansson and Flannagan, 2008; Johnson, 2001). The slowly adapting type I sensory afferents (SA1) are activated by a number of closely spaced Merkel cell receptors located in the superficial skin. These afferents are responsive to light touch on the skin, and continue to respond during a maintained contact or skin indentation. Merkel cells are most dense in the glabrous skin of the fingertips. Thus, SA1 afferents are important for identifying object form and texture.

The rapidly adapting type I (RA1) afferents rapidly adapt to light touch and skin indentation, and are most important for signaling change as a result of stimulus movement, as well as signaling a series of repeated taps in the low frequency range of flutter. RA1 afferents have the smallest receptive fields, and can signal the details of stimulus form. The receptors of RA1 afferents are Meissner corpuscles, which are most densely packed in the skin of the finger tips. Most Meissner corpuscles are innervated by more than one axon, and each axon innervates a tight group of corpuscles. The SA1 and RA1 afferents make up the vast majority of tactile afferents from the hands.

The slowly adapting type 2 afferents from the hand innervate encapsulated Ruffini-like corpuscles that are deeper in the skin, and are also found in ligaments and tendons of the hand and

elsewhere. Movement of the skin stretches the corpuscles and activates the SA2 afferents. The afferents have large receptive fields with uncertain borders. SA2 afferents signal the direction of strain and stress of the skin, and likely have a role in proprioception and motor control. Contributions to tactile sensations, if any, are unknown.

The rapidly adapting type 2 afferents (RA2) innervate Pacinian corpuscles deeper in the skin. The layers of the Pacinian corpuscles filter out slow changes in pressure on the corpuscle, while the corpuscle transmits rapid compressions produced by high frequency vibrations to the axon in the core of the corpuscle. The Pacinian corpuscles are found elsewhere on the body, and in deep tissue. Distant vibrations conducted via a hard surface such as a table or floor to the hand or foot can be detected, and provide useful information. The receptive fields of Pacinian corpuscle afferents are hard to define, as vibrations may extend through body tissue, and the sources of vibrations may be distant from of the body.

Other somatosensory afferents stem from the base of sensory hairs, and from receptors near hairs (Bolanowski et al., 1994). Merkel cell slowly adapting receptors are found both in hair follicles and touch domes on the hairy skin. Rapidly adapting afferents also innervate hair follicles and adjoining skin. The long sensory vibrissae or whiskers found on the face of mice and rats, as well as many other mammals, can be actively moved to explore and detect objects near the face. For example, rats can use their extra-large macro vibrissae to discriminate shapes, texture and the locations of objects near their face (Diamond and Arabzadeh, 2013; Diamond et al., 2008). The primary afferents for touch on the face and mouth form the trigeminal nerve which enters the pons of the brainstem where the afferents branch and terminate in the nuclei of the trigeminal complex. The principal nucleus of this complex receives RA1 and SA1 afferent inputs, and neurons in the principal nucleus project to the contralateral ventroposterior medial nucleus to join those from the dorsal column nuclei from the lower body (Ebner and Kaas, 2015). The neurons in VP project densely to primary somatosensory cortex (S1), which corresponds to Area 3b of Brodmann in primates (Kaas, 1983). Other terminations of VP are in the second somatosensory area, S2, of most mammals, and in Area 1 of primates.

Other afferents that have been related to touch are the wide-dynamic range afferents that respond to increasing pressure on the skin into the range of pain. These afferents terminate on neurons in the dorsal horn of the spinal cord and axons from these neurons project contralaterally to form the spinothalamic pathway that terminates in the ventroposterior inferior nucleus (VPI). The VPI

neurons project to the superficial layers of primary somatosensory cortex (S1) or Area 3b, and in some mammals, other cortical areas including S2 and PV.

Proprioceptive afferents from muscle spindles, which signal muscle length, provide critically important proprioceptive inputs through the dorsal column-medial lemniscal pathway to the ventroposterior superior nucleus, VPS. Thus, the ability to perceive joint position survives after joint removal and replacement in humans. However, Ruffini type receptors in joints and other deep tissues also contribute to the sense of joint position. Unmyelinated, slowly conducting afferents and thinly myelinated, moderately conducting afferents signal slow and fast pain, and other afferents signal temperature (Craig, 2015). Thin, slowly conducting afferents from the hairy skin appear to signal pleasant (affiliative) touch (Keyser et al., 2010), and project to dorsal horn neurons that in turn project to the contralateral somatosensory thalamus via the spinothalamic tract. Thalamic projections are to the insular cortex (Olausson et al., 2002).

AFFERENT PATHWAYS AND TARGET NUCLEI

Peripheral nerves contain a mixture of several afferents of different types, and motor axons that travel to the muscles. The cell bodies of sensory afferents are in the dorsal root ganglia. The inputs to each of the dorsal roots are from receptors in strips of skin, the dermatomes, that form the rough somatotopic sequence from tail to face (e.g., Pubols and Pubols, 1969). The tactile afferents from the arm and hand enter at the cervical level of the spinal cord and branch to ascend in the dorsal columns to terminate in the cuneate nucleus near the spinal cord – brainstem junction (Figure 23.1). The other branches terminate on second-order sensory neurons in the dorsal horn of the spinal cord at the same level. The axons from the second-order tactile neurons of the spinal cord mainly join the cuneate fasciculus, but some travel to the cuneate nucleus via a lateral fasciculus (Liao et al., 2015). Thus, the cuneate nucleus gets primary afferents from the arm and hand, and much of the same information from secondary neurons in the dorsal horn of the spinal cord. The primary afferents terminate in a very precise somatotopic pattern in the cuneate nucleus so that the digits and pads of the hand are represented separately in somewhat reliable species specific somatotopic patterns (Florence et al., 1989). The inputs from the dorsal horn neurons appear to conform to this somatotopic pattern, with perhaps

less precision. Surprisingly, some of these secondary dorsal horn neurons project to the contralateral cuneate nucleus (Liao et al., 2015), possibly contributing to the inhibitory receptive field surrounds of relay neurons in the cuneate nucleus. Overall, the contributions of the second-order afferents to the receptive fields of cuneate neurons are not well understood, but such inputs are thought to modulate the responses of cuneate relay neurons to the driving inputs of the primary afferents (Liao et al., 2018).

The main activating inputs to the central core of the cuneate nucleus in primates are from the RA1 and SA1 afferents from the glabrous hand. Recent electrophysiological recordings indicate that the responding neurons typically receive activating inputs from both RA1 and SA1 afferents (Suresh et al., 2021), although one type or the other may dominate. The cuneate nucleus also receives feedback connections mainly from the hand representations in S1 (Area 3b) and other areas of somatosensory cortex (Liao et al., 2021). These inputs also seem to be mainly suppressive by activating inhibitory neurons (Conner et al., 2021).

Tactile afferents from the lower trunk and leg enter the spinal cord at lower levels, and join the dorsal column pathway and synapse in the gracile nucleus, medial and adjacent to the cuneate nucleus (Qi and Kaas, 2006). These axons also have a branch that terminates on dorsal horn neurons that provide a secondary input to the gracile nucleus. Primary afferents for touch on the face travel in the trigeminal nerve to enter the brainstem and branch to terminate in the principal division of the trigeminal nucleus, analogous to the gracile and cuneate nuclei, and in the spinal division of the trigeminal nucleus, analogous in part to the dorsal horn of the spinal cord. Relay neurons in the gracile, cuneate, and principal trigeminal nuclei project contralaterally to the ventroposterior nucleus, which contains a detailed representation of the contralateral body surface and projects densely to the primary somatosensory area (Area 3b) and less so to Area 1.

Damage to the primary afferents in the cuneate dorsal columns at a high cervical level greatly impairs the use of the ipsilateral hand to the extent that touch on the hand is not felt. However, if a few primary afferents from the hand survive, hand use and the sense of touch on the hand recovers to the extent that nearly normal hand use returns (Qi et al., 2021).

Inputs from proprioceptive afferents, such as muscle spindle, tendon, and joint afferents form pathways to higher centers that are separate from those for tactile afferents. The cuneate dorsal column complex has separate nuclei for muscle spindle and other proprioceptive afferents. Those for the arm terminate in the external cuneate nucleus,

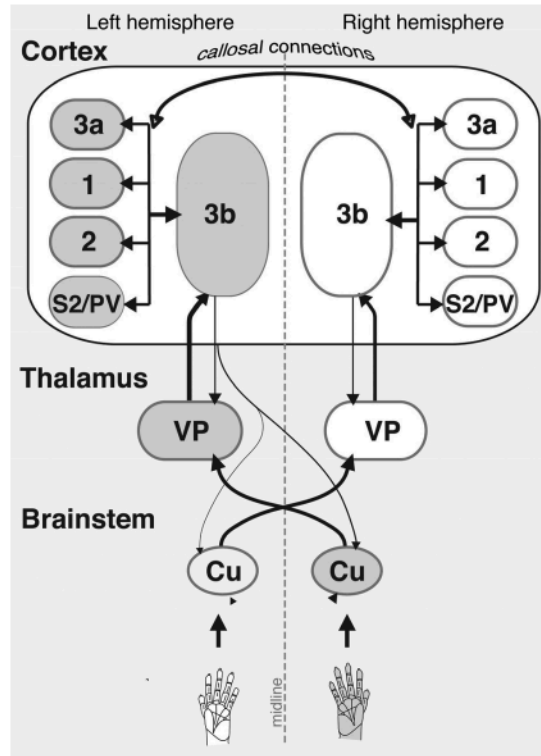


Figure 23.1 Levels of processing in the somatosensory systems of anthropoid primates

Tactile afferents from the hands project to the ipsilateral cuneate nucleus (Cu) at the junction of the spinal cord and brainstem (arrows). These direct projections are joined by those from second-order neurons in the dorsal horn of the spinal cord. The cuneate nucleus neurons then project to the contralateral ventroposterior nucleus (VP) of the thalamus. VP projects to layer 4 of cortical Area 3b (S1 of somatosensory cortex), and less densely to layer 3 of Area 1. Area 3b projects to Areas 3a, 1, 2, the second somatosensory area (S2), and the parietal ventral area PV. These areas provide feedback connections to Area 3b (S1). The hand representation in Area 3b has few callosal connections, but such connections exist between 3a, 1, 2, S2, and PV. The cortical connections of areas S2 and PV include posterior parietal cortex and frontal motor cortex. Somatosensory cortex also projects back to VP and Cu. See text for details.

travel in the gracile dorsal columns at lower levels, but then leave to terminate in Clarke's nucleus in the intermediate zone of the spinal cord. Many of the neurons in Clarke's nucleus project to the cerebellum or project directly to the contralateral thalamus, where they terminate dorsal to the ventroposterior nucleus. While these projections are often described as in a dorsorostral part of the ventroposterior nucleus, in primates this target is widely recognized as a separate ventroposterior superior nucleus (VPS) that caps the tactile ventroposterior nucleus (VP). VPS projects to Area 3a and Area 2 of the anterior parietal cortex, and the somatotopy of VPS mirrors that of VP

(Cusick et al., 1985; Padberg et al., 2009). Area 3a represents body muscles and other proprioceptive inputs in parallel to the tactile representation in Area 3b. Area 2 combines tactile and proprioceptive inputs in a representation that is in parallel with the Area 1 representation.

SPINOTHALAMIC PATHWAYS

Other sensory inputs related to touch, pain, and temperature enter the spinal cord or brainstem to activate neurons in the dorsal horn or in brainstem

nuclei that have axons that cross to the contralateral side to join the lateral spinothalamic tract that terminates in parts of the somatosensory thalamus near and in the ventroposterior nucleus. In primates, one of the targets is identified as the ventroposterior inferior nucleus (VPI; Craig, 2006). Some neurons in VPI and the septal regions of VP are responsive to “wide-dynamic range,” tactile to noxious stimuli. Neurons in VPI project to S1 and more densely to higher-order somatosensory areas such as S2, PV, and Area 1 (Coq et al., 2004; Disbrow et al., 2002; Padberg et al., 2009; Qi et al., 2002).

SOMATOSENSORY MIDBRAIN

For most vertebrates, the midbrain is the major sensorimotor center for controlling behavior. The visual midbrain, the superior colliculus (SC) of mammals receives direct input from the retina, and the inferior colliculus (IC) is a major auditory relay center. Yet, the deeper layers of the SC and the external nucleus of the IC receive ascending somatosensory inputs from the trigeminal nuclei, dorsal column nuclei, and somatosensory cortex (see Kaas and Huerta (1988)), and these inputs are likely important in the multisensory motor functions of the midbrain. The deeper layers of the SC are divided histologically into modular compartments that express acetylcholinesterase (AChE) or receive somatosensory inputs and express parvalbumin (Illing, 1992).

SOMATOSENSORY THALAMUS

The most obvious somatosensory nucleus of the thalamus is the ventroposterior nucleus (VP), which traditionally has been divided into the ventroposterior lateral sub-nucleus (VPL) representing the body, and the ventroposterior medial sub-nucleus (VPM) representing the face, mouth, and head (Figure 23.2). Together, they form the ventroposterior nucleus, VP. The activating inputs are rapidly adapting and slowly adapting afferents from the contralateral dorsal column nuclei, and the trigeminal principal nucleus, respectively (Kaas, 2008). VP represents tactile inputs from the tail to the tongue in a lateromedial sequence. Narrow cell poor septal bands separate the more lateral representation of the foot from that of the hand, and narrower septal areas separate representations of the toes and fingers from each other. A wider septal band separates VPL from VPM. Thus, much of the somatotopy of VP is obvious in

histological preparations. Somewhat surprisingly, the tongue and teeth are represented twice in VPM, one for inputs from the contralateral teeth and tongue, as for the rest of the body, and again for the ipsilateral teeth and tongue (Rausell and Jones, 1991). These representations of the ipsilateral mouth depend on ipsilateral projections from the brainstem trigeminal nuclei. Neurons in VP largely reflect a mixture of the RA1 and SA1 afferent inputs to the spinal cord and brainstem. Individual neurons and clusters of neurons are likely to reflect more or less of these two main classes of peripheral afferents (Sur et al., 1984).

In all mammals, VP projects to primary somatosensory cortex (S1 or Area 3b). In most studied mammals, VP also projects to other areas such as S2 and PV (Krubitzer and Kaas, 1987). In monkeys, and likely humans, VP projections to S2 and PV are greatly reduced or absent (Krubitzer and Kaas, 1992), while other projections include the representations in Area 1, Area 2, and even most of Area 5 (Padberg et al., 2009), areas not generally recognized in non-primate mammals. VP receives feedback connections from primary somatosensory cortex, Area 3b, and from other somatosensory areas (Area 1, Area 2, S2, PV).

Architectonically, the ventroposterior superior nucleus, VPS, resembles VP in histological stains for neurons, while VPI is quite distinct from VP as a cell sparse region that is contiguous with the cell sparse septa that separate the major body parts in VP, which in primates are considered part of VPI, rather than part of VP. However, both VPI and VPS are histologically distinct from VP by having less expression of cytochrome oxidase and more expression of calbindin (Kaas et al., 2006). Unlike neurons in VP which have extremely small receptive fields, neurons in VPS and VPI have much larger receptive fields and a less precise topography.

Two other somatosensory nuclei are important parts of the somatosensory thalamus in primates and other mammals. A nucleus on the medial margin of VPM, the parvocellular nucleus of VPM (VPMpc, also called the basal ventral medial nucleus, VMb), receives taste inputs, as well as tactile inputs from the tongue, and projects to the representation of the tongue in primary somatosensory cortex as well as to gustatory cortex (Iyengar et al., 2007; Kaas et al., 2006). In monkeys, Craig et al. (1984) identified a posterior ventral medial nucleus (VMpo) just caudal to VPMpc that receives nociceptive inputs from the spinothalamic and trigeminothalamic ascending pathways (Craig, 2006, 2015). VMpo is not distinct in non-primates, and may be included in parts of VPI and VP. Other relevant nuclei have not been well established as “somatosensory” nuclei. The anterior pulvinar (PLa), proposed for only primates, is

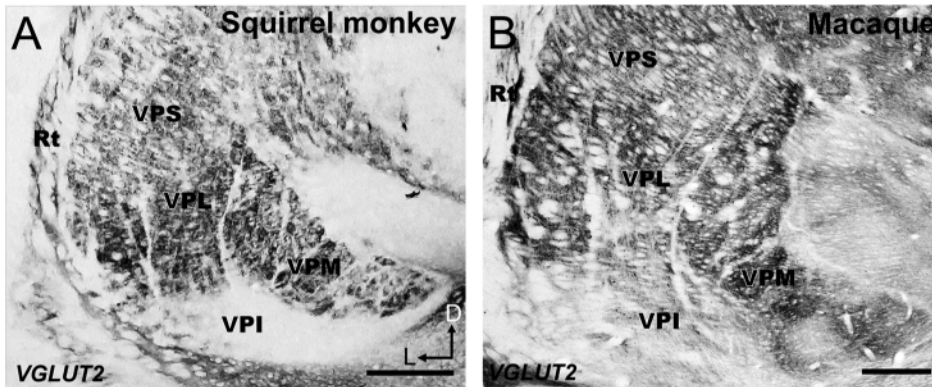


Figure 23.2 The three main somatosensory nuclei of thalamus in primates

The ventroposterior (VP) nucleus, shown here for its two subnuclei, VPL (ventroposterior lateral) for the limbs, trunk and tail body, and VPM (ventral posterior medial) for the head, face, and mouth. VP represents tactile inputs relayed from spinal cord and brainstem nuclei. The ventroposterior inferior nucleus (VPI) receives a mixture of somatosensory inputs from the second-order neurons in the contralateral spinal cord and brainstem. The ventral posterior superior nucleus (VPS) receives inputs from contralateral neurons in the spinal cord and brainstem nuclei that are activated by movement sensitive receptors and afferents from muscles and joints that provide proprioceptive information. Both brain sections are in the frontal (coronal) plane and are processed for the glutamate transporter type 2 (VGLUT2), which is highly expressed in somatosensory nuclei and S1. A brain section is shown for a squirrel monkey (A) and a macaque monkey (B). Notice that VP is darkly stained for both primates. Unstained septal regions separate VPL from VPM, and further divide the two subnuclei. In addition, VPS expresses less VGLUT2 than VP, and VPI expresses much less than VP. The scale bar = 1 mm. Dorsal (D) is up, and lateral (L) is left. Rt is reticular nucleus of the ventral thalamus.

a region of the thalamus with broad connections with areas of somatosensory cortex. Neurons in the PLa respond to cutaneous stimulation of the contralateral body (Padberg et al., 2009; Sherman and Guillery, 2006). The anterior pulvinar projects to cortical regions of posterior parietal cortex that have multisensory or somatosensory functions (Gharbawie et al., 2010). In primates, the lateral posterior nucleus, LP, has connections with posterior parietal cortex (Jones, 2007; Padberg et al., 2009), and thus is involved in somatosensory processing. In non-primate mammals, LP is often identified as the pulvinar or part of the pulvinar, confusing comparisons with primates. In some rodents and other mammals, part of the thalamus just caudal to VP has been identified as the posterior medial nucleus (POM; cf. Audette et al., 2018; Ebner and Kaas, 2015), adding confusion by using different terminologies for rodents and primates.

Somatosensory areas of cortex also project back to somatosensory nuclei. These projections

are mainly from layer 6 neurons, but some layer 5 projections exist (Kaas, 2008). The cortical projections from layer 6 largely appear to modulate thalamic neuron activity by activating local thalamic inhibitory interneurons (Ergenzinger et al., 1998), while layer 5 inputs are activating excitatory neurons (Sherman and Guillery, 2006). Cortical areas also project to brainstem and dorsal column relay nuclei (Liao et al., 2021), where they appear to activate local inhibitory neurons that constrain receptive field sizes.

SOMATOSENSORY CORTEX

All mammals have cortex in which neurons respond to somatosensory stimuli, and these regions are divided into several cortical areas on the basis of having separate representations of

tactile and proprioceptive inputs from the contralateral body surface. These separate representations differ in their patterns of connections, and to varying extents in their cortical architecture. A primary Area, S1, is basic to all mammals, but has been modified in separate lines of mammalian evolution in various ways, most often in relation to changes in peripheral morphology and sensory receptor arrays on specialized body parts associated with ethologically relevant behaviors. Inputs from the face and mouth are extremely important relays in all mammals, and these inputs are represented by more cortical territory and more neurons (cortical magnification). In highly dexterous primates, there is also magnification of the inputs

from the glabrous hands. The primary cortical area, Area 3b in primates, is most distinct in architecture, including a well-developed layer 4 with small, closely packed neurons (Qi et al., 2008). The S1 representation tends to proceed from tail to tongue in a mediolateral sequence across parietal cortex, with representations of the tongue and teeth located most laterally. Most mammals also have two additional somatosensory cortical areas that are well developed; the classical second somatosensory area, S2, and the later discovered parietal ventral area, PV (Krubitzer et al., 1986). Primates have additional areas that are responsive to touch and some may be unique to this order (Figure 23.3).

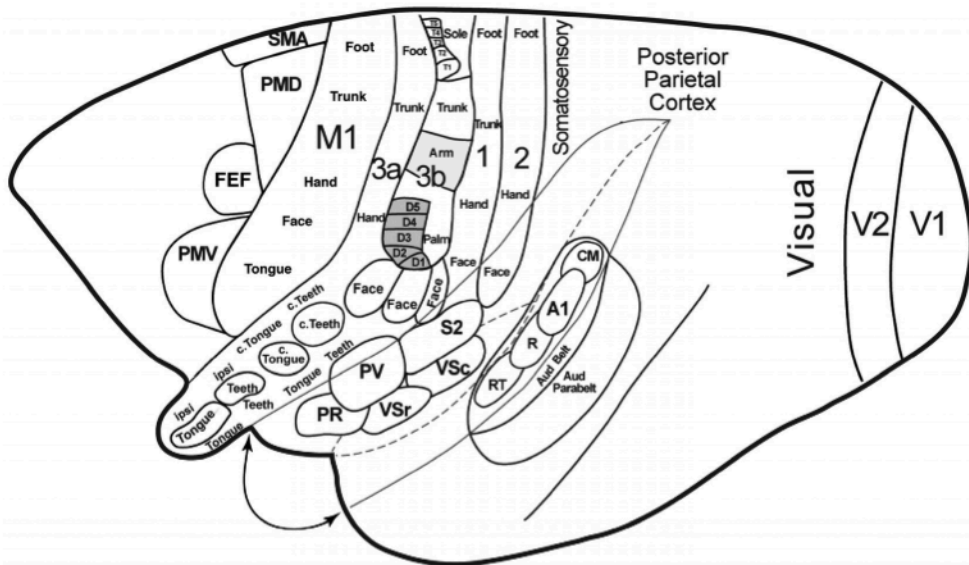


Figure 23.3 Somatosensory areas of the cortex of an owl monkey

This New World monkey does not have a central sulcus, and thus more somatosensory cortex is on the exposed cortical surface. Primary somatosensory cortex, Area 3b, and adjoining Areas 3a, 1, and 2 all contain parallel representations of the contralateral body from foot to mouth in a mediolateral sequence. Areas 3b, 3a, and 1 have representations of both the contralateral (C) and ipsilateral (I) teeth and tongue. Smaller somatosensory representations include the second somatosensory Area (S2), the parietal ventral area (PV), the rostroventral parietal area (PR), which may have gustatory functions (G), and rostral (VSr) and caudal (VSc) divisions of the ventral somatosensory areas. The lateral sulcus has been opened to show these areas. Primary motor cortex (M1) has a crude somatotopic representation of movements and somatosensory responses. The supplementary motor area (SMA), dorsal premotor area (PMD), ventral premotor area (PMv) all have somatosensory inputs. The frontal eye field (FEF), auditory areas, and visual areas 1 and 2 are shown for reference. The anterior part of posterior parietal cortex is highly involved in somatosensory-motor functions. Auditory areas include primary auditory cortex (A1), rostral (R) and rostral temporal (RT) areas, and the caudal medial (CM) area.

Some of the somatosensory areas in primates correspond to architectonic divisions that were recognized by Brodmann, and are now known as Brodmann's areas (3b for primary somatosensory cortex, Area 3a for a rostrally adjoining strip of cortex, Area 1 for a caudally adjoining strip of cortex, and Area 2 for a more caudally adjoining strip of cortex adjacent to area 1; Figure 23.3). These areas form adjoining representations of the contralateral body from toes most medially to tongue and teeth most laterally. These somatosensory areas occupy mediolateral strips of cortex in anterior parietal cortex, including the caudal wall of the deep central sulcus of those primates where such a sulcus is present. Early studies in humans and monkeys confounded most or all of these four representations as parts of S1, as recordings and somatotopic maps were largely based on areas most accessible on the brain surface, area 1 and most of Area 2. While the Area 3b representation has long been known to correspond to the representation of S1 in other mammals (Kaas, 1983), some current researchers still confound the concept of S1 by including representations in Areas 3a, 1, and 2. Areas 3a, 3b, 1, and 2 have been architectonically compared in macaques, chimpanzees, and humans (Qi et al., 2008), and have been described in many other primates.

PRIMARY SOMATOSENSORY CORTEX, AREA 3B

Primary somatosensory cortex, S1 or Area 3b, is present in the neocortex of all mammals, although not always identified as Area 3b. The somatotopic representations across studied mammals are similar, but differ in the proportional representations as some skin surfaces are variably important across taxa (Krubitzer and Stolzenberg, 2014). Thus, most of S1 and other somatosensory areas represent the highly sensitive bill in the duck-billed platypus, the hand and mouth in primates, the glabrous skin of the tail in spider and cebus monkeys, the hand of raccoons, the nose of the star-nosed mole, the wing of bats, and facial vibrissa of rats and mice (Kaas, 2021). The important sensory surfaces have more receptors, and occupy more of subcortical as well as cortical representations, thus providing proportionally more neurons for processing sensory information at every level.

Neurons in Area 3b have the smallest receptive field with excitatory receptive field centers where light touch evokes a large response, while also having receptive field surrounds where touch

suppresses the center response. The response to small receptive field centers on the hand in monkeys are suppressed by touch on other parts of the hand (Reed et al., 2008, 2010), and even by touch on the other hand (Reed et al., 2011), although this likely requires indirect pathways, as the hand representation of Area 3b has few callosal connections (Killackey et al., 1983). Neurons in Area 1 have converging inputs from Area 3b, and thus have larger receptive fields. Area 2 has inputs from 3b and 1, as well as from the thalamic nucleus VPS, so Area 2 neurons are activated by proprioceptive and tactile inputs. Area 3a neurons are most strongly activated by proprioceptive inputs from VPS. Areas S2, PV, and VS are smaller representations with inputs from Areas 3b, 1, and 2, and have large receptive fields. These higher-order somatosensory areas relate to sensorimotor, action specific domains in posterior parietal cortex that project to matching action specific domains in premotor and motor cortex (Kaas et al., 2018). These actions are guided by inputs from higher-order somatosensory and visual areas.

Early microelectrode recordings from hundreds of recording sites in anterior parietal cortex in macaque monkeys first established the existence of multiple, separate somatotopic representations corresponding to Brodmann's Areas 3a, 3b, 1, and 2 (Brodmann, 1909; Kaas, 1983; Krubitzer et al., 2004). Important features of Area 3b include representations of the glabrous surface of digits 1-5 in a lateromedial sequence, with digit tips represented rostrally (deep in the central sulcus) and digit representations separated by narrow, cell poor septa (Qi and Kaas, 2004). The histological characteristics of Area 3b are so clear it was possible to relate a complete representation of the contralateral body surface to a single architectonic area in early studies using myelin stained or Nissl-stained brain sections. The innovation of manually flattening the folded cortex after separating it from the underlying fibers and cutting this flattened cortex parallel to the surface, meant that large portions of the Area 3b borders with adjoining Area 3a and Area 1 could be visualized in single sections. This was even easier to do in rodents with a smooth cortex without any fissures, so that histological preparations, including stains such as cytochrome oxidase, allowed all of S1 (3b) to be viewed in a single section. These preparations revealed the somatotopy of the rodent S1 in such detail that it was possible to determine the sex of the animal from the surface view of the representation (Lenschow and Brecht, 2018). Such preparations also reveal the differences in S1 representation across mammalian taxa. For small mammals with no or few cortical fissures, parts of the tactile representations in S1 have large

separations between the representations of the hindlimb, forelimb, lower face, and upper face, containing neurons that respond to stimulation of proprioceptors. In primates, these interdigitations of proprioceptive cortex have been pushed out as S1 (3b) compressed and elongated. Thus, cortex adjoining Area 3b (Area 3a) has become more strip like, much like Area 3b. Although not widely recognized as such, the proprioceptive cortex along the anterior border of, and interdigitated with Area 3b in non-primate mammals is the homologue of Area 3a in primates (Ebner and Kaas, 2015; Krubitzer et al., 2011; Slutsky et al., 2000). As a further point on the somatotopy of area 3b of primates, the most lateral part of the representation includes, in sequence, the contralateral face, teeth, and tongue, followed by a representation of the ipsilateral teeth and tongue (Kaas et al., 2006). Thus, the sensory inputs from the teeth and tongue are so important that both the ipsilateral and contralateral teeth and tongue are represented in both hemispheres. This depends on both the contralateral and ipsilateral teeth and tongue being represented in the ventroposterior nucleus.

Neurons in Area 3b reflect the relay of SA1, RA1 and RA2 classes of tactile afferents (Carter et al., 2014; Lieber and Bensmaia, 2019). While cortical neurons have responses to tactile stimulation that reflect both SA1 and RA1 afferents, layer 4 neurons are grouped in modules that are more dominated by either SA1 and RA1 classes of afferents (Sur et al., 1984). However, more superficial neurons in S1 lose the slowly adapting component, perhaps as a result of local inputs from inhibitory neurons. The receptive fields of neurons activated by touch on the hand, for example, have an excitatory center for specific locations on the glabrous hand, with an inhibitory surround, so that the response to touch in the center is reduced by touch elsewhere on the hand, and the magnitude of the inhibition decreases with distance from the excitatory center (Qi et al., 2016; Reed et al., 2008). The suppressive surround does not extend beyond the hand to parts of the arm. Surprisingly, a weaker suppressive surround includes the glabrous skin of the opposite hand (Reed et al., 2011). Thus, these neurons in the hand representation in primate S1 have excitatory receptive fields with bilateral inhibitory surrounds. The widespread intrinsic connections within Area 3b likely contribute to these widespread inhibitory surrounds (Liao et al., 2013). The pathways mediating the bilateral effects are not yet known.

The cortical connections of S1 include includes cortex along the anterior and posterior borders of S1, which in primates is Area 3a and area 1 (or Area 1/2 in some New World monkeys and prosimians). Other connections are to areas S2

and PV (Burton et al., 1995; Disbrow et al., 2003; Krubitzer and Kaas, 1990; Liao et al., 2013; Pons et al., 1985). Subcortical connections include those to VP of the thalamus, the superior colliculus, and trigeminal and dorsal column nuclei (Liao et al., 2021).

AREA 1

Area 1 of primates contains a somatotopic representation of the contralateral body surface, that closely mirrors that in Area 3b (Kaas, 1983). Thus, representations of the palm adjoin at the 3b/1border, and the representation of the digits point in opposite directions. The less distinct representation along the posterior border of S1 in some rodents and other mammals contains what may be a homolog of Area 1 (or Area 1/2) of primates (Ebner and Kaas, 2015; Krubitzer et al., 2011; Slutsky et al., 2000). Area 1 receives its driving input from Area 3b, while also receiving direct inputs from VP, which are thought to have modulatory functions (Garraghty et al., 1990).

Other connections of Area 1 include somatotopic interconnections with areas 3a and 2, regions of the posterior parietal cortex, S2 and PV (Cerkevich and Kaas, 2019; Disbrow et al., 2003; Krubitzer and Kaas, 1990), and a less widely recognized area of the lateral sulcus, the ventral somatosensory area (VS), and the rostroventral parietal area (PR) (Cerkevich and Kaas, 2019; Disbrow et al., 2003; Krubitzer and Kaas, 1990; Padberg et al., 2019). Other connections are with motor and premotor cortex. The response properties of neurons in Area 1 largely reflect those of the activating neurons in Area 3b, with some convergence resulting in larger receptive fields (Rossi-Pool et al., 2021).

AREAS 3A AND 2

Just rostral to Area 3b, area 3a is largely activated by proprioceptive inputs (Krubitzer et al., 2004; Krubitzer and Kaas, 1990). Projections from VP and VPS activate neurons in area 3a (Padberg et al., 2009), and some from the same neurons activate neurons in Area 2 (Cusick et al., 1985). Area 3a can be regarded as a primary area for proprioceptive inputs, mainly from muscle spindle afferents. Area 2 is more responsive to tactile inputs, although neurons also respond to stimulation of proprioceptors (Pons et al., 1985).

While Area 3a is widely recognized in the primate taxa, homologs appear to exist in non-primate mammals (Krubitzer et al., 2004). Area 2 is not distinguished from Area 1 in all primates, and the region caudal to Area 3b is designated as Area 1/2 in some primates (Padberg et al., 2005); however, see Cerkevich and Kaas (2019). Area 2 receives much of its input from VPS of the thalamus, and moderate inputs from other thalamic nuclei such as VP and PLa (Padberg et al., 2009; Pons and Kaas, 1986). Cortical connections of Area 2 include those with Areas 3a, 3b, 1, S2, and regions of posterior parietal cortex (Padberg et al., 2009; Pons and Kaas, 1986). Neurons in Areas 3a and 2 respond to manipulating joints and muscles, and movements of hands and digits (Krubitzer et al., 2004; Krubitzer and Kaas, 1990; Pons et al., 1985). Especially in Area 2, the proprioceptive signals interact with tactile signals (Kim et al., 2015). Some neurons in Area 2 have matching excitatory receptive fields on both hands (Iwamura et al., 2001). Area 3a contains a somatotopic representation of the contralateral body that is parallel to that in area 3b (Huffman & Krubitzer, 2001; Krubitzer et al., 2004), while Area 2 has a representation in parallel with Area 1 (Padberg et al., 2007; Pons et al., 1985).

AREAS S2, PV, AND VS

Areas S2, PV, and VS constitute a region of higher-order somatosensory processing located on the upper bank of the lateral sulcus (Figure 23.3). Areas S2 and PV appear to directly border S1 (area 3b) in some primates such as marmosets (Krubitzer and Kaas, 1990). In other primates, such as titi monkeys, PV directly abuts area 3b, and S2 abuts area 3b and area 1 (Coq et al., 2004); and in macaques and squirrel monkeys, S2 adjoins area 1, and PV adjoins areas 3b and 1 along the representation of the face and mouth (Cerkevich and Kaas, 2019; Krubitzer et al., 1995). Representations of the face and mouth in PV and S2 are followed by that of the arm and forearm, and the leg somewhat deeper in the lateral sulcus. The representations of PV and S2 are mirror images of each other. Deeper in the sulcus, PV and S2 are joined by additional representations, the rostral (VSr) and caudal (VSc) divisions of the ventral somatosensory area VS (Coq et al., 2004; Cusick et al., 1989; Krubitzer et al., 1995). These areas get thalamic inputs mainly from the ventroposterior inferior nucleus (VPI), but also from the anterior pulvinar (Disbrow et al., 2002; Krubitzer and Kaas, 1992;

Qi et al., 2002). In addition to connections with each other, and areas 3a, 3b, and 1, PV and S2 have connections with sensorimotor modules of posterior parietal cortex (Padberg et al., 2019; Stepniewska et al., 2009; Wang et al., 2021). Neurons in these areas have large receptive fields and appear to have both tactile and proprioceptive components (Coq et al., 2004). S2 and PV are somatosensory areas that have been described in humans (Disbrow et al., 2000) as well as in a range of non-primate mammals (Beck et al., 1996; Catania and Kaas, 2001; Ebner and Kaas, 2015; Krubitzer and Calford, 1992; Krubitzer et al., 2011). In humans, bilateral stimulation of the hands activates S2 and PV regions more than stimulation of the contralateral hand alone (Disbrow et al., 2001).

SUMMARY AND CONCLUSIONS

All primates appear to have expanded somatosensory networks at the cortical level. These include the traditional areas numbered after Brodmann (Brodmann, 1909), Areas 3a, 3b, 1, and 2; more recently defined areas S2, PV, VSr, and VSc; an array of multisensory domains in posterior parietal cortex; and tactile and proprioceptive components of domains in premotor and motor cortex. The main peripheral afferents that provide information to the vast network include the four members of rapidly and slowly adaptive classes 1 and 2. Afferents related to hair movements, muscle spindles, tendon stretch, nociception, and temperature add to this mixture. Tactile afferents terminate in brainstem and spinal cord nuclei, where neurons have small receptive fields for locations on the body with antagonistic receptive field surrounds. Neurons in the ventroposterior nucleus of the thalamus and primary somatosensory cortex have similar receptive field sizes, while neurons in higher-order areas have larger receptive fields, more extensive antagonistic surrounds, and more sources of influences on response properties, including those from roughly matching inputs stemming from both sides of the body. In posterior parietal cortex and frontal motor areas, multisensory neurons are often sensitive to visual and auditory signals. Non-primate mammals often have less complex somatosensory systems, but like primates, they are specialized in various ways for specific adaptations. However, at the cortical level, the presence of S1 is universal and S1 is commonly bordered by an anterior zone for proprioception much like Area 3a, a posterior zone suggestive of Area 1/2 in primates, and Areas S2 and PV.

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