

Of mice and monkeys: Somatosensory processing in two prominent animal models

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ABSTRACT

Our understanding of the neural basis of somatosensation is based largely on studies of the whisker system of mice and rats and the hands of macaque monkeys. Results across these animal models are often interpreted as providing direct insight into human somatosensation. Work on these systems has proceeded in parallel, capitalizing on the strengths of each model, but has rarely been considered as a whole. This lack of integration promotes a piecemeal understanding of somatosensation. Here, we examine the functions and morphologies of whiskers of mice and rats, the hands of macaque monkeys, and the somatosensory neuraxes of these three species. We then discuss how somatosensory information is encoded in their respective nervous systems, highlighting similarities and differences. We reflect on the limitations of these models of human somatosensation and consider key gaps in our understanding of the neural basis of somatosensation.

1. Introduction

How do humans process a restricted collection of sensory inputs to generate an extraordinarily complex and diverse repertoire of behaviors? While our desire is to understand our own species, much of what we know about the human brain comes from work on other animals, and most of what we know about sensory processing in mammals comes from work on a few animal models, namely mice, rats, and macaque monkeys. Since extrapolation across species is essential to understanding the human brain – and nervous system function more broadly – cross-species comparisons should be made in a well-informed manner (Fig. 1). Somatosensation offers a useful case study of this comparative process, given the extensive work on the organization and function of this sensory system in mice, rats, and macaques.

With this in mind, we explore the neural basis of touch and proprioception in these three species, focusing on the hand in macaques and the whisker system of mice and rats, because these sensory systems have received the bulk of the experimental attention. The adoption of the whisker system of mice and rats as a model for understanding the somatosensory system of humans seems counterintuitive, given the vast

differences between whiskers and hands. While rats have been used in experimental studies for over 150 years, and genetic studies in mice have been done since the early part of the last century, the use of these murine rodents as models for somatosensory processing is likely due to historic happenstance. Traditionally, the barrel system was critical for understanding how sensory input contributes to the development of the neocortex and aspects of cortical organization (Woolsey and Van der Loos, 1970; Rice and Van Der Loos, 1977). Indeed, the one-to-one correspondence between barrels and individual whiskers allowed for a variety of straightforward experimental manipulations to the whiskers (e.g. trimming individual whiskers or rows of whiskers at different developmental time points) coupled with direct examination of the cortical manifestations of these manipulations. The resulting surge in studies on the barrel system was followed by the development of genetic tools and other sophisticated techniques to examine cells and circuits within the mouse brain. Mice and rats have thus become the dominant animal models in neuroscience, including somatosensory neuroscience.

Our objective is to assess the degree to which mouse, rat, and macaque models are synergistic in a quest to understand somatosensation, and to place similarities and differences in a phylogenetic and ecological

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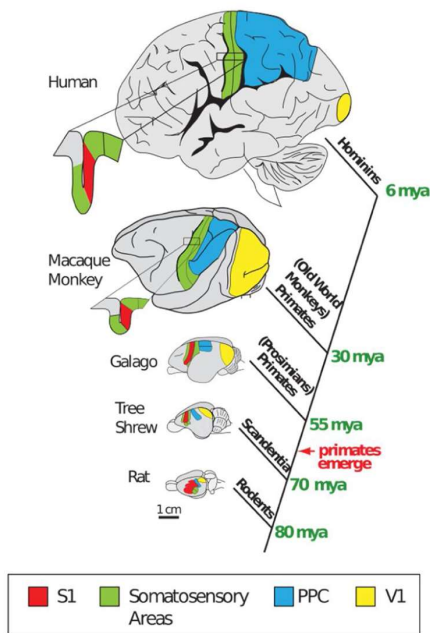


Fig. 1. A cladogram showing the phylogenetic relationship of five different mammals with each branching point indicating the time of the last common ancestor. Brains are drawn to (relative) scale except the human brain, which is substantially scaled down. The location of the primary somatosensory area, S1 (green), the primary visual area, V1 (yellow), and the posterior parietal cortex (PPC, blue) are depicted. Note that somatosensory cortex and the relative size of the PPC are greatly expanded in primates, particularly in humans. Modified from [Goldring and Krubitzer, 2017](#).

context. To this end, we examine the biomechanics of the hands and whiskers, and their sensory innervation, and the neuroanatomy of the associated neuraxes. We then discuss how information is encoded in neuronal populations at different stages of processing to assess whether these three animal models convey a consistent picture of somatosensation.

This review is written from three very distinct perspectives – a mouse neurophysiologist, a monkey neurophysiologist, and an evolutionary neurobiologist – in an attempt to synthesize findings from three widely used animal models and to generate a common framework from which we can understand the somatosensory system of mammals in general. One motivation for this endeavor is the misconception that the somatosensory system is well understood, especially in comparison to the much more advanced understanding of the visual system. Indeed, most information on the somatosensory system comes from textbooks and older reviews, which focus on well-established anatomical pathways or specific features of processing in a few animals. This limited focus impedes a broader understanding of the fundamental, organizational principles of the somatosensory system in mammals in general.

2. Functions of whiskers and hands

The innervation of an effector is dependent on the function of that effector. To understand and compare somatosensory processing in mice and macaque monkeys thus requires that we first place the respective sensory systems in the context of their function ([Fig. 2](#)). Although frequently studied in mice and rats, whiskers are nearly ubiquitous among mammals. The principal function of whiskers is to explore peripersonal space for the purposes of navigation, localization, and identification of nearby objects and surfaces. Whiskers are also used for tracking the contours of a wall during locomotion or rapid prey motions during close-range hunting and pursuit. Some evidence suggests rats also use whiskers to sense airflow ([Yu et al., 2019](#)), akin to the function of whiskers as hydrodynamic sensors in seals ([Dehnhardt et al., 1998](#)). While hands can be used for navigation and for object identification (stereognosis) when vision is not available, their principal function is to grasp and manipulate objects.

Distinct but overlapping forms of sensory information are required to support the various functions of whiskers and hands. Navigation requires information about the spatial location and extent of a landmark. Tracking requires information about object motion to guide rapid compensatory changes in posture. Stereognosis, an ability achieved via both whiskers and hands, requires information about the three-dimensional structure of an object. Manipulation requires information about the location and dynamics of contact events. Of course, these functional domains share informational requirements to a degree – for example some information about the three-dimensional structure of an object is required for manipulation – but their relative importance varies. For comparison, the most conspicuous example of a somatosensory specialization is the snout of the star nosed mole, whose exploratory and grasping function has endowed it with a hand-like sensory innervation ([Catania and Kaas, 1996](#)). These functional requirements have shaped the somatosensory systems of mammals and underscore the importance of the interplay between brain, body, and behavior for understanding how sensory systems evolve.

3. Biomechanics of whiskers and hands

Interactions with objects cause deformations of the whiskers or skin, which then transmit stresses to mechanoreceptors, which in turn convert these stresses into electrical signals. The mechanical properties of the whiskers and skin thus play a role in shaping the sensory signals transmitted to the central nervous system. Whiskers are tapered beams that transmit to the whisker follicle stresses produced during whisker-object interactions ([Birdwell et al., 2007](#); [Solomon and Hartmann, 2006](#)). A variety of different types of receptors in the whisker follicle, each sensitive to different aspects of the deflection, transduce local stresses into action potentials. Whisker follicles have a complex structure into which receptors take up formation at specific loci that likely expose them to distinct features of the mechanical input ([Ebara et al., 2002](#)). The transmission of stresses applied to different locations along the whisker, and the dependence of this process on the geometry of the whiskers, which varies systematically across the face, has been successfully modeled using quantitative approaches ([Birdwell et al., 2007](#); [Solomon and Hartmann, 2006](#); [Lucianna et al., 2016](#)).

The glabrous skin of the hand provides an obviously different



Fig. 2. Functions of hands and whiskers. Both whiskers and hands can sense object properties such as texture and shape, but only hands can grasp and manipulate objects.

coupling between the outside world and mechanoreceptors than does the whisker. Simple biomechanical models of the skin based on continuum mechanics capture some essential features of how the skin deforms when indented, including the enhancement of external features of an object and the obscuration of internal ones due to the way forces propagate through the tissue (Sripati et al., 2006; Philipps and Johnson, 1981). Finite element models (Bischoff et al., 2000; Dandekar et al., 2003; Wu et al., 2006) involve more detailed descriptions of the skin and, unlike their continuum mechanical counterparts, take into account the influence of the bone on the skin's response, particularly near the joints. Regardless, the response properties of mechanoreceptors are critically dependent on skin mechanics. For example, nerve fibers that innervate receptors located deeper in the skin tend to have larger receptive fields, a phenomenon that can be attributed to skin mechanics, as can the enhanced afferent responses to edges and corners (Sripati et al., 2006; Philipps and Johnson, 1981).

The respective morphologies and mechanical properties of the whiskers and skin differ substantially, and these differences can lead to important differences in the resulting neuronal representations. For example, whiskers sample an object sparsely and provide a time-varying signal at each contact point that is determined by the forces applied on the whisker. In contrast, hands provide a spatio-temporal signal at each point of contact – reflecting the spatio-temporal pattern of skin deformation – a signal that is shaped by skin biomechanics as forces applied to the skin's surface propagate through the tissue. The disparate morphologies and mechanical properties lead to differences in the resulting sensory representations, as discussed below.

4. Peripheral innervation

The peripheral innervation of whisker follicles and the fingertips are distinct, although both share Merkel-type afferents (Fig. 3). In mice, each follicle is innervated by 100–300 sensory fibers, each of which terminates in one of roughly 8 distinct types of mechanoreceptors (Ebara et al., 2002; Rice et al., 1986). The cell bodies of these mechanoreceptors are located in the trigeminal ganglion, and each includes a single whisker in its receptive field (Zucker and Welker, 1969). Nerve fibers can be categorized electrophysiologically into slowly adapting and rapidly adapting classes based on whether or not they produce a sustained response to a sustained whisker deflection. However, this dichotomy only captures one of many ways in which afferent responses differ across classes (Szwed et al., 2003). So far, only Merkel afferents of the follicle have been studied during behavior (Severson et al., 2017), but advances in genetic labeling will likely lead to rapid progress in characterizing other afferent types.

The glabrous skin of the macaque hand is innervated by three types

of tactile nerve fibers, each of which innervates a different type of mechanoreceptor and responds best to different aspects of skin deformations. The cutaneous innervation of the palm is similar in macaques and humans except that macaques lack the Ruffini-type nerve fiber, which sparsely innervates human glabrous skin (Paré et al., 2003). Analogously to whisker follicle afferents, cutaneous nerve fibers can be classified based on their adaptation properties: rapidly adapting fibers respond only to the onset and offset of an indentation whereas slowly adapting fibers respond throughout the stimulus presentation. Nerve fibers are also classically divided according to the size of their receptive fields (RF): type 1 fibers have small RFs, type 2 have large ones. During most manual interactions with objects, all three types of nerve fiber are activated and convey distinct but overlapping information about object features (Saal et al., 2017; Saal and Bensmaia, 2020).

While the substrates are very different – whisker vs. skin – the peripheral innervation is qualitatively similar across rats, mice and macaques, consisting of an overlapping set of afferent classes. The hand and whiskers are innervated by approximately 18,000 and 5,000 tactile nerve fibers, respectively, making them the most densely innervated regions of their respective organisms. As a point of comparison, however, the star of the star-nosed mole is innervated by 100,000 nerve fibers, making it the most densely innervated organ in the animal kingdom (Catania, 2011).

5. Organization of the somatosensory neuraxis

5.1. Cortical organization

Perhaps the most profound differences in the somatosensory systems of rats, mice, and macaque monkeys are at the level of the neocortex (Fig. 4). While these three species all have a primary somatosensory area (S1 or area 3b), a second somatosensory area (S2), and a parietal ventral area (PV) that process cutaneous inputs, there the similarities end. The extent of cortex that processes somatic input, the number of cortical fields involved in this network, and the interconnections of this network are radically different in rats, mice, and macaque monkeys. In addition to the areas noted above, macaque monkeys have three additional anterior parietal fields including area 1, which processes cutaneous input, area 3a, which processes proprioceptive input, and area 2, which integrates cutaneous and proprioceptive inputs (Nelson et al., 1980; Pons et al., 1985; Krubitzer et al., 2004). While many use the term “primary somatosensory cortex” (“S1”) to refer collectively to areas 3a, 3b, 1, and 2 in macaque monkeys, this is an outmoded concept since it has been well established for decades that only area 3b is homologous to S1 in a range of other mammals (Kaas, 1983). Although the dysgranular zone in mice and rats has been proposed to be the homologue of area 3a

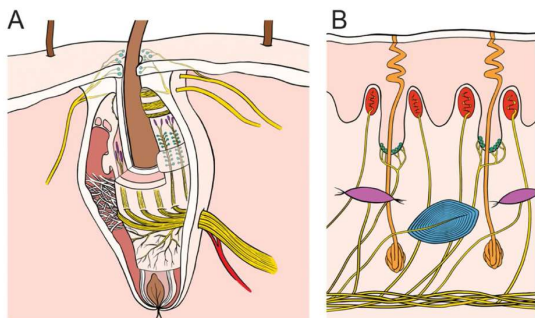


Fig. 3. Innervation of the whisker follicle and fingertip. A| Whisker follicles in mice and rats are complex encapsulated structures containing ~8 different mechanoreceptor types (Ebara et al., 2002; Rice et al., 1986), including Merkel cell (cyan) and lanceolate-type (purple) endings. The responses of many types to sensory input remain unknown. The entire follicle rotates together with the whisker during whisking, due to the action of intrinsic and extrinsic muscles. B| The primate fingertip contains three main types of mechanoreceptors including Merkel cell (cyan), innervated by slowly adapting type 1 nerve fibers, Meissner corpuscles (red), innervated by rapidly adapting fibers, Pacinian corpuscles (blue), innervated by Pacinian corpuscle associated fibers. A fourth type, Ruffini endings (purple), innervated by slowly adapting type 2 fibers, is absent in macaques and sparse in human glabrous skin.

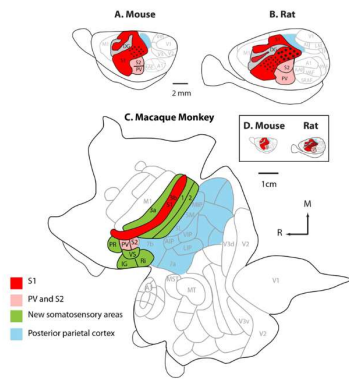


Fig. 4. The organization of somatosensory cortex in mice, rats and macaque monkeys. All three species have a primary somatosensory area (red), a second somatosensory area, and a parietal ventral area (pink). In macaque monkeys, additional areas that process somatosensory inputs have emerged over the course of evolution (green). Posterior parietal cortex has greatly expanded and includes multiple cortical fields in macaque monkeys. When mouse and rat cortices are drawn to scale (D) the enormous difference in the size of the cortical sheet in these rodent models and macaque monkeys is striking. Adapted from Krubitzer and Dooley, 2013.

in primates (Krubitzer et al., 2011), this is still speculative, and there are no clear homologues of macaque areas 1 and 2 in rats and mice. In addition to the expansion of anterior parietal cortex, the number of somatosensory areas in the lateral sulcus of macaque monkeys has increased to include the ventral somatosensory area (VS), the parietal rostral region (PR), and the retroinsular area (RI) (Krubitzer et al., 1995). Finally, similar changes have emerged in the posterior parietal cortex (PPC) of monkeys (Figs. 1 and 4), which spans several centimeters of cortex and includes multiple cortical areas associated with hand use (Mooshagian et al., 2018; Rathelot et al., 2017) (see Goldring and Krubitzer, 2020; Kaas et al., 2018) for a review). In rats and mice, a small strip of cortex – located between S1 and primary visual cortex and occupying about 1×2 mm of cortical territory (Olsen and Witter, 2016) – may be the homologue of some part of PPC in macaque monkeys (Fig. 4). Because of these extreme differences, it is difficult to make comparisons of somatosensory cortical areas between commonly used rodent models and macaque monkeys outside of S1, S2 and PV.

In addition to the differences in the number of cortical areas that process tactile and proprioceptive inputs, the somatotopic organization is also distinct in these animal models, even in homologous cortical areas. In macaque monkeys, the primary somatosensory cortex (area 3b) is dominated by the representation of the glabrous hand and comprises a detailed representation of the individual digits and the palmar surface of the hand (Nelson et al., 1980). In macaque monkeys, S1 neurons that respond to stimulation of the glabrous hand have very small receptive fields, particularly on the digit tips. In contrast, approximately 50 % of S1 in mice and rats is devoted to representing the vibrissae and perioral structures and the RFs of these neurons are small (Chapin and Lin, 1984), like their hand counterparts in macaques. While there is a wealth of data on the whisker representation (barrel cortex) in mice, to our knowledge there are no detailed maps of the entire body representation in S1 of mice; however early studies by Woolsey indicate that the overall organization of S1 in mice is much like that in rats (Krubitzer et al., 2011; Woolsey, 1967). Differences in somatotopic organization and cortical magnification are maintained to some degree in higher order

fields such as S2 and PV in macaque monkeys, rats, and mice (Krubitzer et al., 1995; Rempel et al., 2003; Carvell and Simons, 1986). In areas 3a, 1, and 2 in macaque monkeys, the dominance of the hand and digit representation is maintained such that a huge swath of anterior parietal cortex is devoted to representing the glabrous skin, reflecting the importance of the palmar surface of the hand in touch-mediated behaviors (Nelson et al., 1980; Pons et al., 1985; Krubitzer et al., 2004). Similarly, higher order somatosensory cortices in mice and rats comprise an enlarged representation of the whiskers (Krubitzer et al., 2011).

Finally, PPC in monkeys occupies a huge expanse of cortex and is composed of multiple, well defined cortical fields (Goldring and Krubitzer, 2020; Hadjimitsakis et al., 2019; Borra et al., 2017; Gamberini et al., 2020). Most of the rostral portions of posterior parietal cortex in macaques are associated with the somatosensory system. These cortical fields are devoted almost exclusively to representing the forelimb and are involved in the planning of reaching and grasping (Goldring and Krubitzer, 2020; Kaas et al., 2018; Seelke et al., 2011). The proposed homologue of PPC in rats and mice features a coarse topography of the whiskers (Mohan et al., 2019) and is proposed to be involved in a number of functions including encoding behaviorally relevant tactile information, postural control, and sensory memory to name a few (Mohan et al., 2019; Mimica et al., 2018; Akrami et al., 2018).

These differences in cortical field number and magnification between mice and rats compared to macaque monkeys are not necessarily a “rodent” phenomenon. In squirrels, for example, a cortical field rostral to and partially embedded in S1 comprises neurons that respond to joint and muscle manipulation, and this region may be homologous to area 3a in macaque monkeys and other primates (Slutsky et al., 2000). In a field caudal to S1, neurons are responsive to stimulation of both cutaneous receptors and joint and muscle manipulation. This field, termed the parietal medial area (PM) (Krubitzer et al., 2011; Slutsky et al., 2000), may be homologous to area 2 or to some portion of PPC in macaque monkeys. Furthermore, S1 in squirrels has a large representation of the lower and upper lips, a small representation of the vibrissae, and a large representation of the digits, and forelimb (Sur et al., 1978). The pattern of cortical magnification in squirrels is thus more similar to that in primates than to that in mice and rats.

These types of differences exist in the somatosensory cortex of other rodents as well (Krubitzer et al., 2011). Thus, mice and rats are not necessarily good “models” of the rodent order when considering somatosensory cortex.

5.2. Somatosensory networks

Differences in the number and organizational features of cortical fields in mice, rats, and macaque monkeys are accompanied by differences in the cortical and subcortical networks involved in somatosensory processing. While detailing the specific patterns of connectivity in these animal models falls outside the scope of this review, several fundamental differences in connectivity patterns between these species are noteworthy. The first is in their thalamocortical connections. In macaque monkeys, a large portion of the dorsal thalamus is devoted to somatosensory processing and multiple thalamic nuclei beyond the ventral posterior nucleus (VP) are associated with the somatosensory system (Padberg et al., 2009). In contrast, the somatosensory thalamus of mice and rats is limited to VP and the posterior medial nucleus (POM) (Chmielowska et al., 1989; Carvell and Simons, 1987). Thalamocortical connections between VP and S1 in macaques, mice, and rats are similar, but there the similarities end. Specifically, in macaque monkeys, thalamic projections to S1 are highly convergent and divergent from a number of nuclei including VP, the superior and inferior ventral posterior nuclei, the posterior division of the ventrolateral nucleus, and the anterior pulvinar (Padberg et al., 2009; Rausell et al., 1998). This divergence and convergence in thalamocortical connectivity is also a defining feature of other anterior parietal areas, and of cortical areas in the lateral sulcus of macaque monkeys (Padberg et al., 2009; Rausell

et al., 1998). Given that mice and rats have many fewer cortical fields and thalamic nuclei associated with somatosensory processing, their thalamocortical networks are relatively simple compared to their macaque counterparts (Chmielowska et al., 1989; Carvell and Simons, 1987). Specifically, the patterns of interconnections between higher order somatosensory nuclei of the thalamus in mice and rats (POM) and higher order cortical fields (S2) are limited compared to macaque monkeys, given the huge expanse of the higher order fields associated with somatosensory processing in monkeys (e.g. S2, PV, area 3a, area 2, area 5, VS, PRR) compared to mice and rats (S2 and PV) (Pons et al., 1985; Krubitzer et al., 2004; Krubitzer et al., 1995; Goldring and Krubitzer, 2020).

Second, although S1 has strong cortico-cortical connections with S2 and PV in mice, rats, and macaque monkeys (Carvell and Simons, 1987; Burton et al., 1995; Koralek et al., 1990), comparisons of cortical connections across these species are defined more by differences than similarities. For example, because there are no homologs of areas 3a, 1, 2, VS, PR, and RI in mice and rats, the network of cortical connections of these fields is a feature in macaque monkeys (and other primates) that does not exist in mice and rats. In addition, there are profound differences in corticocortical connections in mice, rats, and macaque monkeys between homologous fields. In mice and rats, S1 has strong connections with primary motor cortex (M1) (Porter and White, 1983; Smith and Alloway, 2013), while S1 (area 3b) in macaque monkeys has little to no connections with M1, and areas 3a and 1 have sparse connections with M1 (Burton and Fabri, 1995; Gharbawie et al., 2011; Jones et al., 1978). Rather, area 2 and posterior parietal area 5 are interconnected with motor cortex forming what is commonly called the frontoparietal network (Borra et al., 2017; Gharbawie et al., 2011; Bakola et al., 2013; Padberg et al., 2019).

Finally, in mice and rats, corticospinal neurons originate primarily in M1 and to a lesser extent in S2 (Ueno et al., 2018), while in macaque monkeys corticospinal inputs arise from M1, as well as from areas 3a, 3b, 1, 2, and 5, and from areas in the lateral sulcus (Borra et al., 2017; Galea and Darian-Smith, 1994). These differences indicate that somatosensory areas play a relatively large role in the motor control of the body in macaque monkeys, particularly the hand. Consistent with this view, movements of the hand and other body parts can be evoked not only from motor and premotor cortex, but also from all anterior parietal areas (3a, 3b, 1 and 2) as well as from posterior parietal cortex (areas 5 and 7) in macaque monkeys (Rathelot et al., 2017; Baldwin et al., 2018). Many of the evoked movements of the hand in motor cortex and parietal areas are complex digit movements including multiple types of precision grips as well as power grips. In mice and rats, movements can only be evoked from M1 and S1 (Neafsey et al., 1986; Halley et al., 2020) and S1 has been implicated in the motor control of whisker retraction movements (Peterson, 2014; Matyas et al., 2010). While stimulation in M1 and S1 can evoke grasp like movements in rats, unlike macaque monkeys there are no evoked movements of individual digits.

6. Neural coding

One of the main insights of modern sensory neuroscience is that sensory information can be encoded by neurons in different ways. Some sensory information is encoded in the strength of the neural response – a rate code – some in the spatial layout of the neural response – a spatial code – some in the precise timing of the response – a temporal code. These different coding schemes allow information to be multiplexed in neural activity: information about one stimulus feature might be encoded in the rate of firing of the activated neurons, while information about another feature might be encoded in its temporal patterning, for example.

Through the whiskers, mice and rats acquire information about the environment that overlaps, at least in part, with the information that monkeys acquire through the glabrous skin of the hand. One might then ask whether sensory information is encoded in the same way across

these organisms given the differences in the sensory organs and in their respective functions. To address this question, we examine how different stimulus features are encoded in the different somatosensory systems.

6.1. Vibration

Vibratory sensitivity provides a window into somatosensory innervation and into the ability of the nervous system to resolve the temporal structure of whisker or skin deformations. In mice, rats, and macaque monkeys, nerve fibers exhibit different frequency preferences, with some nerve fibers more sensitive at low frequencies and others at high frequencies. A prominent feature of afferent responses to vibrations is their phase locking: Nerve fibers will produce one spike or a burst of spikes within a restricted phase of each stimulus cycle such that the frequency composition of the vibration is reflected in the temporal sequence of the evoked spikes (Jones et al., 2004a, b; Birznieks and Vickery, 2017; Mackevicius et al., 2012; Talbot et al., 1968). Even complex multi-harmonic skin vibrations give rise to very repeatable temporal spiking patterns in the nerves (Fig. 5A). The temporal precision of vibratory responses is such that they can encode some types of stimuli with a precision measured in the milliseconds or even microseconds (Mackevicius et al., 2012; Bale et al., 2015). Similarly, neurons in somatosensory cortex produce phase locked responses to vibrations delivered to the whiskers (Ewert et al., 2008) or skin (Harvey et al., 2013; Salinas et al., 2000), though with reduced precision.

The specific behavioral relevance of different features of the response to vibrations has been extensively studied in macaques and to a lesser degree in rats and mice. In macaques, vibratory amplitude has been

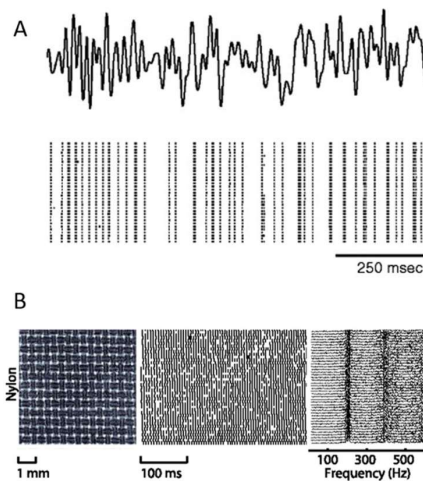


Fig. 5. Temporal precision and repeatability are hallmarks of both whisker and fingertip mechanoreceptors. A] Responses evoked in primary afferents by repeated presentations of the same mechanical noise stimulus delivered to a whisker. The response is temporally patterned and highly repeatable. The same phenomenon is observed when analogous stimuli are delivered to the skin of macaque monkeys. Reproduced from Jones et al., 2004a. B] Responses of a PC fiber to repeated presentations of a finely textured fabric. Left: Laser microscope image of the texture. Middle: Spiking response over 40 repeated presentations. Right: Power spectra of the neuronal responses. When textures are scanned across the skin, PC fibers produce texture-specific temporal spiking patterns. Modified from Weber et al. (2013).

shown to be encoded in the strength of the response evoked in the nerve (Muniak et al., 2008) and in somatosensory cortex (Harvey et al., 2013). In both the nerve (Mackevicius et al., 2012) and cortex (Harvey et al., 2013), the frequency composition of a skin vibration is encoded in the temporal patterning of the response: In the absence of changes in firing rate, the perceived frequency can be extracted from the phase-locked spiking of nerve fibers or of cortical neurons (Fig. 5B). However, while macaques (and humans) can discriminate vibrations on the basis of frequency independent of amplitude (Salinas et al., 2000; LaMotte and Mountcastle, 1975), rats cannot (Gerdjikov et al., 2010), bringing into question the behavioral significance of precise timing periodicity of the whisker vibratory response in rodents.

6.2. Texture

In the macaque monkey fingertip, texture processing relies on two neural mechanisms distributed over three populations of tactile nerve fibers: Coarse textural features – measured in millimeters – are encoded in the spatial pattern of activation across type 1 fibers (Weber et al., 2013). At this scale, individual textural features produce localized and relatively large scale deformations in the skin, which are in turn reflected in the localized activation of tactile fibers with RFs under the deformation (Connor et al., 1990). The nerve fibers thus carry a neural “image” of the stimulus. The spatial resolution of this coding mechanism – limited by the innervation density and the filtering properties of the skin – is too low to discern fine surface features, with sizes and spatial periods measured in the hundreds of nanometers to hundreds of micrometers. At these spatial scales, texture perception requires movement between skin and surface (Hollins and Risner, 2000), which drives vibrations in the skin whose characteristics depend on both the texture and the speed at which it is scanned (Bensmaia and Hollins, 2003; Manfredi et al., 2014; Greenspon et al., 2020). In turn, these skin vibrations elicit temporal spiking patterns in vibration sensitive nerve fibers, which are also dependent on surface and scanning speed (Weber et al., 2013; Lieber et al., 2017) (Fig. 5B). In rats and mice, the sparseness of the whiskers precludes a spatial mechanism of texture processing. Rather, texture information is carried in the time-varying profile of whisker deformations associated with stick-slip events of individual whiskers as they brush against the surface. These texture-dependent whisker deflections activate nerve fibers that innervate the follicle, and texture information is encoded in the pattern and magnitude of such activations over time.

In somatosensory cortex of rats and macaques, texture information is encoded in firing rates evoked during contact with the surface and in the temporal features of the response (Isett et al., 2018; Jadhav et al., 2009; Lieber and Bensmaia, 2019; von Heimendahl et al., 2007; Wolfe, 2008;

Zuo, 2015). In areas 3b, 1, and 2 of macaques, the texture signal carried by the firing rate response of cortical neurons reflects a spatial and temporal differentiation of the afferent input (Lieber and Bensmaia, 2019, 2020). These differentiation operations confer to individual neurons a selectivity for specific spatial or temporal features in the afferent input. Because the computations differ across neurons, individual neurons are selective for different textural features, and the neuronal population carries a high-dimensional representation of texture (Lieber and Bensmaia, 2019). A similar mechanism of differentiation – limited to the time domain – may also underlie the texture signal in barrel cortex given the similarities of the peripheral representation of texture in rats to its primate counterpart.

6.3. Shape and spatial localization

When we grasp and manipulate an object, we can recognize its three-dimensional structure even with vision obscured. This perceptual ability, known as stereognosis (Goodman and Bensmaia, 2018), involves the integration of cutaneous and proprioceptive signals. Signals carried by cutaneous nerve fibers convey information about the local geometry of the object at each point of contact (Goodwin and Wheat, 2004; Phillips et al., 1988) (Fig. 6). These signals are analogous to those that carry information about coarse textural features, described above. In somatosensory cortex (areas 3b, 1, and 2), neurons respond selectively to specific local features of the object, for example edges, via the aforementioned spatial differentiation mechanism (Bensmaia et al., 2008). Signals about the configuration of the hand are carried by different sets of nerve fibers that primarily innervate muscles and ultimately impinge on area 3a (Goodman et al., 2019; Okorokova et al., 2020). This representation thus provides a substrate for the configural component of stereognosis, which carries information about the global shape of the object. However, little is known about how tactile signals about local shape and proprioceptive signals about global shape are combined (Phillips et al., 1988).

The neural processing of shape or form in the whisker system has largely been studied indirectly, via the processing of object localization. Indeed, localization can be construed as an elemental computation that underlies shape processing. A shape can be viewed as a collection of points; if all the points are localized, the shape is determined. Because whiskers form an array on the face, the x-y location (azimuth and elevation) of an object within reach of the whiskers can be coarsely determined by the identity of the contacting whiskers (Knutsen and Ahissar, 2009). For whisking animals such as rats and mice (Sofroniew and Svoboda, 2015), additional strategies for localization beyond a whisker identity code are available. When whiskers sweep across space, the location of the whiskers can be tracked, and spikes arising from

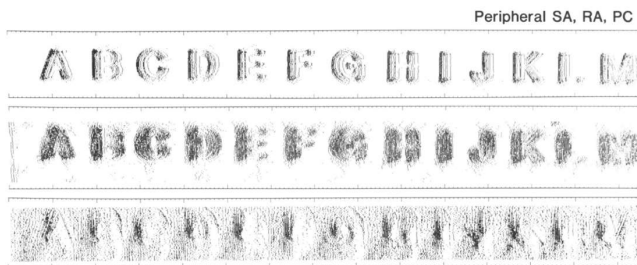


Fig. 6. Spatial coding by fingertip mechanoreceptors. Spatial pattern of activation evoked in populations of SA1 (top row), RA (middle row), and PC fibers when embossed letters are scanned across the fingertip of macaques. The spatial layout of the stimulus is reflected in the spatial layout of the response it evokes in SA1 and RA fibers.

Modified from Phillips et al. (1988).

whisker-object contacts can be referenced against whisker position to determine the location of the touched object. In this way, information about whisker position is combined with contact information to compute location and shape. However, unlike in the primate hand, contact information is carried together with proprioceptive signals in many individual nerve fibers. How whisker position is extracted using afferent responses is an active area of research (Severson et al. (2017); Mehta et al. (2007); O'Connor et al., 2013; Wallach et al., 2016; Knutsen et al., 2008; Pammer et al., 2013; Solomon and Hartmann, 2011).

While many questions remain about the neural basis of stereognosis with hands and its analogue with whiskers, the underlying mechanisms are likely very different because local features and global shape of objects are processed by two sensory modalities – touch and proprioception – that are largely served by separate fibers in the macaque hand, while whisker position and contact are carried largely by the same nerve fibers (but see: (Szwed et al., 2003)). There are two important caveats, however. First, cutaneous afferents of the hand – which carry touch signals – also respond to stretching of the hand's skin and may therefore carry proprioceptive information (Edin and Abbs, 1991). Second, the fact that hand sensing relies on dedicated proprioceptive fibers that are absent in the whisker system may not reflect a difference in species so much as a difference between the trigeminal and spinal somatosensory systems. Further work on macaque facial sensing and mouse paw sensing should resolve this uncertainty.

6.4. Motion

Somatosensory signals associated with object interactions typically arise during actively generated movements. Not surprisingly, then, the movement of objects across the skin or whiskers is explicitly encoded in the responses of neurons along the somatosensory neuraxis. In macaque somatosensory cortex, many neurons respond preferentially when a stimulus moves in their so-called preferred direction and less so when it moves in other directions (Fig. 7) (Pei et al., 2010, 2011; Pei and Bensmaia, 2014). Similarly, neurons in barrel cortex exhibit dramatic selectivity for the direction in which individual whiskers are deflected. This direction tuning is to a large extent likely inherited from the periphery, as follicle afferents often exhibit such tuning (Zucker and Welker, 1969). In contrast, direction tuning is weak or absent in the primate nerve and emerges downstream (Pei et al., 2010). In macaque cortex, local motion signals – which are often ambiguous – are integrated to achieve a global motion signal that is largely independent of the spatial characteristics of the moving object (Pei et al., 2010, 2011). Some neurons in barrel cortex exhibit selectivity for patterns of motion

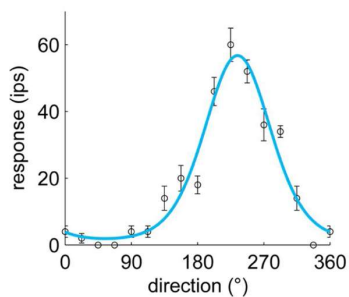


Fig. 7. Direction tuning in area 1. This neuron responds most strongly to an edge scanned across the skin in the distal to proximal direction and does not respond at all to the same edge scanned in the opposite direction. From Pei et al. (2010).

across multiple whiskers (Estebanez et al., 2016, 2012; Laboy-Juárez et al., 2019; Ramírez et al., 2014) and these multi-whisker representations may play a role in the computation of global motion moving across the whisker array. The nature of these computations remains to be elucidated, however.

7. Active touch

While touch is sometimes imposed, such as when we are touched by someone or when a breeze blows against our face, most tactile input occurs as a consequence of self-generated movements. Such “active touch” is the dominant mode of sensing for both whiskers and hands. Despite this, the vast majority of neurophysiological studies investigating touch in macaque monkeys have focused on passive sensing, in which stimuli are applied to the immobilized fingertip. Indeed, nearly all of our textbook knowledge about neural coding of touch has arisen from such studies. The challenge is that touch is very sensitive – detectable touches on the primate hand are measured in microns or even tenths of a micron (Muniak et al., 2008; Bolanowski and Zwislocki, 1984; Freeman and Johnson, 1982). Contact events during active manual interactions with objects, which involve skin deflections orders of magnitude larger, have not been characterized with sufficient precision to understand how they are encoded. Moreover, self-motion creates patterns of skin strain that evoke activity in tactile nerve fibers (Edin and Abbs, 1991; Edin, 2001; Hulliger et al., 1979) upon which contact signals are superimposed. The few studies of active manual touch have thus yielded only very qualitative conclusions about which areas preferentially respond during object contact, and some general observations about the neural dynamics during a contact event (Debowy et al., 2001; Salimi et al., 1999a,b).

In the whisker system, in contrast, methods for estimating forces and moments from whisker bending in high-speed video permit relating minuscule stresses to spiking of single-units (Severson et al., 2017; Bush et al., 2016; Campagner et al., 2016), despite the fact that thresholds are measured in the tens of μN (Pammer et al., 2013). Indeed, the detailed understanding of whisker biomechanics has made it possible to reconstruct, from measured patterns of whisker deformation, the forces acting at the whisker base during active touch (Birdwell et al., 2007; Campagner et al., 2018) (Fig. 8). Direct interrogation of neural activity during active touch has revealed that active whisker sensing differs from

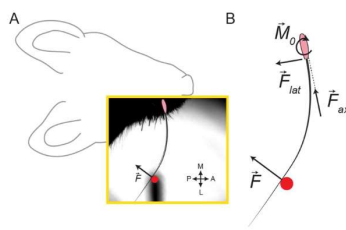


Fig. 8. Forces and moments can be estimated during active touch in the whisker system. A | Example frame (yellow box) from high-speed video of a mouse whisking with a single whisker against an object (indicated by overlaid red circle). The whisker follicle is denoted by the pink oval. Whisking against the object produces a whisker-object contact force, \vec{F} . B | Schematic showing the forces and bending moment that act in the plane of whisking. A whisker-object contact reaction force, \vec{F} , can be split into a lateral force (\vec{F}_{lat}) and an axial force (\vec{F}_{ax}) acting at the follicle, and produces a bending moment at the follicle (\vec{M}_0). These quantities can be estimated based on measurements obtained from high-speed video, together with measurements of whisker geometry.

Modified from Pammer et al. (2013).

its passive counterpart even at the level of mechanoreceptors. Indeed, whisker motion in rats and mice is actuated by muscles that pull on the whisker follicle (Haidarliu et al., 2015; Hill et al., 2008), and the actuation affects the coupling between whisker and mechanoreceptor. As a result, a similar deflection will elicit a different neuronal response if it is actively generated vs. passively imposed (Bush et al., 2016).

Active touch in the whisker system has been most thoroughly studied in the context of object localization (Knutsen and Ahissar, 2009; Diamond et al., 2008; Kleinfeld and Deschenes, 2011). Several quantitative behavioral tasks requiring the active localization of objects – in the azimuthal plane and in terms of radial distance from the face – have been developed for rats and mice (Mehta et al., 2007; Pammer et al., 2013; Knutsen et al., 2006; Krupa et al., 2001; O'Connor et al., 2010; Sofroniew et al., 2014) and the behavioral, mechanical, and neural bases of such object localization have been studied in detail (Birdwell et al., 2007; Solomon and Hartmann, 2006; Szwed et al., 2003; Mehta et al., 2007; O'Connor et al., 2013; Knutsen et al., 2008; Pammer et al., 2013; Solomon and Hartmann, 2011; Campagner et al., 2016; Knutsen et al., 2006; O'Connor et al., 2010; Curtis and Kleinfeld, 2009; Bagdasarian et al., 2013; Cheung et al., 2019; Hires et al., 2015; Petreanu et al., 2012; Quist and Hartmann, 2012; Szwed et al., 2006; Voigts et al., 2015; Xu et al., 2012). To locate objects in the azimuthal plane, mice and rats may use multiple, non-exclusive strategies (Knutsen and Ahissar, 2009; Diamond et al., 2008; Kleinfeld and Deschenes, 2011). One well-investigated strategy involves the integration of whisker self-motion signals with object contact signals. Azimuthal angle relative to the mouse face can be computed in part from the whisk phase (the relative position of the whisker within the whisk cycle) (Kleinfeld and Deschenes, 2011; Hill et al., 2011) as it indicates the location within the currently scanned region of space. Signals about whisk phase are found throughout the neuraxis, from nerves to S1 (Szwed et al., 2003; Severson et al., 2017; Wallach et al., 2016; Campagner et al., 2016; Curtis and Kleinfeld, 2009; Hires et al., 2015; Crochet and Petersen, 2006; Fee et al., 1997; Khatri et al., 2009; Leiser and Moxon, 2007; Moore et al., 2015; Severson et al., 2019; Yu et al., 2006; Yu et al., 2016). During whisking, this phase-based self-motion signal can be combined with touch-evoked activity to code azimuthal object location within the currently scanned region of space (Curtis and Kleinfeld, 2009; Mehta et al., 2007) (Fig. 9). Signals encoding whisk amplitude and mid-point are also present in M1 (Hill et al., 2011; Huber et al., 2012) and are relayed to S1 via direct projections (Petreanu et al., 2012), allowing S1 neurons to encode azimuthal object location in terms of absolute whisker angle (Ranganathan et al., 2018).

While active touch likely shares some common mechanisms and circuitry between the whisker system and the macaque hand, there are reasons to expect major differences. First, manual touch primarily supports object manipulation, whereas whiskers are used for sensing but not manipulating. As stated above, the sensory demands of the two

behaviors are likely to be different, as is the interplay between sensory and motor signals. The regulation of grip force provides an example of tactile processing specific to the demands of manipulation. Grip force must be dynamically and precisely adjusted to prevent a held object from sliding within the hand and is thought to depend on “cancelling” signals triggered in cutaneous afferents by object-skin motion (Johansson and Westling, 1987). Second, touch and proprioception for the hand are (mostly) distinct modalities subserved by cutaneous and muscle receptors, respectively. In contrast, the muscles of the whisker system – as well as most other facial muscles in rats, mice, and humans – contain few or no muscle proprioceptors (Moore et al., 2015). The integration of touch and proprioceptive signals must therefore occur differently. In general, however, the study of active touch in primates is so impoverished that there are few if any relevant data to inform comparisons between the whisker and hand systems.

8. Caveats: the challenge and opportunity of comparative neurophysiology

Over 6000 species of mammals have evolved to adapt to a variety of complex and dynamic niches. Yet, our current understanding of sensory processing is based on only a few mammals and is limited for several reasons. First, the primate and rodent orders are highly diverse. Of the 2500 or so species of rodents, some use their whiskers for sensory exploration while others do not, some have a barrel cortex while others do not (Woolsey et al., 1975). Of the hundreds of species of primates, some have opposable thumbs while others do not, some naturally use tools in the wild while others do not (Murray, 1975). Thus, each of these animal models has derivations that may impact the extent to which we can extrapolate the data we collect to humans. Although, in the field, we often speak of “rodent” and “primate” features of organization and function, we must keep in mind that this shorthand terminology obscures major diversity within each order. Thus, a complete understanding of even rodent and primate somatosensation will not be achieved via work with mice, rats, and macaques alone. Second, we often fail to appreciate that species within both orders have been evolving independently from humans for 80 million years (rodents) or 30 million years (Old World monkeys). This is an enormous amount of time for changes to emerge in each lineage, even between *Rattus* and *Mus* genera. Consider the differences that have emerged between humans and our closest living relatives, chimpanzees, since our lineages diverged some 6 million years ago! Third, our understanding of somatosensory processing comes from animals reared in a highly deprived laboratory environment, where the behavioral and sensory repertoires are limited. As a result, both sensory processing and motor control in laboratory-reared animals may be different from that of their naturally reared counterparts.

As aptly argued by Rosenblueth and Wiener (Rosenblueth and

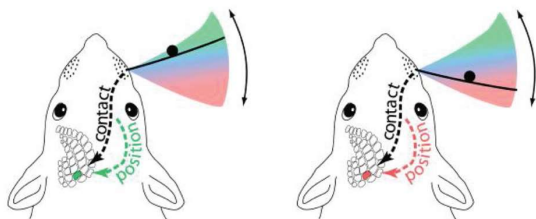


Fig. 9. Object localization during active touch. Rats and mice scan their whiskers across regions near the face to localize objects in the azimuthal plane. The location of an object (black circle) within the region covered by a whisk cycle (pink-to-green gradient) can be determined by combining neural signals for whisker self-motion and whisker-object contact. These signals are encoded throughout the ascending somatosensory system (dashed lines). Modified from Mehta et al. (2007).

Wiener, 1945) "The best material model of a cat is another, or preferably the same cat". While humans cannot be used to understand a number of aspects of the human somatosensory system, we should keep in mind that there is no perfect animal model for the human nervous system. Rather, different models are better suited to address particular aspects of nervous system organization and function than others. The macaque monkey with its glabrous hand and opposable thumb is a good model for understanding the neural control of the human hand. Active sensing is more easily studied in mice and rats than in macaques, and the tools available in mice and rats to uncover fundamental cellular interactions within somatosensory circuits makes them very good models as well. However, whisker somatosensation is not a perfect model of manual somatosensation. Even macaque models of human hand use are limited, since macaques do not naturally engage in tool use in the wild. Other primates, such as capuchin monkeys, do, which makes them more appropriate models for understanding the neural basis of tool use. Only by taking a broad, comparative approach using multiple species can we arrive at a comprehensive understanding of our own species.

9. Open questions

While much has been revealed about somatosensation through studies using the macaque hand and mouse and rat whisker systems, fundamental questions remain.

- **Homolog of area 3a in mice and rats.** In macaque monkeys, proprioceptive signals – driven primarily by muscle- and tendon-associated nerve fibers – converge onto Brodmann's area 3a, the first cortical recipient of proprioceptive signals. Whether the somatosensory cortex of mice and rats has a homologue of area 3a is unknown.
- **Homolog of PPC in mice and rats.** The difference in size, number of cortical fields, and the proposed function of PPC in mice and rats versus macaque monkeys (and primates in general) is notable. While PPC is implicated in macaque somatosensation, it is not clear if any of the cortex termed PPC in mice and rats is homologous or even analogous to PPC in monkeys.
- **Function of identified mechanoreceptor types in the whisker system.** In macaque monkeys, the relationship between mechanoreceptor types and functional properties is well established (SA1 fibers innervate Merkel cells, RA fibers innervate Meissner corpuscles, etc.). The innervation of the follicle remains to be characterized at that level of detail.
- **Active touch in primates.** While naturalistic sensory exploration is increasingly being studied in rats and mice, enabled by computer vision-mediated whisker tracking and models of whisker biomechanics, almost nothing is known about active touch in any primate. Whether the insights that have been gleaned about tactile coding from passive delivery of tactile stimuli will generalize to more naturalistic contexts remains to be determined.
- **Stereognosis.** As sketched out above, stereognosis – the ability to discern the three-dimensional structure of an object based on sensory signals from the hand – implies the integration of tactile and proprioceptive signals. The nature of this integration is almost completely unknown.

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Appendix A. The Peer Review Overview and Supplementary data

The Peer Review Overview and Supplementary data associated with

this article can be found in the online version, at doi:<https://doi.org/10.1016/j.pneurobio.2021.102008>.

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