Cortical Control of Whisker Movement

Carl C.H. Petersen

Laboratory of Sensory Processing, Brain Mind Institute, Faculty of Life Sciences, École Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland; email: carl.petersen@epfl.ch

Annu. Rev. Neurosci. 2014. 37:183–203

First published online as a Review in Advance on May 9, 2014

The *Annual Review of Neuroscience* is online at neuro.annualreviews.org

This article's doi: 10.1146/annurev-neuro-062012-170344

Keywords

motor cortex, somatosensory cortex, whisker motor control, neural circuits

Abstract

Facial muscles drive whisker movements, which are important for active tactile sensory perception in mice and rats. These whisker muscles are innervated by cholinergic motor neurons located in the lateral facial nucleus. The whisker motor neurons receive synaptic inputs from premotor neurons, which are located within the brain stem, the midbrain, and the neocortex. Complex, distributed neural circuits therefore regulate whisker movement during behavior. This review focuses specifically on cortical whisker motor control. The whisker primary motor cortex (M1) strongly innervates brain stem reticular nuclei containing whisker premotor neurons, which might form a central pattern generator for rhythmic whisker protraction. In a parallel analogous pathway, the whisker primary somatosensory cortex (S1) strongly projects to the brain stem spinal trigeminal interpolaris nucleus, which contains whisker premotor neurons innervating muscles for whisker retraction. These anatomical pathways may play important functional roles, since stimulation of M1 drives exploratory rhythmic whisking, whereas stimulation of S1 drives whisker retraction.

Contents

INTRODUCTION

Mice and rats use their whiskers extensively to gather tactile sensory information about their immediate environment. The whiskers are typically moved backward and forward at high frequencies during exploratory behavior. As a moving whisker encounters an object, it bends and exerts forces within the whisker follicle. These mechanical forces are thought to open stretch-activated ion channels driving action potential firing in whisker sensory neurons. Self-generated movements of the whiskers, driven by the animal's own muscles, are therefore responsible for an important component of sensory input. Conversely, sensory input from whisker-object contacts alters whisker movements (Mitchinson et al. 2007, Grant et al. 2009, Crochet et al. 2011), presumably to optimize the quality of incoming sensory information. Interactions between sensory and motor components of the whisker system are therefore prominent.

The primary whisker sensory neurons have cell bodies in the trigeminal ganglion, and they innervate the principal trigeminal nucleus and the spinal trigeminal nuclei. These brain stem nuclei in turn send whisker sensory information to various downstream pathways, including the trigemino-thalamo-cortical (Brecht 2007, Petersen 2007, Feldmeyer et al. 2013); trigemino-tectal/-collicular (Steindler 1985, Cohen et al. 2008); trigemino-facial (Nguyen & Kleinfeld 2005); and trigemino-pontine/-olivary/-cerebellar pathways (Swenson et al. 1984, Molinari et al. 1996, Yatim et al. 1996). Sensory signals from the whiskers are thus processed in a large number of interconnected brain areas, which together underlie whisker sensorimotor coordination and sensory perception. Because the tactile whisker sensory signals are often actively gathered, they relate closely to self-generated whisker and head movements. To derive a self-consistent percept of the tactile environment, rats and mice must therefore integrate sensory information and motor commands. The neocortex is a prominent region for sensorimotor integration. Recent reviews cover cortical processing of sensory signals from whiskers (Brecht 2007, Petersen 2007, Diamond et al. 2008, Bosman et al. 2011, Feldmeyer et al. 2013). This review focuses on the cortical control of whisker movement.

The cortex has long been known to play an important role in motor control, beginning with the pioneering experiments of Fritsch & Hitzig (1870). These first investigations of movements evoked by electrical stimulation of the cortex in dogs were later extended to monkeys by Ferrier (1874) and Sherrington (1906). The important experiments of Penfield & Boldrey (1937) defined motor maps of awake human patients undergoing neurosurgical interventions, finding an organization broadly similar to that observed in the previous animal experiments. Electrical

stimulation of a wide variety of brain regions evoked diverse sensations and movements (Penfield & Boldrey 1937). A region anterior to the central sulcus evoked robust movements, defining the primary motor cortex (M1). Stimulation of medial M1 evoked primarily lower limb movements, whereas stimulation of more lateral M1 evoked upper limb movements and, further laterally, head and face movements. The maps of evoked movements suggested a motor homunculus, whereby movements of nearby body parts were controlled by nearby regions of the cortex, mirroring the somatotopic organization of the primary somatosensory cortex (S1). However, even in the initial report (Penfield & Boldrey 1937) it was clear that movements could also be evoked from stimulation of other cortical areas, such as by stimulating the somatosensory cortex lying posterior to the central sulcus. More recent experiments in monkeys confirm that motor-related neurons are widely distributed in the monkey brain, with transneuronal retrogradely labeled neurons from muscles being found in both M1 and S1 (Rathelot & Strick 2006). This study agrees with data from monkeys showing that neurons in both M1 and S1 project to the spinal cord (Coulter & Jones 1977). Together these data raise questions about the definition of M1. Further questions about the overall organization of motor maps in the monkey cortex have been raised by the work of Graziano and colleagues (Graziano et al. 2002, Cooke et al. 2003, Graziano & Aflalo 2007). Rather than the motor cortex containing a map of muscles as implied by the motor homunculus, Graziano suggests that the motor cortex is divided into areas controlling different types of behaviors. Through applying intracortical microstimulation for long durations compatible with the timescale of behavior, Graziano and colleagues found that complex sequences of movements were evoked by stimulating localized regions of the frontal and parietal cortices. Stimulation of specific cortical regions evoked reproducible behaviors, including climbing, feeding, defensive movements, and reaching to defined locations in space. Whether motor maps in monkeys are organized as a homunculus, or rather in terms of behavioral repertoire, remains controversial. As one thinks about the general role of the cortex in controlling movement, it may also be useful to consider an evolutionary perspective. The neocortex, as its name implies, was added at a late time in the evolution of the brain. In terms of motor control, the cortex therefore may serve as a high-order sensorimotor circuit interacting with a series of lower-level sensorimotor circuits in basal ganglia, the midbrain, and the brain stem, all of which are evolutionarily older. Such considerations suggest that cortical activity is likely to affect motor output through interactions with many different subcortical pathways.

Investigation into the detailed mechanisms underlying cortical motor control has begun in rats and mice. Early experiments used intracortical microstimulation to evoke movements, which were only qualitatively evaluated. Similar to the results in humans and monkeys, in rodents, movements could be evoked by stimulating a large fraction of the neocortex, including M1 and S1 (Hall & Lindholm 1974, Donoghue & Wise 1982, Neafsey et al. 1986). Motor maps based on surface stimulation (Woolsey 1958) and intracortical microstimulation (Hall & Lindholm 1974, Donoghue & Wise 1982, Gioanni & Lamarche 1985, Neafsey et al. 1986, Miyashita et al. 1994, Brecht et al. 2004a) reveal forelimb and hindlimb representations bordering (and overlapping) with their S1 representations. Head, whisker, and eye movements map to more anterior and medial locations. Although these motor maps are reproducible, the experimental methods suffer from numerous important limitations. Intracortical microstimulation affects neurons near the electrode but also stimulates axons of passage, limiting the spatial resolution of these motor-mapping experiments and reducing the possibility for causal interpretations of the data. New stimulation techniques are therefore desirable. In addition, most motor-mapping experiments have been carried out in lightly anesthetized animals, a condition designed to minimize movement and sensation. The overall brain state may influence how neural circuits in the neocortex connect to motor output (Tandon et al. 2008), and thus motor maps in awake animals may differ substantially

from those obtained under anesthesia. Quantitative analysis of movements evoked by precise stimulation in awake animals is therefore necessary. Powerful molecular and genetic tools have now been developed for investigating the mouse brain, raising interest in defining cortical circuits for motor control in the mouse. Recent advances in optogenetics (Nagel et al. 2003, Boyden et al. 2005, Zhang et al. 2007, Chow et al. 2010, Zhang et al. 2011) have helped improve the specificity of stimulation, which is useful for defining more precise neocortical motor maps (Matyas et al. 2010, Harrison et al. 2012). Furthermore, new transsynaptic viral methods can now label and genetically manipulate specifically connected synaptic circuits (Wickersham et al. 2007, Osakada et al. 2011). These new methods have recently been applied to the mouse whisker motor system, providing new insights reviewed here in the context of existing knowledge.

MUSCLES DRIVING WHISKER MOVEMENT

The whiskers are moved back and forth through large angles (~90°) and at high frequencies (~5–20 Hz) during active exploratory whisking (**Figure 1*a***). Although it is important to note that the whiskers can move in complex multidimensional ways (Knutsen et al. 2008), a simple one-dimensional variable, the whisker angle, accounts for much of the overall movement of whiskers. Most of the time, the whiskers all move bilaterally in synchrony, but whiskers can also move independently (Sachdev et al. 2002), which occurs extensively during whisker-object contact. The whisker can be thought of as pivoting around its insertion point in the mystacial pad. Intrinsic muscles within the mystacial pad (Dörfl 1982, Hill et al. 2008) attach superficially on one whisker and form a sling around the base (deep in the pad) of the immediately anterior whisker follicle. Each whisker is served by its own intrinsic muscle. Contraction of an intrinsic muscle causes the base of the whisker follicle (located deep in the mystical pad) to move toward the posterior. This contraction rotates the external part of the whisker forward, the pad insertion point acting as the pivot. Intrinsic muscles therefore drive whisker protraction (**Figure 1*b***). Extrinsic muscles nasolabialis and maxillolabialis act on the superficial part of the whisker pad attaching to external anchor points posteriorly. Contraction of these extrinsic muscles drives whisker retraction by translating the whole whisker pad and posteriorly rotating individual follicles (**Figure 1*b***). Electromyograph (EMG) recordings have defined the timing of contraction of different whisker muscles during whisking and have found that the intrinsic muscles are active during whisker protraction and that the extrinsic muscles nasolabialis and maxillolabialis are often active during whisker retraction (Hill et al. 2008, Moore et al. 2013). In addition, several other muscles acting on the whiskers and mystacial pad have been described (Hill et al. 2008, Haidarliu et al. 2012). The whisker muscles are unusual in at least two ways: First, the intrinsic whisker muscles are distinguished from skeletal muscles by predominance of a fast-contracting, fast-fatigable muscle type (Jin et al. 2004); and, second, the whisker muscles do not appear to have spindles and thus there is no direct proprioceptive feedback (Rice et al. 1997).

WHISKER MOTOR NEURONS IN THE FACIAL NUCLEUS

Both the intrinsic and extrinsic whisker muscles are innervated by the facial nerve, with the cell bodies of the cholinergic motor neurons lying in the lateral facial nucleus (**Figure 2*a***). Retrograde labeling from injections into whisker muscles has shown that the motor neurons innervating the intrinsic muscles are located more ventrally within the lateral facial nucleus, whereas the motor neurons that innervate the extrinsic muscle are located more dorsally within the lateral facial nucleus (Takatoh et al. 2013). The lateral facial nucleus therefore appears to have a well-ordered

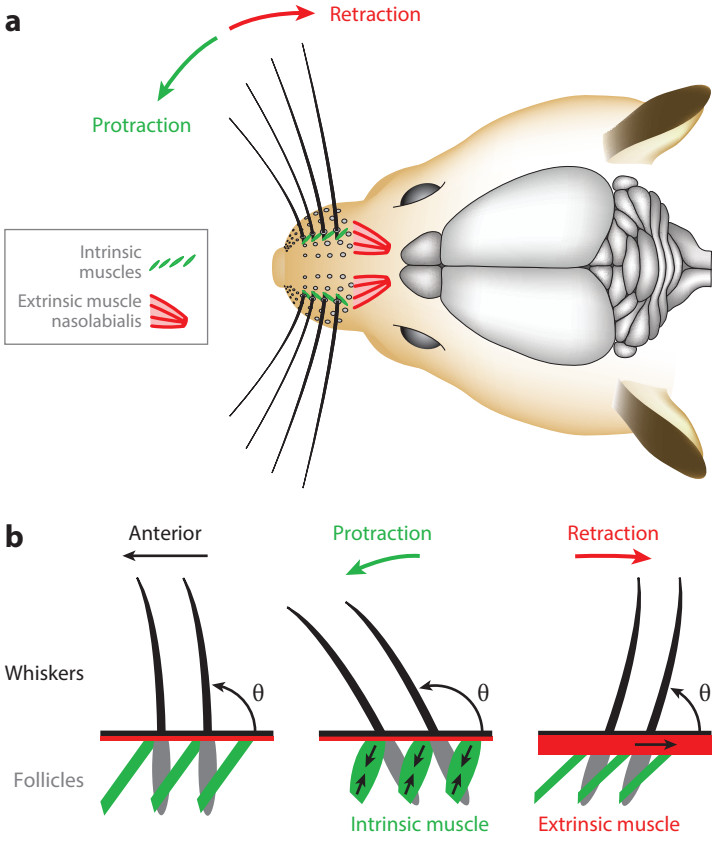
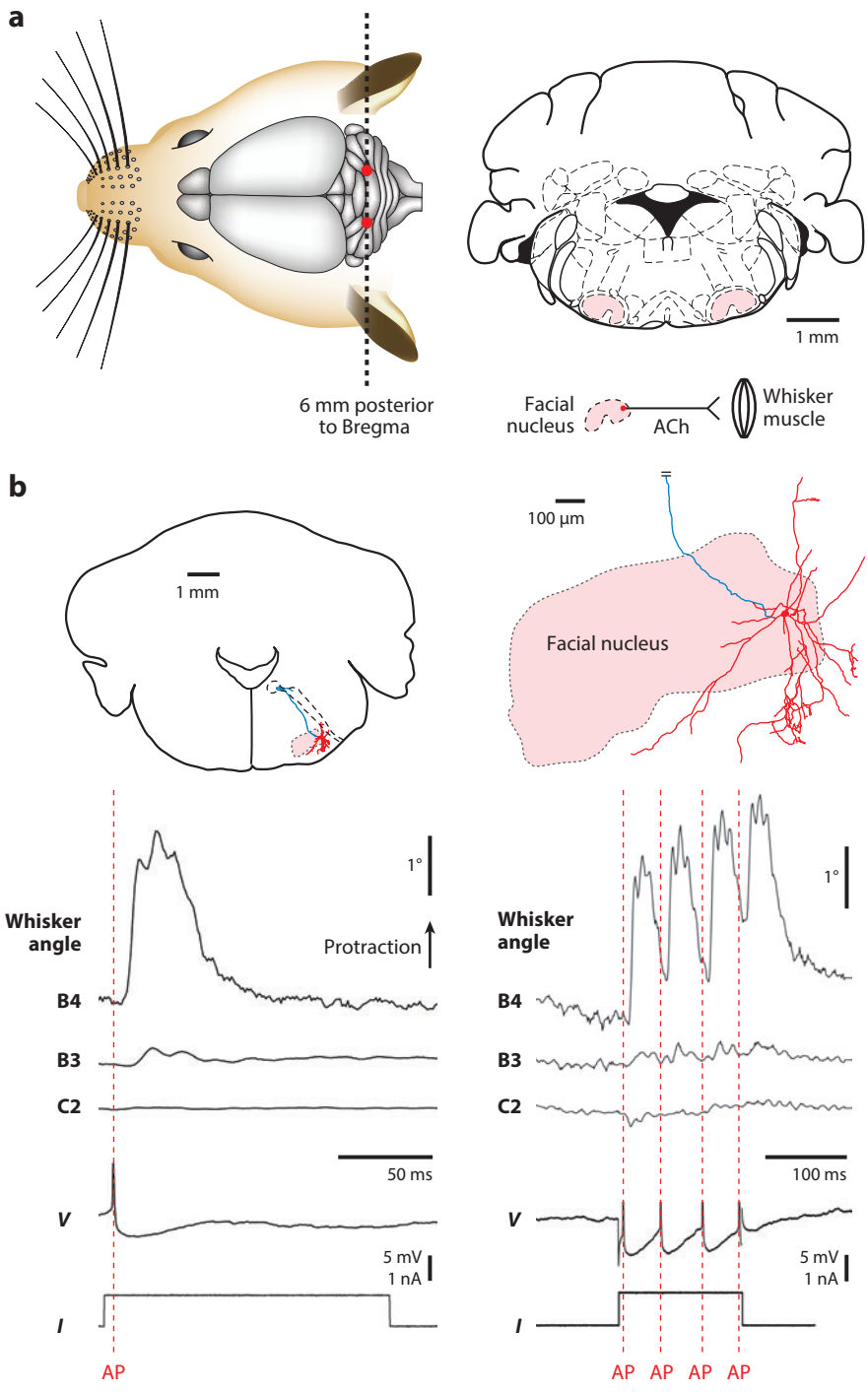


Figure 1

Muscles controlling whisker movement. (*a*) The whiskers on the snout of mice and rats are arranged in a stereotypical highly ordered manner in the mystacial pad. Although whiskers have several degrees of freedom, the most important whisker movement is one-dimensional: forward (protraction) and backward (retraction). (*b*) The whisker follicle inserts into the pad, and movements of the whisker are generated by two types of muscle (*left*). Intrinsic muscle (*green*) forms a sling around the deep base of one whisker follicle and attaches to the upper part of the immediately posterior whisker follicle. Contraction of intrinsic muscle pulls the base of the whisker posteriorly, generating rotation of the whisker such that it protracts (*middle*). Extrinsic muscles (*red*) nasolabialis and maxillolabialis attach posteriorly to bone and act superficially on the whisker pad. Contraction of these extrinsic muscles causes whisker retraction by pulling the whisker pad backward and also causing backward rotation of whiskers (*right*).

map, with ventral protraction motor neurons innervating intrinsic whisker muscles and dorsal retraction motor neurons innervating extrinsic whisker muscles.

In an elegant series of experiments, Herfst & Brecht (2008) made whole-cell membrane potential recordings from whisker motor neurons in the lateral facial nucleus of the anesthetized rat. Injection of depolarizing current triggered action potential firing in the single neuron being recorded, which evoked reliable whisker movements with short latency (**Figure 2*b***). Most whisker motor neurons evoked protraction of only a single whisker, presumably through contraction of the intrinsic muscle attached to an individual whisker. A smaller fraction of neurons recorded in the facial nucleus evoked whisker retraction, typically involving multiple whiskers and likely resulting from contraction of extrinsic muscle acting on the whole whisker pad. Single action potentials in different motor neurons of the facial nucleus evoked whisker movements with very


a
6 mm posterior
to Bregma
1 mm
Facial
nucleus
ACh
Whisker
muscle
b
1 mm
100 µm
Facial nucleus
Whisker
angle
1°
Protraction
B4
B3
C2
50 ms
V
5 mV
1 nA
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Whisker
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different amplitudes (ranging from −0.6° to 5.6°), but trial-to-trial variability for an individual motor neuron was low. Latencies from action potential to onset of whisker movement were short (ranging from 4.0 to 11.1 ms). The measurements of Herfst & Brecht (2008) therefore define a fast and reliable pathway for controlling whisker movements by motor neurons located in the lateral facial nucleus.

The firing patterns of whisker motor neurons during behavior are unknown, and future experiments are needed to measure their activity directly during exploratory whisking. It will be of great interest to examine the relative timing of action potential firing in different whisker motor neurons during the whisking cycle. Furthermore, the recruitment patterns of different motor neurons under different behavioral circumstances will be important to study because the whiskers are moved in different ways depending on task requirements. A first step toward such data was made by Cramer & Keller (2006), who recorded from whisker motor neurons during fictive whisking driven by stimulation of whisker M1. Their data suggest that phasic action potential firing of motor neurons occurs shortly before each whisker protraction and that larger-amplitude movements are associated with increases in firing rate of individual motor neurons, as well as with recruitment of additional motor neurons.

WHISKER PREMOTOR NEURONS

The whisker motor neurons located in the lateral facial nucleus therefore directly drive whisker movement. These motor neurons receive synaptic inputs distributed across their somatodendritic compartments, which determine when action potentials are fired. To understand the mechanisms controlling whisker movement, we therefore need to learn about the whisker premotor neurons, which innervate the whisker motor neurons. Hattox et al. (2002) injected the retrograde anatomical tracer cholera toxin subunit B into the lateral facial nucleus and found retrogradely labeled cell bodies in a large number of brain areas including the brain stem reticular formation, the nucleus ambiguus, the pedunculopontine tegmental nucleus, the Kölliker-Fuse nucleus, the parabrachial nuclei, the superior colliculus, the red nucleus, the periaqueductal gray, the mesencephalon, the pons, and several nuclei involved in oculomotor behaviors. However, the specificity of classical retrograde labeling methods is limited. Retrograde transsynaptic viral methods based on modified rabies virus have recently been developed, which promise to reveal specific monosynaptic neural circuits (Wickersham et al. 2007). Rabies virus is well known to spread across neurons in the nervous system, apparently crossing synapses in an exclusively retrograde manner (Ugolini 1995, Kelly & Strick 2000). However, intact rabies virus will replicate and spread sequentially across

Figure 2

Whisker motor neurons are located in the lateral facial nucleus. (*a*) Schematic drawing to indicate the location of the facial nucleus, ~6 mm posterior to Bregma in the mouse (*left*). A schematic drawing of a coronal section of the mouse brain (Paxinos & Franklin 2001) showing the ventral location of the facial nucleus (*right*). The lateral facial nucleus contains the cholinergic motor neurons controlling whisker movement. (*b*) Whole-cell membrane potential recording of an anatomically identified neuron in the lateral facial nucleus in an anesthetized rat (*above*; axon in *blue*, dendrites and soma in *red*) (Herfst & Brecht 2008). Injection of depolarizing current through the recording electrode evoked a single action potential (AP) (*lower left*) or a train of four action potentials (*lower right*). Each action potential in the motor neuron drove a brief forward protraction of the B4 whisker but had little impact on other nearby whiskers B3 and C2. Panel *a* (*right*) is modified from Paxinos & Franklin (2001) and reprinted with permission from Academic Press. Panel *b* is modified from Herfst & Brecht (2008) and reprinted with permission from the American Physiological Society. Other abbreviation: ACh, acetylcholine.

many synapses, which complicates the interpretation of data. A critical step to map monosynaptically connected neurons is thus to restrict the spread of rabies virus so that it can cross only one synapse. One gene in the rabies virus genome encodes for the glycoprotein G, which is essential for infection. Rabies virus lacking G (ΔG-rabies) can then be transcomplemented by expression of rabies G in specific cell types, from which the virus can then spread retrogradely (Wickersham et al. 2007). Because the spreading ΔG-rabies virus does not encode G in its genome, it cannot make its glycoprotein in the upstream infected neurons, and therefore it cannot spread beyond the first-order presynaptic neurons (Wickersham et al. 2007). Replacing the gene encoding G by GFP (ΔG-GFP rabies) allows investigators to visualize infected neurons using fluorescence imaging. Such monosynaptic rabies-based circuit-mapping methods have now been applied to study the organization of premotor neurons in the mouse spinal cord (Stepien et al. 2010) and in whisker premotor neurons (Takatoh et al. 2013).

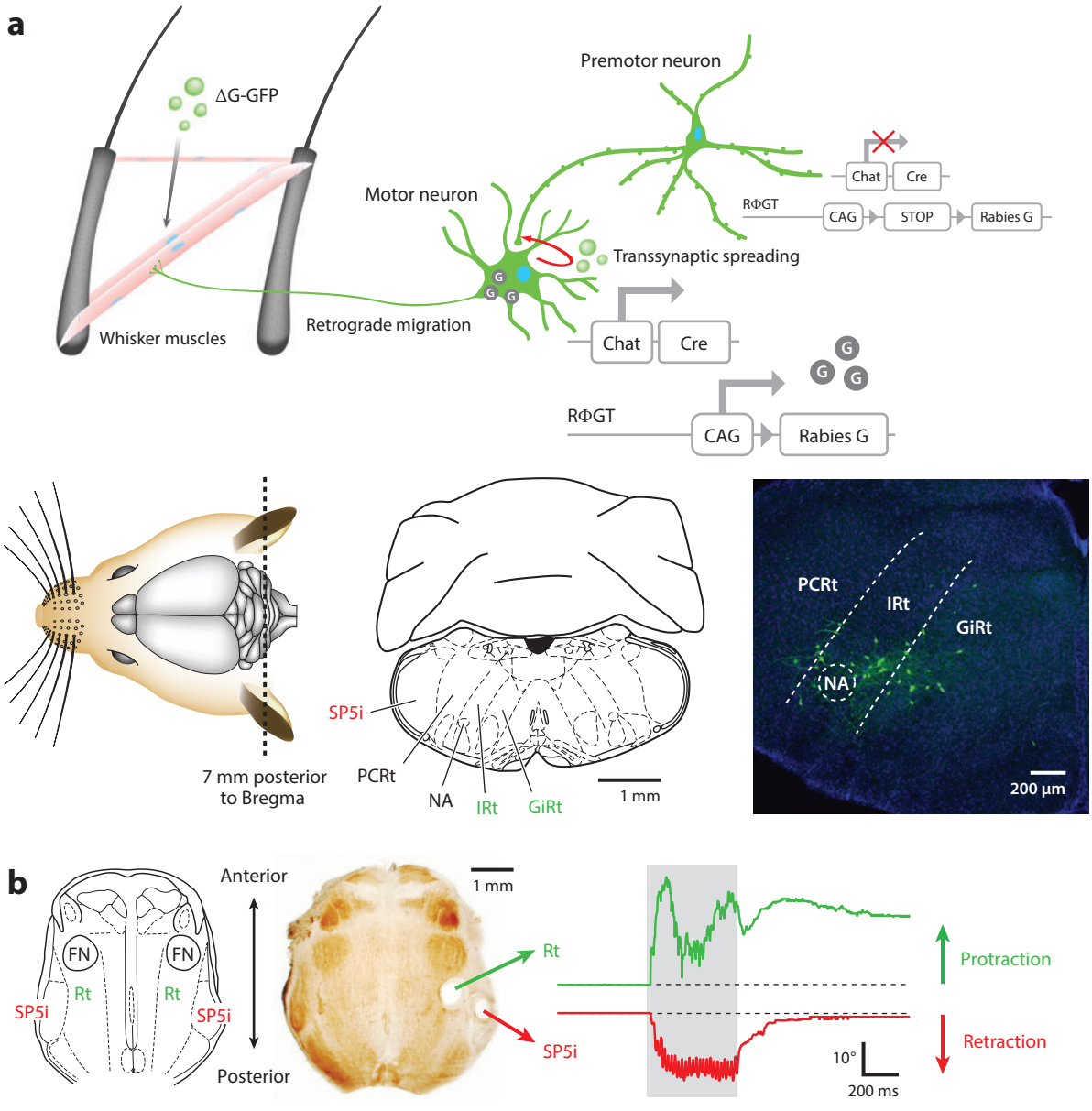
Monosynaptic rabies virus tracing from intrinsic and extrinsic whisker muscles has provided a comprehensive map of whisker premotor neurons (**Figure 3*a***). Takatoh et al. (2013) injected ΔG-GFP rabies into whisker muscles of transgenic mice expressing rabies G in the cholinergic motor neurons. Motor neurons infected with ΔG-GFP rabies could therefore complement the G-deficient rabies with rabies G expressed transgenically from the mouse genome. The rabies thus spread one synapse retrogradely to label premotor neurons with high GFP levels. The locations of whisker premotor neurons found with monosynaptic rabies (Takatoh et al. 2013) generally agreed with previous retrograde labeling (Hattox et al. 2002). Whisker premotor neurons were prominently labeled in the dorsal medullary reticular nucleus of the brain stem, the intermediate reticular nucleus of the brain stem (IRt, **Figure 3*a***), the gigantocellular reticular nucleus of the brain stem (GiRt, **Figure 3*a***), the Kölliker-Fuse nucleus, the pre-Bötzinger and Bötzinger complexes, the rostral part of the lateral paragigantocellular nucleus, the rostral part of the spinal trigeminal interpolaris nucleus (SP5i), the spinal trigeminal oralis nucleus, the superior colliculus, and the mesencephalic reticular nucleus. The rabies-based tracing showed some differences in premotor circuits for intrinsic and extrinsic muscles. Motor neurons controlling intrinsic muscles

Figure 3

Whisker premotor neurons. (*a*) Transsynaptic modified rabies virus can be used to label premotor neurons (Takatoh et al. 2013) (*above*). The glycoprotein G was replaced by GFP in the rabies genome, making ΔG-GFP rabies virus. This virus was injected into whisker muscles to infect motor neurons. The motor neurons of the transgenic mouse specifically express rabies G, generated by Cre recombinase expressed in cholinergic neurons (Chat-Cre) acting on loxP-stop-loxP elements to drive expression of rabies G from the RΦGT transgene. The transgenic rabies G transcomplements the ΔG-GFP rabies virus in whisker motor neurons, making a new infectious virus that can retrogradely specifically infect the presynaptic whisker premotor neurons. Only monosynaptically connected neurons are labeled because the viral genome remains G-deficient and therefore cannot propagate. Infected neurons express GFP and can therefore be visualized through fluorescence microscopy. Premotor neurons expressing GFP are found in many brain locations including the brain stem, the midbrain, and the neocortex. When the rabies virus is injected into intrinsic muscle, many premotor neurons are labeled in brain stem reticular (Rt) nuclei. These Rt nuclei are located posterior to the facial nucleus. The schematic drawings indicate a plane 7 mm posterior to Bregma (*lower left*), which contains brain stem Rt nuclei, shown in the coronal section (*lower middle*) (Paxinos & Franklin 2001). GFP-labeled whisker premotor neurons are evident in intermediate reticular nucleus (IRt) and gigantocellularis (GiRt) (*lower right*) (Takatoh et al. 2013). (*b*) A schematic drawing (*left*) of a horizontal section of the brain stem stained with cytochrome oxidase (*middle*). The section includes the facial nucleus (FN), the Rt nuclei, and the spinal trigeminal interpolaris nucleus (SP5i). The lesion sites, labeled Rt and SP5i, show the locations that had previously been electrically stimulated in the awake head-restrained mouse. Stimulation of the Rt nuclei drove whisker protraction (*green*), whereas stimulation of SP5i drove whisker retraction (*red*) (*right*). Panel *a* (*upper*, *lower right*) is reprinted from Takatoh et al. (2013) with permission from Cell Press. Panel *a* (*lower middle*) is modified from Paxinos & Franklin (2001) and reprinted with permission from Academic Press. Panel *b* is modified from Matyas et al. (2010) and reprinted with permission from the American Association for the Advancement of Science. Other abbreviations: GFP, green fluorescent protein; NA, nucleus ambiguus; PCRt, parvicellular reticular nucleus.

were more strongly innervated by IRt. Motor neurons controlling extrinsic muscle, however, were more strongly innervated by the rostral part of SP5i. In agreement with this spatial difference in the location of premotor neurons for intrinsic and extrinsic muscles, microstimulation of the brain stem reticular nuclei (Rt) evokes whisker protraction presumably by contracting intrinsic whisker muscles, whereas microstimulation of SP5i evokes whisker retraction, presumably by contracting extrinsic muscles (**Figure 3*b***) (Matyas et al. 2010).

Further investigations into the specific neural circuits controlling intrinsic and extrinsic muscles will be of great interest. A key goal is to record the activity of defined whisker premotor neurons during different whisker behaviors. Future experiments could also utilize rabies virus expressing



channelrhodopsin-2 (ChR2) (Boyden et al. 2005) to stimulate specific premotor circuits and measure the evoked movements. Of equal importance would be optogenetic inactivation experiments to investigate the role of the different premotor circuits for specific aspects of whisker behavior.

Recently, Moore et al. (2013) made lesions at various locations in the whisker-related brain stem, finding that a ventral region of the intermediate reticular nucleus of the brain stem (vIRt) lying medial to the nucleus ambiguus was essential for whisking. Furthermore, action potential firing of neurons near vIRt was phase-locked to whisker protraction, and whisking could be induced by pharmacological stimulation of neurons near vIRt. Whisking premotor neurons in vIRt might therefore form a central pattern generator driving rhythmic whisker protraction (Moore et al. 2013).

In addition to the complex distribution of premotor neurons in the brain stem and midbrain, monosynaptic rabies virus injected in whisker muscles also labels a very sparse population of layer-5 pyramidal neurons in the neocortex, with a few premotor neurons apparently residing in both M1 and S1 (see Takatoh et al. 2013, supplemental figure 1). Some neocortical neurons therefore appear to be whisker premotor neurons, directly innervating whisker motor neurons.

INNERVATION OF BRAIN STEM BY THE SENSORIMOTOR CORTEX

Injection of anterograde tracers into M1 and S1 reveals the direct long-range axonal projections from glutamatergic pyramidal neurons in these cortical areas (White & DeAmicis 1977, Wise & Jones 1977, Porter & White 1983, Welker et al. 1988, Miyashita et al. 1994, Grinevich et al. 2005, Aronoff et al. 2010, Matyas et al. 2010, Mao et al. 2011). Both M1 and S1 project to a wide variety of brain regions that could directly or indirectly cause whisker movement, including the striatum, the thalamus, the superior colliculus, the pons, the red nucleus, and various brain stem nuclei. Here, we focus on the extensive cortical innervation of the brain stem, which is among the more direct pathways in which the cortex can drive whisker movement. However, it is important to note that the cortex can affect whisker movement using many alternative routes, notably including pathways via the superior colliculus (Hemelt & Keller 2008) and cerebellar circuits (Legg et al. 1989).

Injection of lentivirus-expressing GFP into whisker M1 served as a viral-based anterograde tracer, labeling axonal output to different brain stem nuclei (Grinevich et al. 2005). Grinevich et al. (2005) found some direct innervation of the lateral facial nucleus from M1 (**Figure 4*a*,*b***), in agreement with the monosynaptic rabies experiments indicating a few premotor neurons in the sensorimotor cortex (Takatoh et al. 2013). However, the most prominent axonal projection to the brain stem from M1 is the strong innervation of the Rt nuclei, including the dorsal medullary reticular nucleus (MDd), the IRt, and the GiRt (**Figure 4*a*,*c***) (Grinevich et al. 2005, Matyas et al. 2010). Monosynaptic rabies tracing from whisker motor neurons retrogradely labeled these brain stem Rt nuclei, so these cortical projections from M1 could directly innervate whisker premotor neurons. In particular, M1 axons innervate vIRt, the region proposed to be the whisking central pattern generator (Moore et al. 2013). Among other possible pathways, M1 might thus drive whisker movement through direct innervation of motor neurons in the facial nucleus and through premotor neurons located in the brain stem reticular nuclei.

Analysis of the axonal projections from whisker S1 shows a pattern of subcortical connectivity very similar to that found from whisker M1 (Matyas et al. 2010). S1 and M1 project to neighboring regions of the striatum, the thalamus, the superior colliculus, the pons, the red nucleus, and the brain stem (Matyas et al. 2010). In the brain stem, S1 strongly innervates SP5i (Matyas et al. 2010). According to monosynaptic rabies tracing, SP5i is supposed to contain whisker premotor neurons preferentially innervating extrinsic whisker muscles (Takatoh et al. 2013). The axonal projection of S1 neurons to the brain stem SP5i could therefore drive whisker retraction via extrinsic whisker muscles.

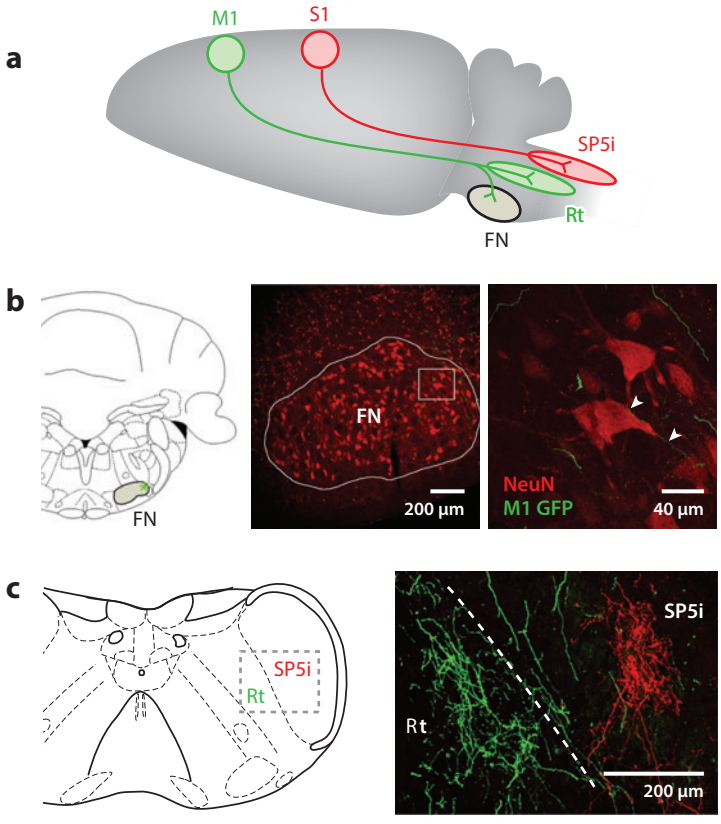


Figure 4

Innervation of the brain stem by the sensorimotor cortex. (*a*) A schematic drawing showing axonal projections from M1 (*green*) innervating the facial nucleus (FN) and brain stem reticular (Rt) nuclei. Axonal projections from S1 (*red*) innervate spinal trigeminal interpolaris (SP5i). (*b*) Lentivirus-expressing GFP was injected into M1, and some labeled axons (*green*) were found in the FN with neurons stained for NeuN (*red*) (Grinevich et al. 2005, an M1 axon in close proximity to a FN cell is highlighted by *arrowheads*). (*c*) Anterograde tracing of axons from M1 (*green*) and S1 (*red*) reveals dense axonal labeling in the brain stem. M1 strongly innervates Rt, whereas S1 strongly innervates SP5i (Matyas et al. 2010). Panels *a* and *c* are modified from Matyas et al. (2010) and reprinted with permission from the American Association for the Advancement of Science. Panel *b* is modified from Grinevich et al. (2005) and reprinted with permission from the Society for Neuroscience.

WHISKER MOVEMENTS EVOKED BY STIMULATION OF THE SENSORIMOTOR CORTEX

The similarity of axonal projections from M1 and S1 to the brain stem suggests that they could equally drive whisker movement through their apparently parallel, analogous projections from M1 to Rt and from S1 to SP5i. Consistent with this hypothesis, stimulation of either M1 or S1 was found to evoke whisker movements (Matyas et al. 2010). Before stimulating, the sensorimotor neocortex was functionally mapped through voltage-sensitive dye imaging (Grinvald & Hildesheim 2004, Ferezou et al. 2007, Matyas et al. 2010). The C2 whisker representation in S1 was defined as the location of the earliest sensory response evoked by whisker deflection (**Figure 5*a***). Neurons in the C2 barrel column project directly to whisker M1 (Ferezou et al. 2007, Matyas et al. 2010, Mao et al. 2011). Whisker M1 therefore receives sensory input, and its location can thus also be

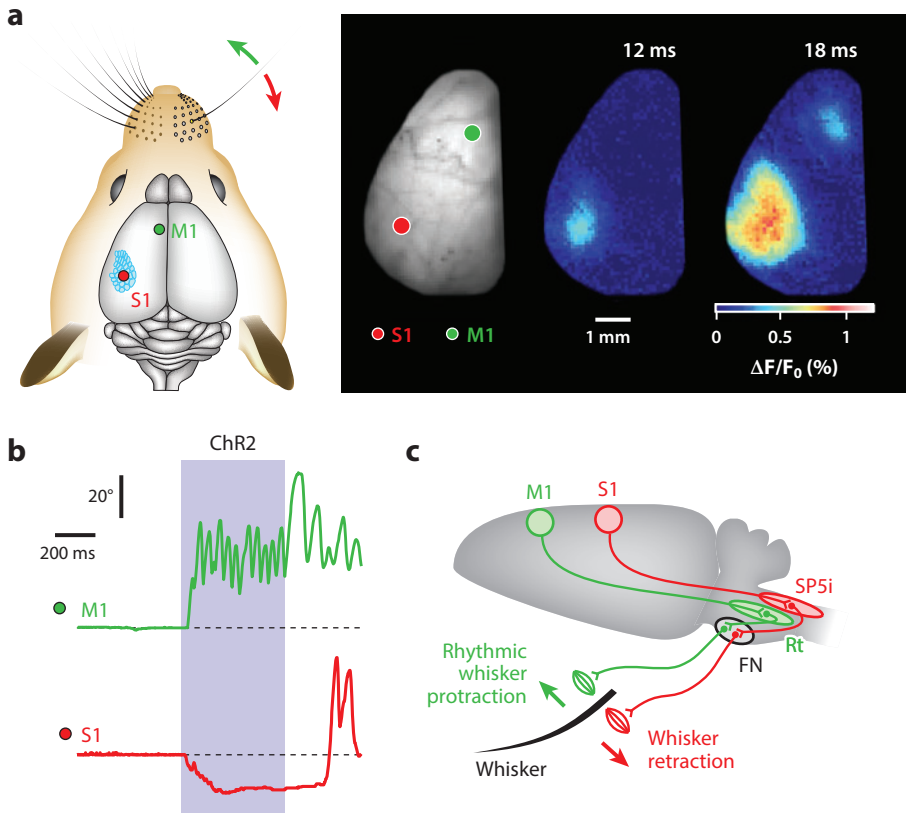


Figure 5

Whisker movements evoked by stimulating the sensorimotor cortex. (*a*) Functional localization of the sensory responses evoked by brief 1-ms deflection of the C2 whisker imaged using voltage-sensitive dye. At 12 ms after whisker deflection (*center right*) a localized depolarization reveals the location of the C2 whisker representation in S1. A few milliseconds later at 18 ms (*far right*), the depolarization has spread within S1 and a second localized hot spot of depolarization appears in the frontal cortex, identifying the location of whisker M1. (*b*) Optogenetic stimulation of M1 with channelrhodopsin-2 (ChR2) drives rhythmic whisker protraction (*green*, with S1 inactivated). Optogenetic stimulation of S1 drives whisker retraction (*red*, with M1 inactivated). (*c*) Schematic summary of the signaling pathway through which M1 and S1 might evoke whisker movements. M1 (*green*) projects to brain stem reticular (Rt) nuclei, exciting Rt premotor neurons, which evoke activity in protraction motor neurons of the facial nucleus (FN) driving contraction of intrinsic whisker muscles. Neural circuits within Rt nuclei may form a central pattern generator underlying rhythmic protraction. S1 (*red*) projects to the spinal trigeminal interpolaris nucleus (SP5i), exciting SP5i premotor neurons, which in turn would evoke activity in FN retraction motor neurons to drive contraction of extrinsic whisker muscles. All panels are modified from Matyas et al. (2010) and reproduced with permission from the American Association for the Advancement of Science.

functionally localized through voltage-sensitive dye imaging (Ferezou et al. 2007, Matyas et al. 2010). Approximately 6 ms after the initial depolarization in S1, a secondary localized hot spot of activity was found in the frontal cortex, defining the location of whisker M1 (**Figure 5*a***). Intracortical microstimulation was then targeted to the functionally identified regions of M1 and S1. To prevent complications induced by cortico-cortical signaling, S1 was inactivated when M1 was stimulated, and vice versa: M1 was inactivated when stimulating S1 (Matyas et al. 2010). These intracortical microstimulation experiments revealed that M1 drives rhythmic whisker protraction,

whereas S1 drives whisker retraction. Latencies for evoking movement were shorter for S1 (14.8 ± 2.8 ms) than for M1 (21.1 ± 5.8 ms) (Matyas et al. 2010). Optogenetic stimulation showed the same whisker motor map, S1 driving short-latency whisker retraction and M1 driving rhythmic whisker protraction (Matyas et al. 2010, Mateo et al. 2011) (**Figure 5*b***). These results are in good agreement with the anatomical connectivity of neural circuits described above. Activity in M1 neurons projecting to reticular nuclei in the brain stem may excite whisker premotor neurons (perhaps in vIRt), which in turn innervate whisker motor neurons in the facial nucleus that preferentially drive whisker protraction (**Figure 5*c***). On the other hand, activity in S1 neurons projecting to the brain stem may drive firing of premotor neurons in SP5i, which preferentially innervate retraction motor neurons (**Figure 5*c***). Future studies must directly test this hypothesis by applying the increasingly precise molecular methods that have been developed, such as rabies virus and optogenetic interventions. Different types of neocortical neurons will likely make different impacts on whisker movement. Action potential firing in some individual cortical neurons appears to evoke a measurable whisker movement, albeit with long latencies (Brecht et al. 2004b). It will therefore be important to study neocortical cell-type specificity in the context of connected neural circuits for motor control.

There is some uncertainty about the overall structure and function of whisker M1 (Brecht 2011). In the discussion above, whisker M1 is defined through its sensory map, as a localized hot spot of whisker-deflection evoked activity, which colocalizes with the axonal projection from S1 to M1. Deflection of different whiskers evokes somatotopically organized hot spots of activity in both S1 and M1 (Ferezou et al. 2007). Thus a well-defined sensory whisker map in M1 has been defined functionally using voltage-sensitive dye imaging (Ferezou et al. 2007) and anatomically through tracing of axonal projections from S1 to M1 (Mao et al. 2011). Intracortical microstimulation experiments suggest well-ordered whisker motor maps in M1 (Brecht et al. 2004a), and in future studies it will therefore be interesting to investigate if the sensory map in M1 aligns and colocalizes precisely with the motor map in M1. This proposed mapping is currently under debate; some studies suggest that the sensory map in M1 does not match the location of the motor map (Smith & Alloway 2013). Intracortical microstimulation studies also suggest that M1 might contain distinct whisker-related subregions, including a whisker retraction area that is supposed to be spatially separated from a rhythmic whisking area (Haiss & Schwarz 2005). However, Matyas et al. (2010) found that the whisker motor maps in M1 change dramatically upon inactivation of S1, the retraction area in M1 becoming a protraction area after S1 inactivation. M1 motor maps are therefore not trivial to interpret, owing to strong cortico-cortical connectivity. Currently, the simplest possibility is that there is only one whisker M1 region, which directly drives exploratory rhythmic whisker protraction and which can also indirectly drive whisker retraction via cortico-cortical connectivity to S1 (Matyas et al. 2010). Areas surrounding whisker M1 also appear to drive whisker protraction, suggesting an overall broad tuning of M1 (Matyas et al. 2010).

CORRELATION OF WHISKER MOVEMENT AND CORTICAL ACTIVITY IN M1 AND S1

So far we have established some possible neural circuits that allow activity in M1 and S1 to drive distinct whisker movements when these cortical regions are directly stimulated. However, to investigate possible physiological roles of these cortical brain regions with respect to whisker motor control, studies must record the activity of neurons in M1 and S1 and correlate their activity with whisker movements during behavior. The neocortex contains a large diversity of cell types, and one might anticipate that the most direct impact of cortical neurons upon whisker movement is via neurons projecting to the whisker motor regions of the brain stem. Unfortunately, measurements

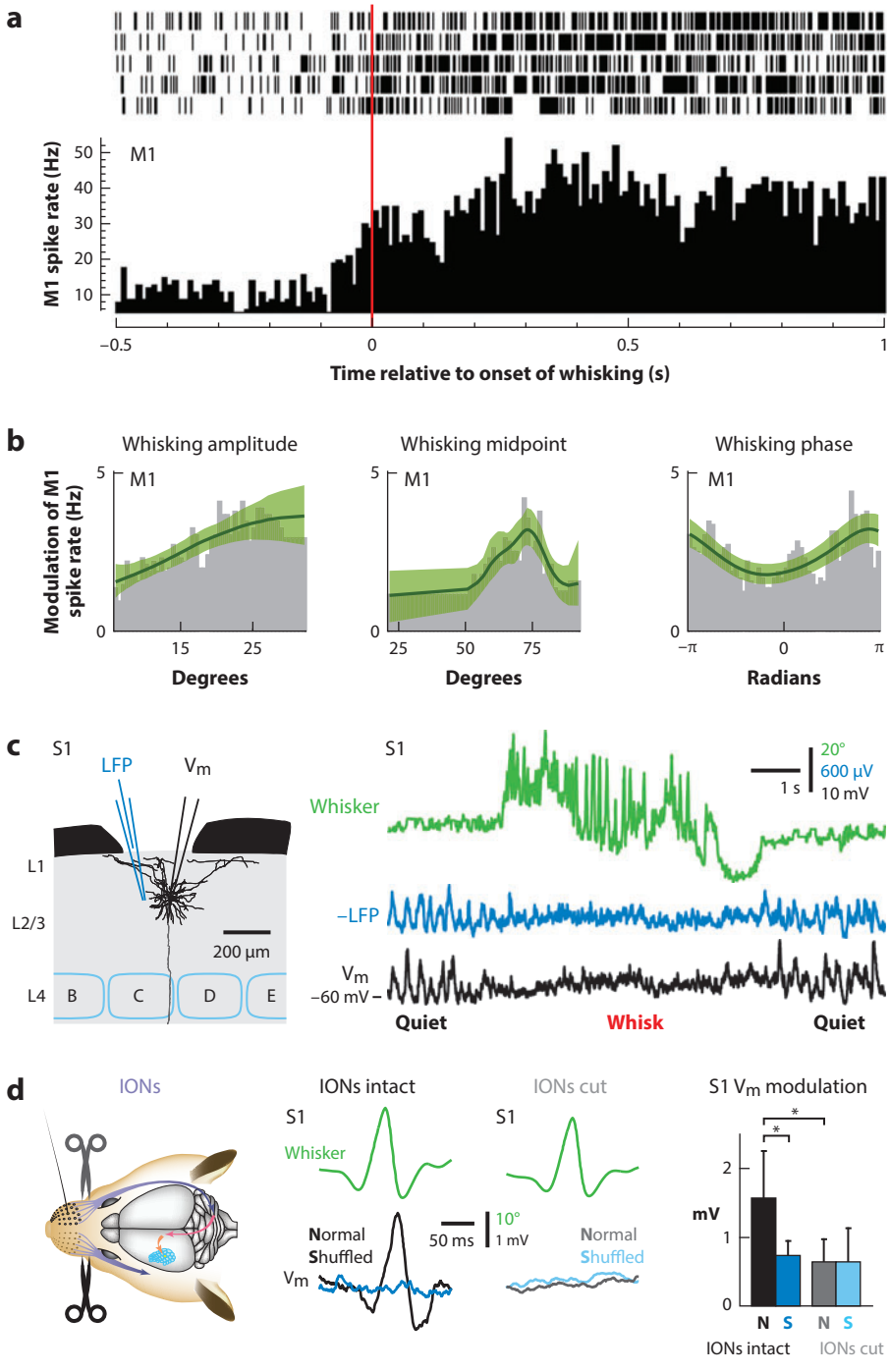
have not yet been made of the activity of these specific brain stem–projecting neocortical neurons during whisker-related behavior. Recordings have, however, been made from unlabeled neurons and other types of neurons in M1 and S1 during whisker-related behavior.

Extracellular recordings of action potential firing of neurons in whisker M1 during quantified whisker movements have been reported in only a small number of studies (Carvell et al. 1996, Hill et al. 2011, Friedman et al. 2012), and there are no published measurements of membrane potential from M1 of awake mice during whisking behavior. In agreement with Carvell et al. (1996), Friedman et al. (2012) found that M1 neurons increase firing rate during whisking compared with nonwhisking periods (**Figure 6*a***). In addition, Friedman et al. (2012) reported that the increased firing in M1 preceded the onset of whisker movement. Increased action potential firing in M1 neurons could therefore contribute to the initiation of whisking, perhaps through the previously discussed projections to the reticular brain stem, for example onto vIRt neurons driving rhythmic whisker protraction. However, in probably the most detailed study of M1 activity during whisking to date, Hill et al. (2011) show that firing rates of M1 neurons both increase and decrease so that the average rate across the population is little changed during whisking. In future studies, it will therefore be important to distinguish different cell types in M1, which could have different activity patterns during whisking. Hill et al. (2011) do, however, find that M1 activity is modulated in important ways during whisking. They report that M1 neurons change firing rate with respect to the amplitude of whisking and the midpoint of whisking, and some cells also showed rapid modulations in firing rate at specific phases during the whisking cycle (**Figure 6*b***). The modulation of M1 activity during whisking was not changed when the sensory whisker nerve (the infraorbital nerve, ION) was cut (Hill et al. 2011). The activity of M1 neurons may therefore relate primarily to motor commands rather than to sensory information.

Researchers have also begun to study the activity of neurons in S1 during whisker-related behavior. Juxtasomal recordings from anatomically identified excitatory neurons in S1 reveal that the overall spike rate is not different when comparing epochs of whisking and no whisking (de Kock & Sakmann 2009). However, slender-tufted pyramidal neurons located in L5A of the S1

Figure 6

Correlation of activity in sensorimotor cortex with whisker movement. (*a*) Example extracellular recording of spiking activity in M1 (Friedman et al. 2012), with a spike raster of five whisking onset epochs (*above*) and the spike time histogram from many epochs (*below*). Time zero is aligned across trials to be the onset time of whisking. Action potential firing increases shortly before onset of whisking and remains elevated during the first second of whisking. (*b*) In a different example extracellular recording of spiking activity in M1 (Hill et al. 2011), the firing rate is modulated by the amplitude of whisking (*left*), by the midpoint of the whisker position during whisking (*middle*), and by the phase of the whisker position within the whisking cycle (*right*). (*c*) Simultaneous recording of local field potential (LFP) and whole-cell recording of membrane potential (V_m) in layer 2/3 of the C2 barrel column of S1 in an awake behaving mouse (Poulet & Petersen 2008). During quiet wakefulness, when the whisker angle (*green*) is not changing, the LFP and V_m show slow, large-amplitude, synchronous fluctuations. When the mouse is actively whisking, the LFP and V_m reduce variance, reduce slow fluctuations, and on average depolarize. Whisking therefore induces an important change in cortical state, which does not depend on sensory input from the whisker. (*d*) When the membrane potential across different whisking cycles is aligned to the peak of protraction and averaged, then there is an obvious fast phase-locked V_m fluctuation (Poulet & Petersen 2008). Averaging at random times (Shuffled, S; Normal unshuffled, N) shows the noise level. The same analysis carried out in mice with cut sensory infraorbital nerves (IONs) reveals that the fast phase-locked V_m modulation during whisking depends on sensory input because it is absent after cutting IONs. Panel *a* is modified from Friedman et al. (2012) and reproduced with permission from the American Physiological Society. Panel *b* is modified from Hill et al. (2011) and reproduced with permission from Cell Press. Panels *c* and *d* are modified from Poulet & Petersen (2008) and reproduced with permission from the Nature Publishing Group.


a
M1
M1 spike rate (Hz)
50
40
30
20
10
−0.5
0
0.5
1
Time relative to onset of whisking (s)
b
Whisking amplitude
Whisking midpoint
Whisking phase
Modulation of M1 spike rate (Hz)
M1
5
0
15
25
Degrees
25
50
75
Degrees
−π
0
π
Radians
c
S1
LFP
Vm
L1
L2/3
L4
B
C
D
E
200 µm
Whisker
−LFP
Vm
−60 mV
1 s
20°
600 µV
10 mV
Quiet
Whisk
Quiet
d
IONs
IONs intact
IONs cut
S1 Vm modulation
S1
Whisker
Normal
Shuffled
Vm
50 ms
10°
1 mV
mV
2
1
0
N
S
N
S
IONs intact
IONs cut

barrel cortex increased their firing rate during whisking (de Kock & Sakmann 2009). Whole-cell membrane potential recordings have been carried out from identified neurons in layer 2/3 during whisking (Crochet & Petersen 2006; Poulet & Petersen 2008; Gentet et al. 2010, 2012). In agreement with extracellular recordings, the whole-cell recordings of excitatory neurons do not, on average, change spike rate during whisking. However, the spike rates of inhibitory γ-aminobutyric acid (GABA)ergic neurons change in a cell-type-specific manner. Parvalbumin-expressing fast-spiking GABAergic neurons reduce firing rate during whisking, non-fast-spiking presumed $5HT_{3A}$-receptor expressing neurons increase firing rate during whisking, and somatostatin-expressing neurons decrease firing rate during whisking (Gentet et al. 2010, 2012; Petersen & Crochet 2013). Thus GABAergic inhibition is significantly reorganized in S1 during whisking. In addition, an important change in brain state that accompanies whisking is clearly observed in S1. During quiet wakefulness (when the whiskers are not moving), the local field potential and membrane potential of neurons in S1 often show slow, large-amplitude fluctuations (Petersen et al. 2003, Crochet & Petersen 2006, Poulet & Petersen 2008, Okun et al. 2010, Zagha et al. 2013). During active whisking, the membrane potential of excitatory neurons depolarizes, the membrane potential variance decreases, and the slow membrane potential fluctuations are suppressed (Crochet & Petersen 2006, Poulet & Petersen, 2008) (**Figure 6*c***). These changes in cortical state do not depend on sensory input because whisking induces a similar change in S1 cortical state when the sensory nerve (ION) is cut (Poulet & Petersen 2008). S1 therefore appears to encode motor-related signals, similar to results in mouse V1 (Niell & Stryker 2010, Keller et al. 2012). Increases in thalamic firing (Poulet et al. 2012), motor cortex firing (Zagha et al. 2013) or neuromodulation (Lee & Dan 2012) likely contribute to driving the brain state changes in S1 during whisking.

Analyzed at higher temporal resolution, extracellular recordings from S1 reveal rapid cycle-by-cycle modulation during whisking, with individual units firing at specific phases of the whisking cycle (Fee et al. 1997, Curtis & Kleinfeld 2009). These firing rate modulations are likely driven by membrane potential fluctuations phase-locked to the whisking cycle (Crochet & Petersen 2006, Poulet & Petersen 2008, Crochet et al. 2011) (**Figure 6*d***). Different neurons depolarize and fire at different phases of the whisking cycle, thus encoding whisker position on the millisecond timescale. This fast phase-locked activity in S1 does depend on sensory signals from the periphery (Fee et al. 1997, Poulet & Petersen 2008) (**Figure 6*d***). This finding contrasts with the phase-locked activity in M1, which is independent of sensory reafference signals. Whereas the fast phase-locked signals in S1 are largely related to sensory signals, the signals in M1 are more likely related to motor commands, which agrees with the overall notions of cortical organization. However, S1 activity may nonetheless impact whisker movement through direct and indirect pathways. S1 activity is rapidly signaled to M1 (Ferezou et al. 2007) and so the whisking-induced changes in S1 activity could also be relayed to M1. S1 activity might also impact whisker movement more directly via brain stem projections and other subcortical projections, as discussed earlier.

IMPACT OF S1 AND M1 INACTIVATION ON WHISKER MOVEMENT

Whereas cortical stimulation reveals pathways for motor control and electrophysiological measurements reveal correlations of neural activity and movement, inactivation experiments investigate the necessity of the neural activity. Precise inactivation experiments with cell-type specificity and spatiotemporal control will be enormously informative in future experiments. Experiments until now have largely been limited to lesions or pharmacological inactivations of S1 or M1, but these experiments have nonetheless revealed some important general insights into whisker motor control. Most importantly, rodents can whisk in a relatively normal way after lesion of M1 (Welker 1964, Semba & Komisaruk 1984, Gao et al. 2003). Thus although M1 activity can

evoke whisking, it appears that other pathways normally drive spontaneous exploratory whisking, including pathways signaling via serotonin (Hattox et al. 2003). Pharmacological inactivation of S1 reduces whisker retraction evoked by high-frequency whisker stimulation (Matyas et al. 2010), but it otherwise appears to make little impact on spontaneous whisker movement. Various brain areas and signaling pathways will likely play diverse roles during different behaviors. In the future, it will therefore be important to investigate the roles of S1 and M1 during specific learned behaviors. Huber et al. (2012) trained mice to locate objects with whiskers and found that pharmacological inactivation of M1 changes whisker movement and behavioral performance in this task.

CONCLUSIONS AND FUTURE PERSPECTIVES

Current evidence suggests that the cortex can drive whisker movements using at least two distinct pathways. Whisker M1 projects to brain stem Rt, which contains whisker premotor neurons and includes the proposed whisking central pattern generator (vIRt), preferentially innervating protraction motor neurons of intrinsic whisker muscles. This anatomical pathway could therefore account for the rhythmic protraction movements evoked by stimulating M1. In an analogous parallel pathway, whisker S1 projects to the brain stem SP5i, which contains whisker premotor neurons preferentially innervating retraction motor neurons of extrinsic whisker muscles. This pathway could therefore account for the whisker retraction evoked by stimulating S1.

These two different cortical regions drive qualitatively different whisker movements. M1 drives rhythmic whisker protraction, which resembles exploratory whisking. M1 activity therefore appears well-suited to increase the amount of sensory information arriving from the whiskers during active sensing. S1, however, drives whisker retraction, which might serve as a negative feedback signal, preventing overstimulation of the whisker system. M1 and S1 therefore appear to play fundamentally different roles in whisker motor control. A region close to, or overlapping with, whisker M1 has been suggested to be a frontal orienting field (Erlich et al. 2011), homologous to the frontal eye field of primates. Whisker M1 may therefore be involved in multiple brain functions, including whisker motor control, spatial attention, and preparation of orienting responses. How actions and action plans are mapped onto the cortex therefore remains poorly understood in mice, rats, and monkeys (Graziano & Aflalo 2007).

Although it is clear from stimulation experiments that the cortex can drive whisker movements, these experiments do not necessarily indicate the physiological role of M1 and S1 in regulating normal whisker movement during behavior. Recordings of M1 and S1 activity in behaving animals have not yet been targeted to the cell types likely to be most directly related to whisker movement, so we currently know rather little about the causal influences of normal patterns of cortical activity upon whisker movement. Future experiments in behaving animals must therefore record the activity of defined types of neurons across the whisker motor control pathways, including the cortical neurons projecting to the brain stem and other motor-related brain regions. To test whether the activity in these neural circuits accounts for the movements, future experimental work must specifically interfere with the proposed synaptic pathways, perhaps through combining retrograde transsynaptic virus (Wickersham et al. 2007) and optogenetic inhibition (Zhang et al. 2007, Chow et al. 2010).

In conclusion, although the synaptic pathways for the cortex to control whisker movement are beginning to be mapped, we still understand little about the normal physiological role of the cortex in whisker motor control. Furthermore, in this review, we have focused only on the simplest pathways from the cortex to whisker motor neurons via brain stem, but it is important to remember that there are many more complex signaling pathways, for example through the basal ganglia, the superior colliculus, and the cerebellum, all of which likely contribute during behavior.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This work was funded by grants from the Swiss National Science Foundation, the Human Frontier Science Program and the European Research Council. I thank Varun Sreenivasan and Alexandros Kyriakatos for valuable discussions.

LITERATURE CITED

Aronoff R, Matyas F, Mateo C, Ciron C, Schneider B, Petersen CCH. 2010. Long-range connectivity of mouse primary somatosensory barrel cortex. *Eur. J. Neurosci.* 31:2221–33

Bosman LW, Houweling AR, Owens CB, Tanke N, Shevchouk OT, et al. 2011. Anatomical pathways involved in generating and sensing rhythmic whisker movements. *Front. Integr. Neurosci.* 5:53

Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. 2005. Millisecond-timescale, genetically targeted optical control of neural activity. *Nat. Neurosci.* 8:1263–68

Brecht M. 2007. Barrel cortex and whisker-mediated behaviors. *Curr. Opin. Neurobiol.* 17:408–16

Brecht M. 2011. Movement, confusion, and orienting in frontal cortices. *Neuron* 72:193–96

Brecht M, Krauss A, Muhammad S, Sinai-Esfahani L, Bellanca S, Margrie TW. 2004a. Organization of rat vibrissa motor cortex and adjacent areas according to cytoarchitectonics, microstimulation, and intracellular stimulation of identified cells. *J. Comp. Neurol.* 479:360–73

Brecht M, Schneider M, Sakmann B, Margrie TW. 2004b. Whisker movements evoked by stimulation of single pyramidal cells in rat motor cortex. *Nature* 427:704–10

Carvell GE, Miller SA, Simons DJ. 1996. The relationship of vibrissal motor cortex unit activity to whisking in the awake rat. *Somatosens. Mot. Res.* 13:115–27

Chow BY, Han X, Dobry AS, Qian X, Chuong AS, et al. 2010. High-performance genetically targetable optical neural silencing by light-driven proton pumps. *Nature* 463:98–102

Cohen JD, Hirata A, Castro-Alamancos MA. 2008. Vibrissa sensation in superior colliculus: wide-field sensitivity and state-dependent cortical feedback. *J. Neurosci.* 28:11205–20

Cooke DF, Taylor CSR, Moore T, Graziano MSA. 2003. Complex movements evoked by microstimulation of the ventral intraparietal area. *Proc. Natl. Acad. Sci. USA* 100:6163–68

Coulter JD, Jones EG. 1977. Differential distribution of corticospinal projections from individual cytoarchitectonic fields in the monkey. *Brain Res.* 129:335–40

Cramer NP, Keller A. 2006. Cortical control of a whisking central pattern generator. *J. Neurophysiol.* 96:209–17

Crochet S, Petersen CCH. 2006. Correlating whisker behavior with membrane potential in barrel cortex of awake mice. *Nat. Neurosci.* 9:608–10

Crochet S, Poulet JFA, Kremer Y, Petersen CCH. 2011. Synaptic mechanisms underlying sparse coding of active touch. *Neuron* 69:1160–75

Curtis JC, Kleinfeld D. 2009. Phase-to-rate transformations encode touch in cortical neurons of a scanning sensorimotor system. *Nat. Neurosci.* 12:492–501

de Kock CP, Sakmann B. 2009. Spiking in primary somatosensory cortex during natural whisking in awake head-restrained rats is cell-type specific. *Proc. Natl. Acad. Sci. USA* 106:16446–50

Diamond ME, von Heimendahl M, Knutsen PM, Kleinfeld D, Ahissar E. 2008. 'Where' and 'what' in the whisker sensorimotor system. *Nat. Rev. Neurosci.* 9:601–12

Donoghue JP, Wise SP. 1982. The motor cortex of the rat: cytoarchitecture and microstimulation mapping. *J. Comp. Neurol.* 212:76–88

Dörfl J. 1982. The musculature of the mystacial vibrissae of the white mouse. *J. Anat.* 135:147–54

Erlich JC, Bialek M, Brody CD. 2011. A cortical substrate for memory-guided orienting in the rat. *Neuron* 72:330–43

Fee MS, Mitra PP, Kleinfeld D. 1997. Central versus peripheral determinants of patterned spike activity in rat vibrissa cortex during whisking. *J. Neurophysiol.* 78:1144–49

Feldmeyer D, Brecht M, Helmchen F, Petersen CCH, Poulet JFA, et al. 2013. Barrel cortex function. *Prog. Neurobiol.* 103:3–27

Ferezou I, Haiss F, Gentet LJ, Aronoff R, Weber B, Petersen CCH. 2007. Spatiotemporal dynamics of cortical sensorimotor integration in behaving mice. *Neuron* 56:907–23

Ferrier D. 1874. Experiments on the brain of monkeys—No. 1. *Proc. R. Soc. Lond.* 23:409–30

Friedman WA, Zeigler HP, Keller A. 2012. Vibrissae motor cortex unit activity during whisking. *J. Neurophysiol.* 107:551–63

Fritsch G, Hitzig E. 1870. Über die elektrische Erregbarkeit des Grosshirns. *Arch. Anat. Physiol. Wiss. Med.* 37:300–32

Gao P, Hattox AM, Jones LM, Keller A, Zeigler HP. 2003. Whisker motor cortex ablation and whisker movement patterns. *Somatosens. Mot. Res.* 20:191–98

Gentet LJ, Avermann M, Matyas F, Staiger JF, Petersen CCH. 2010. Membrane potential dynamics of GABAergic neurons in the barrel cortex of behaving mice. *Neuron* 65:422–35

Gentet LJ, Kremer Y, Taniguchi H, Huang ZJ, Staiger JF, Petersen CCH. 2012. Unique functional properties of somatostatin-expressing GABAergic neurons in mouse barrel cortex. *Nat. Neurosci.* 15:607–12

Gioanni Y, Lamarche M. 1985. A reappraisal of rat motor cortex organization by intracortical microstimulation. *Brain Res.* 344:49–61

Grant RA, Mitchinson B, Fox CW, Prescott TJ. 2009. Active touch sensing in the rat: anticipatory and regulatory control of whisker movements during surface exploration. *J. Neurophysiol.* 101:862–74

Graziano MS, Aflalo TN. 2007. Mapping behavioral repertoire onto the cortex. *Neuron* 56:239–51

Graziano MS, Taylor CS, Moore T, Cooke DF. 2002. The cortical control of movement revisited. *Neuron* 36:349–62

Grinevich V, Brecht M, Osten P. 2005. Monosynaptic pathway from rat vibrissa motor cortex to facial motor neurons revealed by lentivirus-based axonal tracing. *J. Neurosci.* 25:8250–58

Grinvald A, Hildesheim R. 2004. VSDI: a new era in functional imaging of cortical dynamics. *Nat. Rev. Neurosci.* 5:874–85

Haidarliu S, Golomb D, Kleinfeld D, Ahissar E. 2012. Dorsorostral snout muscles in the rat subserve coordinated movement for whisking and sniffing. *Anat. Rec.* 295:1181–91

Haiss F, Schwarz C. 2005. Spatial segregation of different modes of movement control in the whisker representation of rat primary motor cortex. *J. Neurosci.* 25:1579–87

Hall RD, Lindholm EP. 1974. Organization of motor and somatosensory neocortex in the albino rat. *Brain Res.* 66:23–38

Harrison TC, Ayling OG, Murphy TH. 2012. Distinct cortical circuit mechanisms for complex forelimb movement and motor map topography. *Neuron* 74:397–409

Hattox A, Li Y, Keller A. 2003. Serotonin regulates rhythmic whisking. *Neuron* 39:343–52

Hattox AM, Priest CA, Keller A. 2002. Functional circuitry involved in the regulation of whisker movements. *J. Comp. Neurol.* 442:266–76

Hemelt ME, Keller A. 2008. Superior colliculus control of vibrissa movements. *J. Neurophysiol.* 100:1245–54

Herfst LJ, Brecht M. 2008. Whisker movements evoked by stimulation of single motor neurons in the facial nucleus of the rat. *J. Neurophysiol.* 99:2821–32

Hill DN, Bermejo R, Zeigler HP, Kleinfeld D. 2008. Biomechanics of the vibrissa motor plant in rat: rhythmic whisking consists of triphasic neuromuscular activity. *J. Neurosci.* 28:3438–55

Hill DN, Curtis JC, Moore JD, Kleinfeld D. 2011. Primary motor cortex reports efferent control of vibrissa motion on multiple timescales. *Neuron* 72:344–56

Huber D, Gutnisky DA, Peron S, O'Connor DH, Wiegert JS, et al. 2012. Multiple dynamic representations in the motor cortex during sensorimotor learning. *Nature* 484:473–78

Jin TE, Witzemann V, Brecht M. 2004. Fiber types of the intrinsic whisker muscle and whisking behavior. *J. Neurosci.* 24:3386–93

Keller GB, Bonhoeffer T, Hübener M. 2012. Sensorimotor mismatch signals in primary visual cortex of the behaving mouse. *Neuron* 74:809–15

Kelly RM, Strick PL. 2000. Rabies as a transneuronal tracer of circuits in the central nervous system. *J. Neurosci. Methods* 103:63–71

Knutsen PM, Biess A, Ahissar E. 2008. Vibrissal kinematics in 3D: tight coupling of azimuth, elevation, and torsion across different whisking modes. *Neuron* 59:35–42

Lee S-H, Dan Y. 2012. Neuromodulation of brain states. *Neuron* 76:209–22

Legg CR, Mercier B, Glickstein M. 1989. Corticopontine projection in the rat: the distribution of labelled cortical cells after large injections of horseradish peroxidase in the pontine nuclei. *J. Comp. Neurol.* 286:427–41

Mao T, Kusefoglu D, Hooks BM, Huber D, Petreanu L, Svoboda K. 2011. Long-range neuronal circuits underlying the interaction between sensory and motor cortex. *Neuron* 72:111–23

Mateo C, Avermann M, Gentet LJ, Zhang F, Deisseroth K, Petersen CCH. 2011. In vivo optogenetic stimulation of neocortical excitatory neurons drives brain-state-dependent inhibition. *Curr. Biol.* 21:1593–602

Matyas F, Sreenivasan V, Marbach F, Wacongne C, Barsy B, et al. 2010. Motor control by sensory cortex. *Science* 330:1240–43

Mitchinson B, Martin CJ, Grant RA, Prescott TJ. 2007. Feedback control in active sensing: Rat exploratory whisking is modulated by environmental contact. *Proc. Biol. Sci.* 274:1035–41

Miyashita E, Keller A, Asanuma H. 1994. Input–output organization of the rat vibrissal motor cortex. *Exp. Brain Res.* 99:223–32

Molinari HH, Schultze KE, Strominger NL. 1996. Gracile, cuneate, and spinal trigeminal projections to inferior olive in rat and monkey. *J. Comp. Neurol.* 375:467–80

Moore JD, Deschênes M, Furuta T, Huber D, Smear MC, et al. 2013. Hierarchy of orofacial rhythms revealed through whisking and breathing. *Nature* 497:205–10

Nagel G, Szellas T, Huhn W, Kateriya S, Adeishvili N, et al. 2003. Channelrhodopsin-2, a directly light-gated cation-selective membrane channel. *Proc. Natl. Acad. Sci. USA* 100:13940–45

Neafsey EJ, Bold EL, Haas G, Hurley-Gius KM, Quirk G, et al. 1986. The organization of the rat motor cortex: a microstimulation mapping study. *Brain Res.* 396:77–96

Niell CM, Stryker MP. 2010. Modulation of visual responses by behavioral state in mouse visual cortex. *Neuron* 65:472–79

Nguyen QT, Kleinfeld D. 2005. Positive feedback in a brainstem tactile sensorimotor loop. *Neuron* 45:447–57

Okun M, Naim A, Lampl I. 2010. The subthreshold relation between cortical local field potential and neuronal firing unveiled by intracellular recordings in awake rats. *J. Neurosci.* 30:4440–48

Osakada F, Mori T, Cetin AH, Marshel JH, Virgen B, Callaway EM. 2011. New rabies virus variants for monitoring and manipulating activity and gene expression in defined neural circuits. *Neuron* 71:617–31

Paxinos G, Franklin KBJ. 2001. *The Mouse Brain in Stereotaxic Coordinates*. San Diego: Academic. 2nd ed.

Penfield W, Boldrey E. 1937. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 60:389–443

Petersen CCH. 2007. The functional organization of the barrel cortex. *Neuron* 56:339–55

Petersen CCH, Crochet S. 2013. Synaptic computation and sensory processing in neocortical layer 2/3. *Neuron* 78:28–48

Petersen CCH, Hahn TTG, Mehta M, Grinvald A, Sakmann B. 2003. Interaction of sensory responses with spontaneous depolarization in layer 2/3 barrel cortex. *Proc. Natl. Acad. Sci. USA* 100:13638–43

Porter LL, White EL. 1983. Afferent and efferent pathways of the vibrissal region of primary motor cortex in the mouse. *J. Comp. Neurol.* 214:279–89

Poulet JFA, Fernandez LM, Crochet S, Petersen CCH. 2012. Thalamic control of cortical states. *Nat. Neurosci.* 15:370–72

Poulet JFA, Petersen CCH. 2008. Internal brain state regulates membrane potential synchrony in barrel cortex of behaving mice. *Nature* 454:881–85

Rathelot JA, Strick PL. 2006. Muscle representation in the macaque motor cortex: an anatomical perspective. *Proc. Natl. Acad. Sci. USA* 103:8257–62

Rice FL, Fundin BT, Arvidsson J, Aldskogius H, Johansson O. 1997. Comprehensive immunofluorescence and lectin binding analysis of vibrissal follicle sinus complex innervation in the mystacial pad of the rat. *J. Comp. Neurol.* 385:149–84

Sachdev RN, Sato T, Ebner FF. 2002. Divergent movement of adjacent whiskers. *J. Neurophysiol.* 87:1440–48

Semba K, Komisaruk BR. 1984. Neural substrates of two different rhythmical vibrissal movements in the rat. *Neuroscience* 12:761–74

Sherrington CS. 1906. *The Integrative Action of the Nervous System*. New Haven, CT: Yale Univ. Press

Smith JB, Alloway KD. 2013. Rat whisker motor cortex is subdivided into sensory-input and motor-output areas. *Front. Neural Circuits* 7:4

Steindler DA. 1985. Trigeminocerebellar, trigeminotectal, and trigeminothalamic projections: a double retrograde axonal tracing study in the mouse. *J. Comp. Neurol.* 237:155–75

Stepien AE, Tripodi M, Arber S. 2010. Monosynaptic rabies virus reveals premotor network organization and synaptic specificity of cholinergic partition cells. *Neuron* 68:456–72

Swenson RS, Kosinski RJ, Castro AJ. 1984. Topography of spinal, dorsal column nuclear, and spinal trigeminal projections to the pontine gray in rats. *J. Comp. Neurol.* 222:301–11

Takatoh J, Nelson A, Zhou X, Bolton MM, Ehlers MD, et al. 2013. New modules are added to vibrissal premotor circuitry with the emergence of exploratory whisking. *Neuron* 77:346–60

Tandon S, Kambi N, Jain N. 2008. Overlapping representations of the neck and whiskers in the rat motor cortex revealed by mapping at different anaesthetic depths. *Eur. J. Neurosci.* 27:228–37

Ugolini G. 1995. Specificity of rabies virus as a transneuronal tracer of motor networks: transfer from hypoglossal motoneurons to connected second-order and higher order central nervous system cell groups. *J. Comp. Neurol.* 356:457–80

Welker E, Hoogland PV, Van der Loos H. 1988. Organization of feedback and feedforward projections of the barrel cortex: a PHA-L study in the mouse. *Exp. Brain Res.* 73:411–35

Welker WI. 1964. Analysis of sniffing of the albino rat. *Behaviour* 22:223–44

White EL, DeAmicis RA. 1977. Afferent and efferent projections of the region of mouse SmI cortex which contains the posteromedial barrel subfield. *J. Comp. Neurol.* 175:455–82

Wickersham IR, Lyon DC, Barnard RJ, Mori T, Finke S, et al. 2007. Monosynaptic restriction of transsynaptic tracing from single, genetically targeted neurons. *Neuron* 53:639–47

Wise SP, Jones EG. 1977. Cells of origin and terminal distribution of descending projections of the rat somatic sensory cortex. *J. Comp. Neurol.* 175:129–57

Woolsey CN. 1958. Organization of somatic sensory and motor areas of the cerebral cortex. In *Biological and Biochemical Bases of Behavior*, ed. HF Harlow, CN Woolsy, pp. 63–81. Madison: Univ. Wis. Press

Yatim N, Billig I, Compoint C, Buisseret P, Buisseret-Delmas C. 1996. Trigeminocerebellar and trigeminoolivary projections in rats. *Neurosci. Res.* 25:267–83

Zagha E, Casale AE, Sachdev RNS, McGinley MJ, McCormick DA. 2013. Motor cortex feedback influences sensory processing by modulating network state. *Neuron* 79:567–78

Zhang F, Vierock J, Yizhar O, Fenno LE, Tsunoda S, et al. 2011. The microbial opsin family of optogenetic tools. *Cell* 147:1446–57

Zhang F, Wang LP, Brauner M, Liewald JF, Kay K, et al. 2007. Multimodal fast optical interrogation of neural circuitry. *Nature* 446:633–39