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Sensorimotor processing in the rodent barrel cortex

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Abstract

Tactile sensory information from facial whiskers provides nocturnal tunnel-dwelling rodents such as mice and rats with important spatial and textural information about their immediate surroundings. Whiskers are moved back and forth to scan the environment, and touch signals from each whisker evoke sparse patterns of neuronal activity in primary somatosensory barrel cortex (wS1). Whisking is accompanied by desynchronised brain states with cell-type-specific changes in spontaneous and evoked neuronal activity. Many tactile features, including texture and object location, appear to be computed in wS1 through integration of motor and sensory signals. wS1 also directly controls whisker movements and contributes to learned, whisker-dependent goal-directed behaviors. The cell-type-specific neuronal circuitry in wS1 that contributes to whisker sensory perception is beginning to be defined.

Introduction

Understanding sensorimotor processing is central to comprehending the neural mechanisms underlying behavior. Sensory information is important for action planning, and every action is executed with the help of sensory feedback. Conversely, sensory information is actively gathered through motor commands to position sensors, and is actively processed in the brain in a context-, motivation- and learning-dependent manner. Active sensing is obvious in vision through foveation of selected visual targets, olfaction through sniffing, and touch through palpation.

Sensorimotor processing takes place across many regions of the mammalian brain, which likely serve distinct functions. Here, in this review, I focus on sensorimotor processing in neuronal circuits of rodent primary whisker somatosensory cortex (wS1). The whisker sensorimotor system provides rodents with spatial and textural information about their immediate surroundings, useful for these nocturnal tunnel-dwelling animals. Whisker sensation is an active process, in which mice and rats scan their environment by moving their whiskers back and forth at high frequency (~10 Hz) when aroused or curious. The connectivity of wS1 is thought to facilitate the integration of sensory, motor and top-down signals for specific computations in individual neurons in wS1. Cortical whisker-related sensorimotor processing takes place within complex neuronal circuits, which are being

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elucidated with the help of new tools for labelling, recording and manipulating specific cell-types during behavior. The goal is to define the precise mechanisms by which the synaptically connected neuronal networks of wS1 contribute to sensory perception, learning and motor output.

Signalling pathways

Nearly 50 years ago, Woolsey and Van der Loos published a seminal paper[1] describing the somatotopic **[G]** map of mouse wS1. Each mystacial **[G]** whisker on the snout was found to be individually represented in mouse wS1 by an obvious large-scale (~200-300 μm) structure, termed a 'barrel'. The whisker and barrel maps are organized similarly across rats and mice, and a standard nomenclature has been developed. For example, the C2 whisker is represented in wS1 by the C2 barrel (FIG. 1a). The whisker barrel map in wS1 appears to develop through genetic programs and is refined through experience and activity[2–7].

The deflection of a whisker evokes a volley of sensory information signaled through glutamatergic synapses in brainstem and thalamus before reaching cortex (FIG. 1b). Primary sensory neurons of the trigeminal ganglion **[G]** that have mechanosensitive nerve endings in whisker follicles directly innervate neurons in the whisker-related principal trigeminal brainstem nucleus (Pr5)[8,9]. The Pr5 neurons are somatotopically arranged in discrete units termed 'barrelettes' and send large-amplitude excitatory 'driver' inputs to neurons in the primary whisker somatosensory thalamus (the ventral posterior medial nucleus, VPM). The excitatory VPM neurons cluster in discrete somatotopic 'barreloids', and individual neurons in VPM largely innervate just a single barrel[10,11]. The one-to-one anatomical mapping of whiskers along this 'lemniscal' sensory pathway to wS1 suggests labelled-line whisker-specific signaling. The relay of sensory information is fast, with latencies as short as ~5 ms from whisker deflection to depolarization of neurons in wS1[12–14].

Incoming sensory information is processed in neuronal microcircuits in wS1 and signaled onwards to many directly connected downstream cortical and subcortical brain regions (FIG. 1c)[15–19]. In addition to its defining input from VPM, wS1 also receives important input from higher-order parts of the thalamus and many other cortical regions, as well as various neuromodulatory inputs. The barrel cortex, with its precisely defined maps, offers a unique opportunity for detailed analysis of causal mechanisms that drive processing in well-defined cell-type-specific neuronal circuitry of the mammalian brain during sensory perception.

Microcircuits in wS1

Columns and layers

Columns and layers are important organizing principles of neocortex. The cortical columns of wS1 can be defined as the thickness of the cortex that is laterally bounded by the dimensions of the barrel. For the mouse C2 barrel column, the cortical (vertical) thickness is ~1.2 mm and the horizontal extent is ~200 μm x ~300 μm. The C2 barrel column is estimated to contain ~6,500 neurons, of which ~85% are excitatory glutamatergic neurons, with the remaining ~15% being inhibitory GABAergic neurons[20]. The column can be subdivided into different cortical layers. Axons, dendrites and synapses are present across all

cortical layers. The most superficial layer (layer 1, L1) contains exclusively inhibitory GABAergic neurons, whereas all deeper layers (layers 2-6, L2-6) contain various types of excitatory and inhibitory neurons. VPM input arrives most prominently within layer 4 (L4), and this is where the clearest whisker barrel map is found (FIG. 2a). VPM also innervates the L3 cortex immediately above the L4 barrels, and provides axonal collaterals deeper in the cortex at the border of L5 and L6[21,22]. L4 contains many excitatory spiny stellate neurons, which are small and tightly packed, giving this layer a granular appearance. The axons of the excitatory L4 neurons extensively branch in the home L4 barrel, and the more superficial L2 and L3 of the same barrel column[23]. Both VPM thalamic input and the L4 neurons also excite pyramidal neurons in L5 and L6, which have vertically arranged apical dendrites further supporting columnar processing. The first signals evoked by a whisker deflection are therefore spatially localized to the aligned barrel column in wS1[24–26]. However, sensory-evoked signals rapidly spread across wS1 (within ~20 ms), likely, at least in part, through lateral synaptic connectivity, giving rise to broad and complex receptive fields of individual neurons[13,14,27,28].

Local connectivity

The excitatory and inhibitory neurons are synaptically connected within their home barrel column, with surrounding barrel columns and with other cortical and subcortical brain regions. Within the local microcircuit, on average, ~10% of excitatory neurons form glutamatergic synapses with other nearby excitatory neurons, whereas the rates of connectivity between excitatory and inhibitory neurons, as well as between inhibitory neurons, are typically higher[29–33]. Unitary (single axon) excitatory and inhibitory postsynaptic potentials (uEPSPs and uIPSPs) are usually small in amplitude (~0.1-1 mV) and brief (~5-50 ms), suggesting the need for individual neurons to integrate input from many presynaptic neurons in order to fire action potentials. Although much remains to be discovered, it is clear that there is a great deal of cell-type and layer specificity in the synaptic wiring diagram (recently reviewed[34–39]). Here, I briefly outline major layer-specific excitatory pathways (FIG. 2b), thought to be responsible for signal propagation, leaving the possible roles of different classes of inhibitory neurons to be covered in later sections.

Sensory input from VPM arrives most prominently within L4, and the excitatory L4 neurons provide excitatory input to neurons in all other cortical layers of the barrel column. A dense column of axon from L4 excitatory neurons innervates L2 and L3 of the same barrel column. L4 neurons in wS1 only have local axonal arborisations and are therefore excitatory interneurons. L2 and L3 are largely composed of excitatory pyramidal projection neurons with dendrites in L1–L3 and extensive local axonal arborisations in L2, L3 and L5, and with a large horizontal spread across wS1[40,41]. Lateral connectivity across barrel columns likely underlies multiwhisker integration necessary for perception of complex features, such as object shape. L2/3 pyramidal neurons can be classified as intratelencephalon-projecting (IT) neurons, sending long-range axonal projections to other cortical regions (primarily to ipsilateral whisker motor cortex and whisker secondary somatosensory cortex) and the striatum, as well as showing callosal connectivity[19].

The excitatory L5 pyramidal neurons have apical dendrites that extend to L1, and receive input from all cortical layers, as well as from thalamus. Indeed subsets of L5 pyramidal neurons receive sufficiently strong thalamic input to drive action potential firing[42]. The excitatory L5 neurons can be divided into IT neurons and pyramidal tract (PT) neurons[34]. The L5 IT neurons (similar to L2/3 pyramidal neurons) project extensively within wS1[43], to other neocortical areas and striatum, as well as showing callosal projections[44]. PT neurons typically show relatively few local axons in wS1, but project strongly to subcortical structures such as striatum, the posterior medial nucleus of the thalamus (POm), pons, superior colliculus and spinal trigeminal brainstem[43,45,46]. PT neurons do not have callosal projections. Highly specific innervation by the higher-order somatosensory thalamic nucleus POm defines L5A, the most superficial part of L5[22,47,48]. In addition, POm also prominently innervates L1. Neurons in L5A are IT neurons, whereas neurons in L5B include both IT and PT neurons, with PT neurons only being found in L5B. In the local microcircuit, excitatory L5A neurons seem to preferentially innervate L2, L5A and L5B[20,48,49].

L6 contains diverse neurons, including corticothalamic (CT) neurons that project to VPM and POm, probably serving a modulatory, rather than driving, function. These same CT neurons specifically innervate L5A[50], thus also playing a direct role in modulating cortical activity in addition to modulating the thalamus. Other L6 neurons project broadly across wS1 and other cortical regions[51].

Distinct functional roles of subtypes of excitatory and inhibitory neurons in different layers with different projections receiving diverse synaptic inputs are gradually emerging through cell-type-specific measurements and perturbations during behavior, as discussed later in this review. One potentially useful concept might be to consider the neocortex, including primary sensory cortices, as high-order association areas, contributing to behavior as part of hierarchical nested sensorimotor loops. In this respect, one could view thalamocortical input to L5, as a minimal input-output circuit of cortex, upon which is superimposed a higher order thalamocortical loop via L4→L2/3→L5, with L2/3 perhaps contributing top-down high-order associative input (along with L1 input) useful for the selection of which L5 neurons should be active during specific sensorimotor tasks.

Sparse coding

Most neurons in wS1 respond to whisker deflection with a depolarizing response, presumably resulting from excitatory glutamatergic input from thalamus and local excitatory neurons. The shortest-latency responses are found in L4 and L5B/6, where the VPM thalamic input arrives[13,14,42]. More superficial neurons in L2/3 respond with longer latencies and typically also have longer-lasting responses[52]. Although almost all neurons in wS1 receive whisker sensory-evoked excitatory synaptic input, only a small proportion (typically less than 10%) of neurons fire action potentials in response to deflection of a whisker. The reason for this seems to be a fast recruitment of inhibition, likely mediated in large part by a fast-spiking subtype of GABAergic inhibitory neurons that express the calcium-binding protein parvalbumin (PV) (FIG. 2c). The PV^+ neurons located in L3, L4 and L5 receive prominent short-latency thalamic input, and are strongly reciprocally connected to nearby excitatory neurons[53,54]. They thus provide both feedforward and feedback inhibition within

local microcircuits. Neurons in wS1 therefore receive near simultaneous excitatory and inhibitory input in response to whisker deflection, and these combined conductances, with excitation having a reversal potential near 0 mV and inhibition having a reversal potential near -75 mV, act to transiently clamp the somatic membrane potential to a value that for most neurons is hyperpolarized relative to action potential threshold. Thus, only a subset of neurons receiving large excitatory synaptic inputs are able to fire action potentials in response to whisker deflection, but they can do so reliably[52,55–57]. Large (several mV) unitary excitatory synaptic connections are rare within the local microcircuit of excitatory neurons[20], but they might wire specific neurons together for reliable sensory processing (FIG. 2d), and might emerge through activity-dependent strengthening of useful connections[58].

Such sparse **[G]** reliable coding enforced by rapid inhibition seems to be a general rule in wS1 across various whisker-related behaviors[52,55,56,59]. The massive expansion in the number of neurons associated with each whisker in neocortex, compared with the previous processing stations in thalamus and brainstem, allows for such sparse representations, which may help integration of specific top-down or motor-related signals and simplify decoding in downstream brain regions.

Cortical states

Ongoing behavior and diverse brain states strongly modulate cortical function. Here, we will contrast typical patterns of neural activity in wS1 during active whisking and during quiet wakefulness (when the whiskers are not moving).

Quiet wakefulness

During quiet wakefulness, various classes of excitatory and inhibitory L2/3 neurons — except a class of GABAergic neurons expressing somatostatin (SST)[60] — show highly correlated, slow V_m fluctuations[61,62]. For example, during quiet periods, L2/3 excitatory and PV^+neurons typically display large (~10 mV) slow (1-5 Hz) synchronous V_m fluctuations[12,60–63] (FIG. 3a). The slow synchronous activity is likely driven by thalamic input and local recurrent excitation. Inhibitory neurons on average fire at much higher rates than the excitatory neurons, thus maintaining sparse activity in the excitatory neurons. In contrast, L2/3 SST^+ neurons have much reduced slow V_m fluctuations, and SST^+ V_m dynamics have little correlation to V_m of nearby neurons[60,63]. L2/3 SST^+ neurons must therefore receive or process synaptic inputs differently compared to their surrounding neurons. The L2/3 SST^+ neurons are unusual in that they: receive strong inhibition from another class of GABAergic neuron characterized by expression of vasoactive intestinal peptide (VIP)[64–66]; receive little input from the thalamus[29,47,67]; receive inputs from nearby excitatory neurons showing strong frequency-dependent short-term synaptic facilitation[68–71]; and have a relatively long membrane time-constant **[G]**, promoting summation of synaptic potentials[68–71].

Active state during whisking

Active behavioral states that involve movements are typically accompanied by active cortical states that are characterized by desynchronized neuronal activity with reduced slow-frequency V_m fluctuations[12,72–81]. Motor control is crucial for the somatosensory system, as tactile sensory information is often actively acquired by touching and palpating objects. During active cortical states accompanying whisking, the slow V_m fluctuations of excitatory L2/3 neurons are suppressed, their V_m variance is strongly reduced, and their V_m is typically slightly depolarized[12] (FIG. 3a). Action potential firing of L2/3 excitatory neurons remains sparse, with some excitatory neurons increasing firing rate and others decreasing. Fast-spiking PV^+ GABAergic neurons in L2/3 follow a very similar pattern of V_m changes, with an obvious reduction in slow V_m fluctuations during whisking and slight depolarization[61,63]. On average, the action potential rate in PV^+ neurons is much higher than for excitatory neurons. During whisking, the firing rate of L2/3 PV^+ neurons on average decreases slightly, because the V_m variance is strongly reduced and the V_m therefore crosses the firing threshold less often[61,63]. VIP^+neurons in L2/3 depolarize strongly during whisking and increase action potential rate, likely driven in part by inputs from motor cortex[64] and also by cholinergic input[82] that activates nicotinic acetylcholine receptors (nAChRs)[83]. VIP^+ neurons strongly inhibit SST^+ neurons[64–66] (FIG. 3b), which thus hyperpolarize and reduce action potential firing rate during whisking[60,64]. Excitatory neurons within L2/3 receive strong GABAergic inhibitory synaptic input from PV^+ neurons[30,31,84] and SST^+ neurons[69,85], both of which exhibit lower firing rates during whisking. Thus, excitatory neurons in L2/3 may be somewhat disinhibited during whisking, which might contribute to enhance sensorimotor integration and processing. Less is known about the activity of neurons in deeper layers, although increased firing during whisking has been reported for fast-spiking inhibitory L4 neurons[86], a subset of deep layer SST^+ neurons[87] and pyramidal neurons in L5A[88].

Mechanisms regulating the active state

Changes in thalamic activity contribute strongly to driving the changes in cortical state. Action potential firing increases in both VPM and POm neurons during whisking, with VPM neurons showing a stronger modulation[89–91]. Optogenetic stimulation of thalamic activity is sufficient to evoke an active cortical state in wS1[90]. Pharmacological inactivation of the somatosensory thalamus increases slow V_m fluctuations in quiet periods, whereas, during whisking, V_m of excitatory neurons in wS1 is hyperpolarized with little variance[90]. Physiologically, the increase in thalamic action potential firing during whisking therefore seems to drive the depolarized active cortical state measured in excitatory L2/3 neurons. The reduced V_m variance of these cells during whisking probably results from a combination of excitatory and inhibitory conductances that clamp V_m at intermediate levels of depolarization, usually hyperpolarized with respect to action potential threshold. Experiments in deafferented animals show that neither the increase in thalamic firing[90] nor the active cortical state[62] during whisking depend on input from the sensory periphery, and thus appear to be driven by internally generated signals. Interestingly, wS1 is also predominantly in an active desynchronized state during goal-directed whisker-dependent tasks not involving whisking[55], further supporting the idea that internal mechanisms drive active cortical states.

Cholinergic input also seems to serve an important function in regulating cortical state during whisking. In the absence of thalamic input, spontaneous activity in wS1 cortex is suppressed during whisking, largely owing to the activation of muscarinic acetylcholine receptors (mAChRs)[82]. Cholinergic axons from the nucleus basalis innervating wS1 are more active during whisking compared to quiet periods, and optogenetic stimulation of the cholinergic neurons mimics the effects of whisking that were observed in excitatory L2/3 wS1 neurons of thalamus-inactivated mice[82]. In addition to depolarizing VIP^+ neurons through nAChRs, the released ACh acts on mAChRs, which are expressed by various cortical neurons. Notably, L4 SST^+ neurons were recently demonstrated to be excited through mAChR activation during whisking[87], and thus these cholinergic inputs could contribute to the hyperpolarization of excitatory wS1 neurons during whisking in the absence of thalamic input. ACh probably acts on many presynaptic and postsynaptic targets, giving rise to complex network effects. There are many other neuromodulatory inputs to wS1, including prominent serotonergic and noradrenergic[92] innervation, and each probably contributes to regulating distinct aspects of wS1 function.

State-dependent sensory processing

As described above, several mechanisms thus seem to contribute to controlling the active cortical state in wS1 during whisking. These changes are likely to contribute to the profound differences in the processing of brief whisker stimuli delivered during whisking versus quiet periods. Notably, the same brief whisker deflection evokes a high-amplitude sensory response in wS1 during quiet wakefulness, but a smaller response during whisking (FIG. 3c,d)[12,15,93,94]. Furthermore, the sensory-evoked response visualized by voltage-sensitive dye imaging can spread across a large part of sensorimotor cortex if the whisker is deflected during quiet wakefulness, but if the same stimulus is delivered during whisking, the evoked response is more localized (FIG. 3c)[15]. The reduced sensory-evoked response in cortex during whisking probably contributes to the lower performanceof mice performing a simple detection task when stimuli are delivered during whisking, compared to during quiet periods[95]. The whisker system therefore seems to be more sensitive to detection of stimuli during quiet periods. This makes intuitive sense, for example if we consider our reduced ability to detect a vibrating cell phone in a pocket while we are walking compared to when we are sitting still.

Mechanistically, this state-dependent sensory processing in wS1 might relate to the whisking-dependent modulation of thalamic firing rates. During quiet wakefulness, the rates of spontaneous thalamic firing are low, and whisker deflection will evoke thalamic activity with a high contrast relative to baseline firing, which probably helps to drive strong wS1 responses to whisker deflection. The reduced responsiveness of wS1 to whisker deflection during whisking is likely, at least in part, to be mediated by the high spontaneous firing rate of thalamic neurons, onto which a sensory signal must be superimposed with a relatively reduced contrast. Furthermore, thalamocortical synapses exhibit pronounced short-term depression[96,97], and thus the high baseline firing rates of thalamic neurons during whisking may suppress the release of glutamate from thalamocortical synapses evoked by whisker stimulation.

Although passively evoked sensory responses are reduced during whisking, active touch of real objects nonetheless evokes strong sensory responses in wS1[12,15]. A brainstem sensorimotor loop may help amplify the touch response of real objects, but not of a passively applied stimulus[98]. Upon active touch, sensory trigeminal neurons drives a sequence of whisker retraction followed by protraction[98]. The secondary protraction (termed a 'double pump') will evoke a sensory signal only if the whisker is contacting a real object. Thus active touch might evoke larger responses than expected from the analysis of passively applied test stimuli.

Computations in wS1

The intricate neuronal circuits of wS1 and interconnected brain areas are thought to perform many different computations that involve context-, motivation- and learning-dependent sensorimotor integration and transformation. Here, I discuss the possible contributions of the neuronal circuitry of wS1 to two computations: object localization and texture coding.

Object localization

Behavioral experiments revealed that head-restrained rats can accurately localize the position of an object (for example a pole) using a single whisker[99,100]. The animals scanned their facial environment by moving their whiskers backandforth, evoking active touch signals upon whisker-object contact. Object location can be computed from the timing of active touch events in the context of the time-varying position of the whisker[101]. This computation therefore requires the integration of motor and sensory signals.

The V_m and action potential firing rate of many neurons in wS1 are modulated on a rapid time-scale, phase-locked with the ~10 Hz whisking cycle[12,61,62,102,103], with different neurons showing peak depolarization at different phases of the whisking cycle (FIG. 4a). Touch-evoked postsynaptic potentials might thus bring the V_m of different subsets of neurons to action potential threshold depending on the phase of the whisking cycle at contact time (FIG. 4a). Indeed, extracellular spike recordings from wS1 during active touch revealed that the phase of the maximally tuned touch response of a subset of neurons was similar to the preferred phase of these neurons during free whisking[103]. These data are thus consistent with the notion that motor-related and touch-related signals converge in wS1 to contribute to the coding of object location.

Motor-related signals in wS1 likely originate from at least two sources: sensory reafference signals **[G]** [62,102], which are generated by whisking-related stressesaffecting primary sensory afferents[104–106], and efference copies **[G]** (also known as corollary discharge) of motor commands. Exploratory whisking is thought to be controlled in part by neurons in the whisker-related primary motor cortex (wM1), which encode the phase, amplitude and set-point **[G]** of whisking movements[107,108]. wM1 strongly innervates L1 and L5/6 of wS1[109], and motor commands from wM1 might therefore contribute to the computation of object location in wS1. Indeed, imaging in L1 of the distal dendrites of excitatory L5 pyramidal neurons in wS1 during an object localization task suggest a prominent role for wM1[110]. Touch-evoked calcium signals in tuft dendrites of individual neurons were highly tuned to object location and were suppressed if wM1 was inactivated[110,111] (FIG. 4b). Neuronal

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activity in wM1 is likely to affect distal dendrites in wS1 both through its direct innervation of wS1, and also indirectly via POm thalamus. Distal dendrites are electrically excitable exhibiting NMDA spikes, calcium spikes and plateau potentials **[G]** which can interact with somatic action potential firing[112]. Motor-related input to distal dendrites might interact with sensory input arriving on basal dendrites of pyramidal neurons through non-linear dendritic integration thus contributing to the computation of object location[110,111].

Texture coding

Rodents typically actively sweep their whiskers across a surface to obtain textural information, and are able to discriminate different textures using their whiskers, for example distinguishing a smooth surface from one with shallow grooves spaced less than 100 μm apart, similar to the acuity of the human fingertip[113]. As the moving whisker encounters surface irregularities, it will in some cases become 'stuck' on the surface feature. As the whisker continues to protract (or retract), the frictional forces are overcome, inducing a rapid acceleration of the whisker, termed a 'slip'[114–117]. The frequency and pattern of slips encodes texture roughness **[G]** [117]. The large acceleration of the whisker induced by a slip evokes action potential firing in wS1[115], and the patterns of neuronal activity recorded in wS1 can be used to decode different presented textures[114,118–121].

Brief, rapid deflection of whiskers seems to be an elementary tactile feature in many whisker-dependent tasks, perhaps representing a quantum of tactile information that plays a prominent part in: detection tasks in which a brief stimulus is typically applied to a whisker; object localization in which the whisker typically only bends briefly during object contact; and texture discrimination, in which brief slip events seem to be particularly important.

Sensorimotor integration is also essential for texture coding, as the rate of slips will depend upon how quickly the whisker is moved across the surface. Many aspects of texture discrimination remain to be investigated, including a likely role for temporal and spatial integration across multiple barrels in wS1 through lateral connectivity of axons in L2/3 and L5/6, as typically many whiskers simultaneously sample features of a surface.

Goal-directed sensorimotor processing

Although wS1 has a direct role in whisker motor control (BOX 1), its largest contribution to governing behavior is likely to be more indirect. Through associative learning **[G]**, whisker sensory information can become important for goal-directed behavior. Context-, motivation- and learning-dependent processing of whisker-related sensory information is likely to involve many brain regions including wS1 and its many downstream targets (FIG. 1c). An important goal is to uncover the neuronal circuits underlying the transformation of whisker sensory information into goal-directed motor output.

Simple behaviors that are amenable to detailed analysis of neuronal circuit function during task learning and execution include detection tasks in which animals learn to lick a reward spout in response to perceived whisker stimuli (typically a brief ~1 ms deflection of a single whisker)[55,57,99,100,118,122–124]. Head-restrained mice readily learn such tasks through trial-and-error, and neuronal recordings in wS1 reveal trial-by-trial correlates of task

performance[55–57,118,124]. Optogenetic and pharmacological inactivation of wS1 decreases hit rates **[G]** in such tasks, suggesting that neuronal activity in wS1 participates in task execution[55,57,125,126]. Conversely, optogenetic stimulation of wS1 can substitute for whisker stimulation during both learning and execution[55,127,128]. Remarkably, in trained animals, even the stimulation of single wS1 neurons can drive licking responses[129,130].

Local processing in wS1 probably contributes to the generation of sensory percepts that are necessary for the successful performance of whisker-dependent tasks. Evidence suggests that PV^+ neurons in wS1 can contribute to gating sensory-to-motor (or sensorimotor) transformations. In a simple detection task, L2/3 PV^+ neurons fired more in miss trials than in hit trials[131]. Optogenetic stimulation of PV^+ neurons reduced hit rates[55], presumably by suppressing the activity of nearby excitatory neurons. Conversely, optogenetic inhibition of PV^+ neurons enhanced hit rates[131], presumably by increasing the activity of nearby excitatory neurons. The reduced firing of PV^+ neurons in hit trials relative to miss trials could result from various mechanisms, such as inhibitory input from the basal forebrain[132,133] and local microcircuits, including PV^+-targeting inhibitory neurons[134] and VIP^+ neurons, which might receive reward-related cholinergic input[135].

Dendritic processing in tuft dendrites of L5 pyramidal neurons of wS1 has also been shown to make an important contribution during whisker detection tasks. Imaged calcium responses in these tuft dendrites correlated with task performance, and optogenetic suppression of tuft dendrite activity reduced task performance, by shifting the perceptual threshold to a stronger stimulation strength[136].

In various whisker-dependent tasks, tactile information therefore seems to transit through wS1, where it is presumably processed in a context-, motivation- and learning-dependent manner before being signalled to downstream brain regions contributing to task execution. Electrophysiological[137] and optical[57,118,119,138] measurements have revealed that task learning is accompanied by changes in the differential routing of signals from L2/3 of wS1 to two important downstream cortical targets: wS2 and wM1. The subset of neurons in wS1 that project to wS2 (wS1→wS2 neurons) do not substantially innervate wM1, and conversely neurons in wS1 that project to wM1 (wS1→wM1 neurons) show little innervation of wS2[19,93,118]. The gene expression patterns of wS1→wS2 neurons and wS1→wM1 neurons also differs[139]. Therefore, wS1→wS2 neurons and wS1→wM1 neurons might form two distinct cell-classes. L2/3 wS1→wS2 neurons were found to signal decision-related and licking-related activity more strongly than do wS1→wM1 neurons, in an experience-dependent manner[57,118,119,137,138] (FIG. 5a). Interestingly wS1 and wS2 are reciprocally connected[16,140], and decision-related activity is prominent in both areas[138,141].Thus, positive-feedback loops comprising excitatory glutamatergic neurons between these two areas might help to select and maintain important aspects of sensory information relating to the brief whisker deflection (typically ~1 ms). Interactions between wS1 and wS2 could therefore be an early processing step in converting relevant whisker sensory information into goal-directed licking (FIG. 5b). Many other brain areas are undoubtedly involved, with evidence for involvement of frontal cortex[95,110,125,142,143], medial prefrontal cortex (mPFC)[126], dorsal hippocampal area CA1 (dCA1)[126], and striatum[144] in the execution of simple goal-directed sensorimotor transformations. Notably,

there are probably multiple parallel pathways involved, and wS1 may have a more (or less) important role depending upon the precise task conditions[145,146]. The mechanisms underlying the reward-based learning of these whisker-dependent tasks remain to be explored, and some possible hypotheses are discussed below.

Reward-based sensorimotor learning

Trial-and-error exploration of rewarded and unrewarded actions, given incoming sensory information and internal state, underlies important aspects of goal-directed sensorimotor learning. For the tasks discussed in this Review, thirsty mice are rewarded with a drop of liquid if they lick a spout in response to a specific whisker stimulus. Appropriate conversion of a whisker stimulus into licking is therefore rewarded, and correct learning should reinforce this sensory-to-motor transformation.

This reinforcement could occur through strengthening of specific neural circuits that link whisker-related to licking-related parts of the brain (FIG. 5b,c). Synaptic plasticity therefore provides a plausible mechanism for learning. However, rewards are delivered after sensory processing and after motor commands have been issued, and determining how to link delayed reward signals with appropriate synaptic plasticity in the specific neural circuits that contributed to success is not trivial, termed the credit-assignment problem **[G]**.

Goal-directed learning is very important for animal behavior, and probably involves many different mechanisms. One hypothesis suggests that a global plasticity signal, released in response to reward, enhances synaptic plasticity specifically at tagged, recently active synapses[147–149]. Theoretical work on such eligibility traces **[G]** and three factor plasticity rules **[G]** to solve the credit-assignment problem of what synaptic weights to change in response to reward-related feedback shows that such signals are useful for learning in neuronal networks[150–153]. Neuromodulators, including acetylcholine[135,154] and dopamine[155,156], have been proposed to contribute such signals in the mammalian brain.

Acetylcholine

Cholinergic neurons increase firing in response to unexpected rewards[135], and cholinergic innervation is prominent in wS1[82]. Acetylcholine acts on many different receptors in various neocortical cell types. As discussed earlier, nAChRs are prominently expressed on VIP^+ neurons[83,157], which disinhibit excitatory neurons[64–66]. Interestingly, acetylcholine has been proposed to enhance plasticity through disinhibition in the auditory cortex during auditory fear learning[134]. In L2/3 of wS1, VIP^+ neurons strongly inhibit SST^+ neurons[64], which prominently inhibit L1 distal tuft dendrites of pyramidal neurons. A cholinergic reward signal in wS1 might therefore disinhibit distal dendrites, which could enhance glutamatergic synaptic plasticity, perhaps linking top-down or motor-related signals in L1 axons with sensory signals in basal dendrites of L2/3 and L5 neurons. Coincidence of excitatory input in basal and distal dendrites can cause burst firing of excitatory pyramidal neurons[158], an important pattern of neuronal activity for inducing synaptic plasticity. In the context of the reward-based learning underlying the whisker detection task, acetylcholine might contribute to enhance recurrent excitation between excitatory neurons in wS1 and wS2[118,119,137,138]. In naïve mice, whisker deflection only evokes transient action potential firing of excitatory

neurons in wS1 and wS2, but the released glutamate likely remains bound to NMDA receptors for hundreds of milliseconds, and these NMDA receptors can then be activated by delayed depolarization removing the Mg^{2+} block[159]. If reward is delivered, this might evoke a cholinergic reward signal, exciting VIP^{+} neurons and thus relieving the distal dendritic inhibition imposed by SST^{+} neurons. Upon such disinhibition, the glutamate bound to NMDA receptors might then give rise to dendritic NMDA spikes[112,160,161] causing long-term potentiation between synaptically-coupled wS1 and wS2 neurons, as well as other glutamatergic inputs to wS1[162,163]. The cholinergic reward signal would thus enhance recurrent signaling between wS1 and wS2, which might prolong the sensory responses evoked by whisker deflections predicting reward, consistent with experimental observations[55,137]. This recurrent excitation could serve as a short-term memory trace of recent important sensory input, which might be useful for driving motor circuits downstream of wS1 and wS2, ultimately reaching tongue and jaw motor neurons (tjMn) responsible licking, through as yet unknown signaling pathways likely involving basal ganglia and frontal cortex, as well as other brain areas.

Dopamine

Midbrain dopamine neurons show some of the most prominent reward-related signals in the brain[155,156]. Unexpected rewards give rise to a transient increase in the firing rate of midbrain dopaminergic neurons, which project prominently to striatum (including nucleus accumbens) and, to a lesser extent, to prefrontal cortex, with little or no innervation of wS1[164,165].

The activation of dopamine type 1 receptors (D1Rs) promotes long-term potentiation of glutamatergic synaptic input onto D1R-expressing medium spiny neurons (MSNs) in the striatum[166]. Interestingly, dopamine signals arrivingup to ~1 s after the glutamatergic input scan still enhance plasticity[166,167], providing a possible mechanism for bridging the time between the activity in the sensorimotor circuits that drive the conversion of whisker sensation to licking, and the reward feedback signal.

The striatum is thought to contribute importantly to action selection and initiation: the enhanced firing of D1R-expressing MSNs (which form the so-called direct pathway striatal projection neurons, dSPNs) could suppress inhibitory neurons in the substantia nigra pars reticulata, in turn leading to disinhibition of motor-related regions in the brainstem and thalamus (FIG. 5c). Consistent with this hypothesis, in a whisker detection task, D1R-expressing striatonigral projection neurons (dSPNs) in the whisker-related dorsolateral striatum showed larger short-latency sensory responses than did D2R-expressing striatopallidal projection neurons in the same region[144]. Furthermore, optogenetic stimulation of D1R-expressing neurons, but not D2R-expressing neurons, could substitute for the whisker stimulus[144], suggesting a possible causal role for D1R-expressing MSNs in goal-directed sensorimotor transformation. In the auditory system, increases in corticostriatal signalling have also been suggested to contribute importantly in a frequency discrimination task[168,169]. In these auditory tasks, inhibition of corticostriatal signaling impaired task performance, and cortical evoked local field potential signals were enhanced across task learning, suggesting that long-term synaptic plasticity at corticostriatal synapses

could contribute to task learning[168,169]. One hypothesis to account for reward-based learning in the whisker detection task is therefore that the dopamine reward signal strengthens corticostriatal synapses from wS1 onto D1R-expressing MSNs, which in turn would enhance the whisker-deflection evoked inhibition of tonically-active neurons in substantia nigra pars reticulata involved in suppressing licking (FIG. 5c). Importantly, the striatal neurons also receive thalamic input, and it is possible that cortex plays a key role in directing appropriate plasticity of thalamostriatal synapses, especially as learning progresses and stimulus-action coupling evolves into a habit[170,171]. Although the increased whisker-evoked sensory response found in D1R-expressing MSNs in mice carrying out the whisker detection task may result from potentiation of cortical input from wS1, it could therefore also reflect potentiation of input from the whisker-related POm thalamus.

Conclusions and future perspectives

Important principles of whisker-related sensorimotor processing in cell-type-specific neuronal circuits of wS1 are now beginning to be understood. However, much remains to be explored including the relationship between local microcircuits in wS1 and the inputs they receive from (and send to) many other brain regions. Investigation of learning mechanisms and the effects upon local and long-range wS1 circuits will be of special importance. Further important integrative roles for cell-type-specific circuit function in wS1 will likely be discovered through experiments involving more complex multiwhisker-dependent behaviors, such as aperture discrimination[172–174] and shape discrimination[175] tasks, as well as multisensory tasks[176], navigation[127,177] and social behaviors[178,179].

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Glossary definitions

Somatotopic
well-ordered body map

Mystacial
area around the facial whiskers

Trigeminal ganglion
sensory ganglion of the trigeminal nerve

Sparse
small fraction of neurons

Membrane time-constant
time needed to discharge the membrane capacitance

Reafference signals
sensory signals generated by self-driven motion

Efference copies
internal motor-related signals used for sensory processing

Set-point
angle around which the whisker is moved back and forth

Plateau potentials
persistent inward currents giving long-lasting depolarisation

Roughness
uneven irregular surface feature

Associative learning
learning of the relationship between sensorimotor events

Hit rates
fraction of stimulus trials in which licking is evoked

Credit assignment problem
many circuits are typically active during trial-and-error based learning and it is difficult to determine which synapses should change

Eligibility traces
short-term memory of recently active circuit eligiblefor undergoinglearning changes

Three-factor plasticity rules
synaptic plasticity rules depending upon presynaptic activity, postsynaptic activity and an additional factor, typically a neuromodulator

References

1. Woolsey TA, Van der Loos H. The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex. The description of a cortical field composed of discrete cytoarchitectonic units. Brain Res. 1970; 17:205–242. [PubMed: 4904874]
2. Van der Loos H, Woolsey TA. Somatosensory cortex: structural alterations following early injury to sense organs. Science. 1973; 179:395–398. [PubMed: 4682966]
3. Welker E, Van der Loos H. Quantitative correlation between barrel-field size and the sensory innervation of the whiskerpad: a comparative study in six strains of mice bred for different patterns of mystacial vibrissae. J Neurosci. 1986; 6:3355–3373. [PubMed: 3772437]
4. Welker E, et al. Altered sensory processing in the somatosensory cortex of the mouse mutant barrelless. Science. 1996; 271:1864–1867. [PubMed: 8596955]
5. Hannan AJ, et al. PLC-beta1, activated via mGluRs, mediates activity-dependent differentiation in cerebral cortex. Nat Neurosci. 2001; 4:282–288. [PubMed: 11224545]
6. Iwasato T, et al. Cortex-restricted disruption ofNMDAR1 impairs neuronal patterns in the barrelcortex. Nature. 2000; 406:726–731. [PubMed: 10963597]
7. Fukuchi-Shimogori T, Grove EA. Neocortex patterning by the secreted signalingmolecule FGF8. Science. 2001; 294:1071–1074. [PubMed: 11567107]
8. Deschênes M, Timofeeva E, LavallDeschêe P. The relay of high-frequency sensory signals in the Whisker-to-barreloid pathway. J Neurosci. 2003; 23:6778–6787. [PubMed: 12890771]
9. Arsenault D, Zhang Z. Developmental remodelling of the lemniscal synapse in the ventral basal thalamus of the mouse. J Physiol (Lond.). 2006; 573:121–132. [PubMed: 16581865]

10. Arnold PB, Li CX, Waters RS. Thalamocortical arbors extend beyond single cortical barrels: an in vivo intracellular tracing study in rat. Exp Brain Res. 2001; 136:152–168. [PubMed: 11206278]
11. Furuta T, Deschênes M, Kaneko T. Anisotropic distribution of thalamocortical boutons in barrels. J Neurosci. 2011; 31:6432–6439. [PubMed: 21525284]
12. Crochet S, Petersen CCH. Correlating whisker behavior with membrane potential in barrel cortex of awake mice. Nat Neurosci. 2006; 9:608–610. [PubMed: 16617340]
13. Zhu JJ, Connors BW. Intrinsic firing patterns and whisker-evoked synaptic responses of neurons inthe rat barrel cortex. J Neurophysiol. 1999; 81:1171–1183. [PubMed: 10085344]
14. Moore CI, Nelson SB. Spatio-temporal subthreshold receptive fields in the vibrissa representation of rat primary somatosensory cortex. J Neurophysiol. 1998; 80:2882–2892. [PubMed: 9862892]
15. Ferezou I, et al. Spatiotemporal dynamics of cortical sensorimotor integration in behaving mice. Neuron. 2007; 56:907–923. [PubMed: 18054865]
16. Aronoff R, et al. Long-range connectivity of mouse primary somatosensory barrel cortex. Eur J Neurosci. 2010; 31:2221–2233. [PubMed: 20550566]
17. Welker E, Hoogland PV, Van der Loos H. Organization of feedback and feedforward projections of the barrel cortex: a PHA-L study in the mouse. Exp Brain Res. 1988; 73:411–435. [PubMed: 3215316]
18. White EL, DeAmicis RA. Afferent and efferent projections of the region in mouse SmL cortex which contains the posteromedial barrel subfield. J Comp Neurol. 1977; 175:455–482. [PubMed: 915034]
19. Yamashita T, et al. Diverse Long-Range Axonal Projections of Excitatory Layer 2/3 Neurons in Mouse Barrel Cortex. Front Neuroanat. 2018; 12:33. [PubMed: 29765308]
20. Lefort S, Tomm C, SarriaFloyd J-C, Petersen CCH. The excitatory neuronal networkof the C2 barrel column in mouse primary somatosensory cortex. Neuron. 2009; 61:301–316. [PubMed: 19186171]
21. Jensen KF, Killackey HP. Terminal arbors of axons projecting to the somatosensory cortex of the adult rat. I. The normal morphology of specific thalamocortical afferents. J Neurosci. 1987; 7:3529–3543. [PubMed: 3316525]
22. Wimmer VC, Bruno RM, de Kock CPJ, Kuner T, Sakmann B. Dimensions of a projection column and architecture of VPM and POm axons in rat vibrissal cortex. Cereb Cortex. 2010; 20:2265–2276. [PubMed: 20453248]
23. Feldmeyer D, Lübke J, Silver RA, Sakmann B. Synaptic connections between layer 4 spiny neurone-layer 2/3 pyramidal cell pairs in juvenile rat barrel cortex: physiologyand anatomy of interlaminar signalling within a cortical column. J Physiol. (Lond.). 2002; 538:803–822. [PubMed: 11826166]
24. Harris JA, Petersen RS, Diamond ME. Distribution of tactile learning and its neural basis. Proc Natl Acad Sci USA. 1999; 96:7587–7591. [PubMed: 10377459]
25. Ferezou I, Bolea S, Petersen CCH. Visualizing the cortical representation of whisker touch: voltage-sensitive dye imaging in freely moving mice. Neuron. 2006; 50:617–629. [PubMed: 16701211]
26. Peron SP, Freeman J, Iyer V, Guo C, Svoboda K. A Cellular Resolution Map of Barrel Cortex Activity during Tactile Behavior. Neuron. 2015; 86:783–799. [PubMed: 25913859]
27. Estebanez L, ElBoustani S, Destexhe A, Shulz DE. Correlated input reveals coexisting coding schemes in a sensory cortex. Nat Neurosci. 2012; 15:1691–1699. [PubMed: 23160042]
28. Brecht M, Roth A, Sakmann B. Dynamic receptive fields of reconstructed pyramidal cells in layers 3 and 2 of rat somatosensory barrel cortex. J Physiol (Lond.). 2003; 553:243–265. [PubMed: 12949232]
29. Gibson JR, Beierlein M, Connors BW. Two networks of electrically coupled inhibitory neurons in neocortex. Nature. 1999; 402:75–79. [PubMed: 10573419]
30. Avermann M, Tomm C, Mateo C, Gerstner W, Petersen CCH. Microcircuits of excitatory andinhibitory neurons in layer 2/3 of mouse barrel cortex. J Neurophysiol. 2012; 107:3116–3134. [PubMed: 22402650]

31. Holmgren C, Harkany T, Svennenfors B, Zilberter Y. Pyramidal cell communication within local networks in layer 2/3 of rat neocortex. J Physiol (Lond.). 2003; 551:139–153. [PubMed: 12813147]
32. Helmstaedter M, Staiger JF, Sakmann B, Feldmeyer D. Efficient recruitment of layer 2/3 interneurons by layer 4 input in single columns of rat somatosensory cortex. J Neurosci. 2008; 28:8273–8284. [PubMed: 18701690]
33. Urban-Ciecko J, Jouhanneau J-S, Myal SE, Poulet JFA, Barth AL. Precisely Timed Nicotinic Activation Drives SST Inhibition in Neocortical Circuits. Neuron. 2018; 97:611–625.e5. [PubMed: 29420933]
34. Harris KD, Shepherd GMG. The neocortical circuit: themesand variations. Nat Neurosci. 2015; 18:170–181. [PubMed: 25622573]
35. Feldmeyer D, Qi G, Emmenegger V, Staiger JF. Inhibitory interneurons and their circuit motifs in the many layers of the barrel cortex. Neuroscience. 2018; 368:132–151. [PubMed: 28528964]
36. Tremblay R, Lee S, Rudy B. GABAergic Interneurons in the Neocortex: From Cellular Properties to Circuits. Neuron. 2016; 91:260–292. [PubMed: 27477017]
37. Luo L, Callaway EM, Svoboda K. Genetic Dissection of Neural Circuits: A Decade of Progress. Neuron. 2018; 98:256–281. [PubMed: 29673479]
38. Adesnik H, Naka A. Cracking the Function of Layersin the Sensory Cortex. Neuron. 2018; 100:1028–1043. [PubMed: 30521778]
39. Feldmeyer D. Excitatory neuronal connectivity in the barrel cortex. Front Neuroanat. 2012; 6:24. [PubMed: 22798946]
40. Petersen CCH, Grinvald A, Sakmann B. Spatiotemporal dynamics of sensory responses in layer 2/3 of rat barrel cortex measured in vivo by voltage-sensitivedye imaging combined with whole-cell voltage recordings and neuron reconstructions. J Neurosci. 2003; 23:1298–1309. [PubMed: 12598618]
41. Narayanan RT, et al. Beyond Columnar Organization: Cell Type- and Target Layer-Specific Principlesof Horizontal Axon Projection Patterns in Rat Vibrissal Cortex. Cereb Cortex. 2015; 25:4450–4468. [PubMed: 25838038]
42. Constantinople CM, Bruno RM. Deep cortical layers are activated directly by thalamus. Science. 2013; 340:1591–1594. [PubMed: 23812718]
43. Oberlaender M, et al. Three-dimensional axon morphologies of individual layer 5 neurons indicate cell type-specific intracortical pathways for whisker motion and touch. Proc Natl Acad Sci USA. 2011; 108:4188–4193. [PubMed: 21368112]
44. Kiritani T, Wickersham IR, Seung HS, Shepherd GMG. Hierarchical connectivity and connection-specific dynamics in the corticospinal-corticostriatal microcircuit in mouse motorcortex. J Neurosci. 2012; 32:4992–5001. [PubMed: 22492054]
45. Guo C, et al. Single-axon level morphologicalanalysis of corticofugal projection neurons inmouse barrel field. Sci Rep. 2017; 7:2846. [PubMed: 28588276]
46. Rojas-Piloni G, et al. Relationships between structurein vivo function and long-range axonal target of cortical pyramidal tract neurons. Nat Commun. 2017; 8:870. [PubMed: 29021587]
47. Audette NJ, Urban-Ciecko J, Matsushita M, Barth AL. POm Thalamocortical Input Drives Layer-Specific Microcircuits in Somatosensory Cortex. Cereb Cortex. 2018; 28:1312–1328. [PubMed: 28334225]
48. Bureau I, von SaintPaul F, Svoboda K. Interdigitated paralemniscal and lemniscal pathways in the mouse barrel cortex. PLoS Biol. 2006; 4:e382. [PubMed: 17121453]
49. Schubert D, Kötter R, Staiger JF. Mapping functional connectivityin barrel-related columns reveals layer- and cell type-specific microcircuits. Brain Struct Funct. 2007; 212:107–119. [PubMed: 17717691]
50. Kim J, Matney CJ, Blankenship A, Hestrin S, Brown SP. Layer 6 corticothalamic neuronsactivate a cortical output layer, layer 5a. J Neurosci. 2014; 34:9656–9664. [PubMed: 25031405]
51. Pichon F, Nikonenko I, Kraftsik R, Welker E. Intracortical connectivity of layer VI pyramidal neurons in the somatosensorycortex of normal and barrelless mice. Eur J Neurosci. 2012; 35:855–869. [PubMed: 22356566]

52. Crochet S, Poulet JFA, Kremer Y, Petersen CCH. Synaptic mechanisms underlying sparse coding of active touch. Neuron. 2011; 69:1160–1175. [PubMed: 21435560]
53. Gabernet L, Jadhav SP, Feldman DE, Carandini M, Scanziani M. Somatosensory integration controlled by dynamic thalamocortical feed-forward inhibition. Neuron. 2005; 48:315–327. [PubMed: 16242411]
54. Cruikshank SJ, Lewis TJ, Connors BW. Synaptic basis for intense thalamocortical activation of feedforward inhibitory cells in neocortex. Nat Neurosci. 2007; 10:462–468. [PubMed: 17334362]
55. Sachidhanandam S, Sreenivasan V, Kyriakatos A, Kremer Y, Petersen CCH. Membrane potential correlates of sensory perception in mouse barrel cortex. Nat Neurosci. 2013; 16:1671–1677. [PubMed: 24097038]
56. O'Connor DH, Peron SP, Huber D, Svoboda K. Neural activity in barrel cortex underlying vibrissa-based object localization in mice. Neuron. 2010; 67:1048–1061. [PubMed: 20869600]
57. Yang H, Kwon SE, Severson KS, 'Connor DH. Origins of choice-related activity in mouse somatosensory cortex. Nat Neurosci. 2016; 19:127–134. [PubMed: 26642088]
58. Cheetham CEJ, Barnes SJ, Albieri G, Knott GW, Finnerty GT. Pansynaptic enlargement at adult cortical connections strengthened by experience. Cereb Cortex. 2014; 24:521–531. [PubMed: 23118196]
59. Barth AL, Poulet JFA. Experimental evidence for sparse firing in the neocortex. Trends Neurosci. 2012; 35:345–355. [PubMed: 22579264]
60. Gentet LJ, et al. Unique functional properties ofsomatostatin-expressing GABAergic neurons in mouse barrel cortex. Nat Neurosci. 2012; 15:607–612. [PubMed: 22366760]
61. Gentet LJ, Avermann M, Matyas F, Staiger JF, Petersen CCH. Membrane potential dynamics of GABAergic neurons in the barrel cortex of behaving mice. Neuron. 2010; 65:422–435. [PubMed: 20159454]
62. Poulet JFA, Petersen CCH. Internal brain state regulates membrane potential synchrony in barrel cortex of behaving mice. Nature. 2008; 454:881–885. [PubMed: 18633351]
63. Pala A, Petersen CC. State-dependent cell-type-specific membrane potential dynamics and unitary synaptic inputs in awake mice. Elife. 2018; 7
64. Lee S, Kruglikov I, Huang ZJ, Fishell G, Rudy B. A disinhibitory circuit mediates motor integration in the somatosensory cortex. Nat Neurosci. 2013; 16:1662–1670. [PubMed: 24097044]
65. Pfeffer CK, Xue M, He M, Huang ZJ, Scanziani M. Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons. Nat Neurosci. 2013; 16:1068–1076. [PubMed: 23817549]
66. Pi H-J, et al. Cortical interneurons that specialize in disinhibitory control. Nature. 2013; 503:521–524. [PubMed: 24097352]
67. Cruikshank SJ, Urabe H, Nurmikko AV, Connors BW. Pathway-specific feedforward circuits between thalamus and neocortex revealed by selective optical stimulation of axons. Neuron. 2010; 65:230–245. [PubMed: 20152129]
68. Reyes A, et al. Target-cell-specific facilitation and depression in neocorticals. Nat Neurosci. 1998; 1:279–285. [PubMed: 10195160]
69. Kapfer C, Glickfeld LL, Atallah BV, Scanziani M. Supralinear increase of recurrent inhibition during sparse activity in the somatosensory cortex. Nat Neurosci. 2007; 10:743–753. [PubMed: 17515899]
70. Silberberg G, Markram H. Disynaptic inhibition between neocortical pyramidal cells mediated by Martinotti cells. Neuron. 2007; 53:735–746. [PubMed: 17329212]
71. Pala A, Petersen CCH. In vivo measurement of cell-type-specific synaptic connectivity and synaptic transmission in layer 2/3 mouse barrel cortex. Neuron. 2015; 85:68–75. [PubMed: 25543458]
72. Steriade M, Timofeev I, Grenier F. Natural waking and sleep states: a view from inside neocortical neurons. J Neurophysiol. 2001; 85:1969–1985. [PubMed: 11353014]
73. Bennett C, Arroyo S, Hestrin S. Subthreshold mechanisms underlying state-dependent modulation of visual responses. Neuron. 2013; 80:350–357. [PubMed: 24139040]

74. Polack P-O, Friedman J, Golshani P. Cellular mechanisms of brain state-dependent gain modulation in visual cortex. Nat Neurosci. 2013; 16:1331–1339. [PubMed: 23872595]
75. Schneider DM, Nelson A, Mooney R. A synaptic and circuit basis for corollary discharge in the auditory cortex. Nature. 2014; 513:189–194. [PubMed: 25162524]
76. Reimer J, et al. Pupil fluctuations track fast switching of cortical states during quiet wakefulness. Neuron. 2014; 84:355–362. [PubMed: 25374359]
77. Zhao W-J, Kremkow J, Poulet JFA. Translaminar Cortical Membrane Potential Synchrony in Behaving Mice. Cell Rep. 2016; 15:2387–2399. [PubMed: 27264185]
78. Buzsáki G, Draguhn A. Neuronal oscillations in cortical network. Science. 2004; 304:1926–1929. [PubMed: 15218136]
79. Berger H. Electroencephalogram in humans. Arch Psychiatr Nervenkr. 1929; 87:527–570.
80. McGinley MJ, et al. Waking State: Rapid Variations Modulate Neural and Behavioral Responses. Neuron. 2015; 87:1143–1161. [PubMed: 26402600]
81. Batista-Vinck M, Brito R, Knoblich U, Cardin JA. Arousal and locomotion make distinct contributions to cortical activity patterns and visual encoding. Neuron. 2015; 86:740–754. [PubMed: 25892300]
82. Eggermann E, Kremer Y, Crochet S, Petersen CCH. Cholinergic signals in mouse barrel cortex during active whisker sensing. Cell Rep. 2014; 9:1654–1660. [PubMed: 25482555]
83. Fu Y, et al. A cortical circuit for gain control by behavioral state. Cell. 2014; 56:1139–1152.
84. Packer AM, Yuste R. Dense, unspecific connectivity of neocortical parvalbumin-positive interneurons: a canonical microcircuit for inhibition? J Neurosci. 2011; 31:13260–13271. [PubMed: 21917809]
85. Fino E, Yuste R. Dense inhibitory connectivity in neocortex. Neuron. 2011; 69:1188–1203. [PubMed: 21435562]
86. Yu J, Gutnisky DA, Hires SA, Svoboda K. Layer 4 fast-spiking interneurons filter thalamocortical signals during active somatosensation. Nat Neurosci. 2016; 19:1647–1657. [PubMed: 27749825]
87. Muñoz W, Tremblay R, Levenstein D, Rudy B. Layer-specific modulation of neocortical dendritic inhibition during active wakefulness. Science. 2017; 355:954–959. [PubMed: 28254942]
88. de Kock CPJ, Sakmann B. Spiking in primary somatosensory cortex during natural whisking in awake head-restrained rats is cell-type specific. Proc Natl Acad Sci USA. 2009; 106:16446–16450. [PubMed: 19805318]
89. Urbain N, et al. Whisking-Related Changes in Neuronal Firing and Membrane Potential Dynamics in the Somatosensory Thalamus of Awake Mice. Cell Rep. 2015; 13:647–656. [PubMed: 26489463]
90. Poulet JFA, Fernandez LMJ, Crochet S, Petersen CCH. Thalamic control of cortical states. Nat Neurosci. 2012; 15:370–372. [PubMed: 22267163]
91. Moore JD, Mercer Lindsay N, Deschênes M, Kleinfeld D. Vibrissa Self-Motion and Touch Are Reliably Encoded along the Same Somatosensory Pathway from Brainstem through Thalamus. PLoS Biol. 2015; 13:e1002253. [PubMed: 26393890]
92. Constantinople CM, Bruno RM. Effects and mechanisms of wakefulness on local cortical networks. Neuron. 2011; 69:1061–1068. [PubMed: 21435553]
93. Yamashita T, et al. Membrane potential dynamics of neocortical projection neurons driving target-specific signals. Neuron. 2013; 80:1477–1490. [PubMed: 24360548]
94. Hentschke H, Haiss F, Schwarz C. Central signals rapidly switch tactile processing in rat barrel cortex during whisker movements. Cereb Cortex. 2006; 16:1142–1156. [PubMed: 16221924]
95. Kyriakatos A, et al. Voltage-sensitive dye imaging of mouse neocortex during a whisker detection task. Neurophotonics. 2017; 4
96. Gil Z, Connors BW, Amitai Y. Differential regulation of neocortical synapses by neuromodulators and activity. Neuron. 1997; 19:679–686. [PubMed: 9331357]
97. Castro-Alamancos MA, Oldford E. Cortical sensory suppression during arousal is due to the activity-dependent depression of thalamocortical synapses. J Physiol (Lond.). 2002; 541:319–331. [PubMed: 12015438]

98. Bellavance M-A, et al. Parallel Inhibitory and Excitatory Trigemino-Facial Feedback Circuitry for Reflexive Vibrissa Movement. Neuron. 2017; 95:673–682.e4. [PubMed: 28735746]

99. Mehta SB, Whitmer D, Figueroa R, Williams BA, Kleinfeld D. Active spatial perception in the vibrissa scanning sensorimotor system. PLoS Biol. 2007; 5:e15. [PubMed: 17227143]

100. Knutsen PM, Pietr M, Ahissar E. Haptic object localization in the vibrissal system: behavior and performance. J Neurosci. 2006; 26:8451–8464. [PubMed: 16914670]

101. Kleinfeld D, Deschênes M. Neuronal basis for object location in the vibrissa scanning sensorimotor system. Neuron. 2011; 72:455–468. [PubMed: 22078505]

102. Fee MS, Mitra PP, Kleinfeld D. Central versus peripheral determinants of patterned spike activity in rat vibrissa cortex during whisking. J Neurophysiol. 1997; 78:1144–1149. [PubMed: 9307141]

103. Curtis JC, Kleinfeld D. Phase-to-rate transformations encode touch in cortical neurons of a scanning sensorimotor system. Nat Neurosci. 2009; 12:492–501. [PubMed: 19270688]

104. Severson KS, et al. Active Touch and Self-Motion Encoding by Merkel Cell-Associated Afferents. Neuron. 2017; 94:666–676.e9. [PubMed: 28434802]

105. Campagner D, Evans MH, Bale MR, Erskine A, Petersen RS. Prediction of primary somatosensory neuron activity during active tactile exploration. Elife. 2016; 5

106. Wallach A, Bagdasarian K, Ahissar E. On-going computation of whisking phase by mechanoreceptors. Nat Neurosci. 2016; 19:487–493. [PubMed: 26780508]

107. Sreenivasan V, et al. Movement Initiation Signals in Mouse Whisker Motor Cortex. Neuron. 2016; 92:1368–1382. [PubMed: 28009277]

108. Hill DN, Curtis JC, Moore JD, Kleinfeld D. Primary motor cortex reports efferent control of vibrissa motion on multiple timescales. Neuron. 2011; 72:344–356. [PubMed: 22017992]

109. Matyas F, et al. Motor control by sensory cortex. Science. 2010; 330:1240–1243. [PubMed: 21109671]

110. Xu N, et al. Nonlinear dendritic integration of sensory and motor input during an active sensing task. Nature. 2012; 492:247–251. [PubMed: 23143335]

111. Ranganathan GN, et al. Active dendritic integration and mixed neocortical network representations during an adaptive sensing behavior. Nat Neurosci. 2018; 21:1583–1590. [PubMed: 30349100]

112. Major G, Larkum ME, Schiller J. Active properties of neocortical pyramidal neuron dendrites. Annu Rev Neurosci. 2013; 36:1–24. [PubMed: 23841837]

113. Carvell GE, Simons DJ. Biometric analyses of vibrissal tactile discrimination in the rat. J Neurosci. 1990; 10:2638–2648. [PubMed: 2388081]

114. Isett BR, Feasel SH, Lane MA, Feldman DE. Slip-Based Coding of Local Shape and Texture in Mouse S1. Neuron. 2018; 97:418–433.e5. [PubMed: 29307709]

115. Jadhav SP, Wolfe J, Feldman DE. Sparse temporal coding of elementary tactile features during active whisker sensation. Nat Neurosci. 2009; 12:792–800. [PubMed: 19430473]

116. Ritt JT, Andermann ML, Moore CI. Embodied information processing: vibrissa mechanics and texture features shape micromotions in actively sensing rats. Neuron. 2008; 57:599–613. [PubMed: 18304488]

117. Wolfe J, et al. Texture coding in the rat whisker system: slip-stick versus differential resonance. PLoS Biol. 2008; 6:e215. [PubMed: 18752354]

118. Chen JL, Carta S, Soldado-Magraner J, Schneider BL, Helmchen F. Behaviour-dependent recruitment of long-range projection neurons in somatosensory cortex. Nature. 2013; 499:336–340. [PubMed: 23792559]

119. Chen JL, et al. Pathway-specific reorganization of projection neurons in somatosensory cortex during learning. Nat Neurosci. 2015; 18:1101–1108. [PubMed: 26098757]

120. Safaai H, von Heimendahl M, Sorando JM, Diamond ME, Maravall M. Coordinated population activity underlying texture discrimination in rat barrel cortex. J Neurosci. 2013; 33:5843–5855. [PubMed: 23536096]

121. Zuo Y, et al. Complementary contributions of spike timing and spike rate to perceptual decisions in rat S1 and S2 cortex. Curr Biol. 2015; 25:357–363. [PubMed: 25619766]

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122. O'Connor DH, et al. Vibrissa-based object localization in head-fixed mice. J Neurosci. 2010; 30:1947–1967. [PubMed: 20130203]
123. Musall S, et al. Tactile frequency discrimination is enhanced by circumventing neocortical adaptation. Nat Neurosci. 2014; 17:1567–1573. [PubMed: 25242306]
124. Stüttgen MC, Schwarz C. Psychophysical and neurometric detection performance under stimulusy. Nat Neurosci. 2008; 11:1091–1099. [PubMed: 19160508]
125. Guo ZV, et al. Flow of cortical activity underlying a tactile decision in mice. Neuron. 2014; 81:179–194. [PubMed: 24361077]
126. Le Merre P, et al. Reward-Based Learning Drives Rapid Sensory Signals in Medial Prefrontal Cortex and Dorsal Hippocampus Necessary for Goal-Directed Behavior. Neuron. 2018; 97:83–91.e5. [PubMed: 29249287]
127. Sofroniew NJ, Vlasov YA, Hires SA, Freeman J, Svoboda K. Neural coding in barrel cortex during whisker-guided locomotion. Elife. 2015; 4
128. O'Connor DH, et al. Neural coding during active somatosensation revealed using illusory touch. Nat Neurosci. 2013; 16:958–965. [PubMed: 23727820]
129. Houweling AR, Brecht M. Behavioural report of single neuron stimulation in somatosensory cortex. Nature. 2008; 451:65–68. [PubMed: 18094684]
130. Tanke N, Borst JGG, Houweling AR. Single-Cell Stimulation in Barrel Cortex Influences Psychophysical Detection Performance. J Neurosci. 2018; 38:2057–2068. [PubMed: 29358364]
131. Sachidhanandam S, Sermet BS, Petersen CCH. Parvalbumin-Expressing GABAergic Neurons in Mouse Barrel Cortex Contribute to Gating a Goal-Directed Sensorimotor Transformation. Cell Rep. 2016; 15:700–706. [PubMed: 27149853]
132. Kim T, et al. Cortically projecting basal forebrain parvalbumin neurons regulate cortical gamma band oscillations. Proc Natl Acad Sci USA. 2015; 112:3535–3540. [PubMed: 25733878]
133. Freund TF, Meskenaite V. gamma-Aminobutyric acid-containing basal forebrain neurons innervate inhibitory interneurons in the neocortex. Proc Natl Acad Sci USA. 1992; 89:738–742. [PubMed: 1731348]
134. Letzkus JJ, et al. A disinhibitory microcircuit for associative fear learning in the auditory cortex. Nature. 2011; 480:331–335. [PubMed: 22158104]
135. Hangya B, Ranade SP, Lorenc M, Kepecs A. Central Cholinergic Neurons Are Rapidly Recruited by Reinforcement Feedback. Cell. 2015; 162:1155–1168. [PubMed: 26317475]
136. Takahashi N, Oertner TG, Hegemann P, Larkum ME. Active cortical dendrites modulate perception. Science. 2016; 354:1587–1590. [PubMed: 28008068]
137. Yamashita T, Petersen CC. Target-specific membrane potential dynamics of neocortical projection neurons during goal-directed behavior. Elife. 2016; 5
138. Kwon SE, Yang H, Minamisawa G, O'Connor DH. Sensory and decision-related activity propagate in a cortical feedback loop during touch perception. Nat Neurosci. 2016; 19:1243–1249. [PubMed: 27437910]
139. Sorensen SA, et al. Correlated gene expression and target specificity demonstrate excitatory projection neuron diversity. Cereb Cortex. 2015; 25:433–449. [PubMed: 24014670]
140. Minamisawa G, Kwon SE, Chevée M, Brown SP, O'Connor DHA. Non-canonical Feedback Circuit for Rapid Interactions between Somatosensory Cortices. Cell Rep. 2018; 23:2718–2731.e6. [PubMed: 29847801]
141. Chen JL, Voigt FF, Javadzadeh M, Krueppel R, Helmchen F. Long-range population dynamics of anatomically defined neocortical networks. Elife. 2016; 5
142. Guo ZV, et al. Maintenance of persistent activity in a frontal thalamocortical loop. Nature. 2017; 545:181–186. [PubMed: 28467817]
143. Petreanu L, et al. Activity in motor-sensory projections reveals distributed coding in somatosensation. Nature. 2012; 489:299–303. [PubMed: 22922646]
144. Sippy T, Lapray D, Crochet S, Petersen CCH. Cell-Type-Specific Sensorimotor Processing in Striatal Projection Neurons during Goal-Directed Behavior. Neuron. 2015; 88:298–305. [PubMed: 26439527]

145. Hutson KA, Masterton RB. The sensory contribution of a single vibrissa's cortical barrel. J Neurophysiol. 1986; 56:1196–1223. [PubMed: 3783236]
146. Hong YK, Lacefield CO, Rodgers CC, Bruno RM. Sensation, movement and learning in the absence of barrel cortex. Nature. 2018; 561:542–546. [PubMed: 30224746]
147. Gerstner W, Lehmann M, Liakoni V, Corneil D, Brea J. Eligibility Traces and Plasticity on Behavioral Time Scales: Experimental Support of NeoHebbian Three-Factor Learning Rules. Front Neural Circuits. 2018; 12:53. [PubMed: 30108488]
148. Crow TJ. Cortical synapses and reinforcement: a hypothesis. Nature. 1968; 219:736–737. [PubMed: 5667068]
149. Frey U, Morris RG. Synaptic tagging and long-term potentiation. Nature. 1997; 385:533–536. [PubMed: 9020359]
150. Mnih V, et al. Human-level control through deep reinforcement learning. Nature. 2015; 518:529–533. [PubMed: 25719670]
151. Silver D, et al. Mastering the game of Go with deep neural networks and tree search. Nature. 2016; 529:484–489. [PubMed: 26819042]
152. LeCun Y, Bengio Y, Hinton G. Deep learning. Nature. 2015; 521:436–444. [PubMed: 26017442]
153. Rumelhart D, Hinton G, Williams R. Learning Representations by Back-Propagating Errors. Nature. 1986; 323:533–536.
154. Hasselmo ME. The role of acetylcholine in learning and memory. Curr Opin Neurobiol. 2006; 16:710–715. [PubMed: 17011181]
155. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997; 275:1593–1599. [PubMed: 9054347]
156. Cohen JY, Haesler S, Vong L, Lowell BB, Uchida N. Neuron-type-specific signals for reward and punishment in the ventral tegmental area. Nature. 2012; 482:85–88. [PubMed: 22258508]
157. Férézou I, et al. 5-HT3 receptors mediate serotonergic fast synaptic excitation of neocortical vasoactive intestinal peptide/cholecystokinin interneurons. J Neurosci. 2002; 22:7389–7397. [PubMed: 12196560]
158. Larkum ME, Zhu JJ, Sakmann BA. A new cellular mechanism for coupling inputs arriving at different cortical layers. Nature. 1999; 398:338–341. [PubMed: 10192334]
159. Kampa BM, Clements J, Jonas P, Stuart GJ. Kinetics of Mg2+ unblock of NMDA receptors: implications for spike-timing dependent synaptic plasticity. J Physiol (Lond.). 2004; 556:337–345. [PubMed: 14754998]
160. Palmer LM, et al. NMDA spikes enhance action potential generation during sensory input. Nat Neurosci. 2014; 17:383–390. [PubMed: 24487231]
161. Smith SL, Smith IT, Branco T, Häusser M. Dendritic spikes enhance stimulus selectivity in cortical neurons in vivo. Nature. 2013; 503:115–120. [PubMed: 24162850]
162. Williams LE, Holtmaat A. Higher-Order Thalamocortical Inputs Gate Synaptic Long-Term Potentiation via Disinhibition. Neuron. 2019; 101:91–102.e4. [PubMed: 30472077]
163. Gambino F, et al. Sensory-evoked LTP driven by dendritic plateau potentials in vivo. Nature. 2014; 515:116–119. [PubMed: 25174710]
164. Matsuda W, et al. Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. J Neurosci. 2009; 29:444–453. [PubMed: 19144844]
165. Björklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. Trends Neurosci. 2007; 30:194–202. [PubMed: 17408759]
166. Yagishita S, et al. A critical time window for dopamine actions on the structural plasticity of dendritic spines. Science. 2015; 345:1616–1620.
167. Brzosko Z, Schultz W, Paulsen O. Retroactive modulation of spike timing-dependent plasticity by dopamine. Elife. 2015; 4
168. Znamenskiy P, Zador AM. Corticostriatal neurons in auditory cortex drive decisions during auditory discrimination. Nature. 2013; 497:482–485. [PubMed: 23636333]
169. Xiong Q, Znamenskiy P, Zador AM. Selective corticostriatal plasticity during acquisition of an auditory discrimination task. Nature. 2015; 521:348–351. [PubMed: 25731173]

170. Kawai R, et al. Motor cortex is required for learning but not for executing a motor skill. Neuron. 2015; 86:800–812. [PubMed: 25892304]
171. Grillner S. Action: the role of motor cortex challenged. Curr Biol. 2015; 25:R508–511. [PubMed: 26079084]
172. Krupa DJ, Wiest MC, Shuler MG, Laubach M, Nicolelis MAL. Layer-specific somatosensory cortical activation during active tactile discrimination. Science. 2004; 304:1989–1992. [PubMed: 15218154]
173. Krupa DJ, Matell MS, Brisben AJ, Oliveira LM, Nicolelis MA. Behavioral properties of the trigeminal somatosensory system in rats performing whisker-dependent tactile discriminations. J Neurosci. 2001; 21:5752–5763. [PubMed: 11466447]
174. Shuler MG, Krupa DJ, Nicolelis MAL. Integration of bilateral whisker stimuli in rats: role of the whisker barrel cortices. Cereb Cortex. 2002; 12:86–97. [PubMed: 11734535]
175. Brecht M, Preilowski B, Merzenich MM. Functional architecture of the mystacial vibrissae. Behav Brain Res. 1997; 84:81–97. [PubMed: 9079775]
176. Nikbakht N, Tafreshiha A, Zoccolan D, Diamond ME. Supralinear and Supramodal Integration of Visual and Tactile Signals in Rats: Psychophysics and Neuronal Mechanisms. Neuron. 2018; 97:626–639.e8. [PubMed: 29395913]
177. Sofroniew NJ, Cohen JD, Lee AK, Svoboda K. Natural whisker-guided behavior by head-fixed mice in tactile virtual reality. J Neurosci. 2014; 34:9537–9550. [PubMed: 25031397]
178. Bobrov E, Wolfe J, Rao RP, Brecht M. The representation of social facial touch in rat barrel cortex. Curr Biol. 2014; 24:109–115. [PubMed: 24361064]
179. Lenschow C, Brecht M. Barrel cortex membrane potential dynamics in social touch. Neuron. 2015; 85:718–725. [PubMed: 25640075]
180. Sreenivasan V, Karmakar K, Rijli FM, Petersen CCH. Parallel pathways from motor and somatosensory cortex for controlling whisker movements in mice. Eur J Neurosci. 2015; 41:354–367. [PubMed: 25476605]
181. Auffret M, et al. Optogenetic stimulation of cortex to map evoked whisker movements in awake head-restrained mice. Neuroscience. 2018; 368:199–213. [PubMed: 28412497]
182. Grant RA, Mitchinson B, Fox CW, Prescott TJ. Active touch sensing in the rat: anticipatory and regulatory control of whisker movements during surface exploration. J Neurophysiol. 2009; 101:862–874. [PubMed: 19036871]
183. Moore JD, et al. Hierarchy of orofacial rhythms revealed through whisking and breathing. Nature. 2013; 497:205–210. [PubMed: 23624373]
184. Deschênes M, et al. Inhibition, Not Excitation, Drives Rhythmic Whisking. Neuron. 2016; 90:374–387. [PubMed: 27041498]
185. Grinevich V, Brecht M, Osten P. Monosynaptic pathway from rat vibrissa motor cortex to facial motor neurons revealed by lentivirus-based axonal tracing. J Neurosci. 2005; 25:8250–8258. [PubMed: 16148232]
186. Chen S, Augustine GJ, Chadderton P. The cerebellum linearly encodes whisker position during voluntary movement. Elife. 2016; 5:e10509. [PubMed: 26780828]
187. Takatoh J, et al. New modules are added to vibrissal premotor circuitry with the emergence of exploratory whisking. Neuron. 2013; 77:346–360. [PubMed: 23352170]
188. Hattox AM, Priest CA, Keller A. Functional circuitry involved in the regulation of whisker movements. J Comp Neurol. 2002; 442:266–276. [PubMed: 11774341]
189. Hattox A, Li Y, Keller A. Serotonin regulates rhythmic whisking. Neuron. 2003; 39:343–352. [PubMed: 12873389]
190. Rathelot J-A, Dum RP, Strick PL. Posterior parietal cortex contains a command apparatus for hand movements. Proc Natl Acad Sci USA. 2017; 114:4255–4260. [PubMed: 28373554]

Box 1

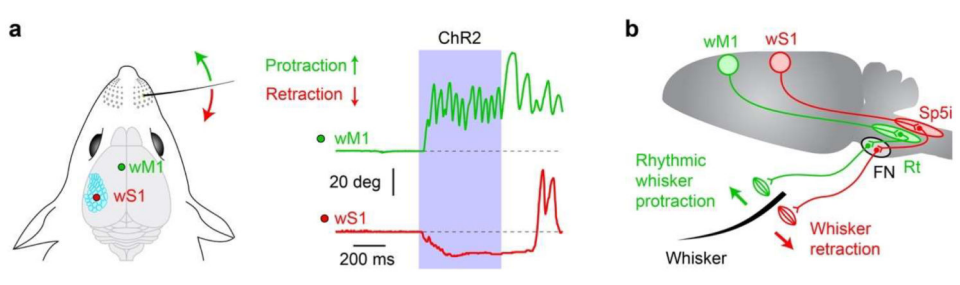
Whisker motor control by wS1

Interestingly, wS1 is not only involved in processing whisker sensory information but also directly involved in whisker motor control. The movements evoked by stimulating wS1 and wM1 are qualitatively different. Specifically, electrical or optogenetic stimulation of wS1 drives retraction of the contralateral whiskers[109,180,181] (see the figure, part **a**), whereas stimulating wM1 evokes rhythmic whisker protraction. Neuronal activity in wM1 therefore seems to drive exploratory whisker movements, presumably to enhance the acquisition of tactile sensory information during active touch. By contrast, the contralateral whisker retraction caused by neuronal activity in wS1 reduces whisker–object contacts and thus reduces the influx of whisker-related sensory information. wS1-driven whisker retraction might therefore serve a negative-feedback role, preventing over-excitation of wS1. Consistent with this hypothesis, pharmacological inactivation of wS1 prevented the contralateral whisker retraction that was induced by strong repetitive stimulation of whiskers[109]. Such a negative-feedback signal, as well as a prominent negative feedback loop in the brainstem[98], might also have a role in governing whisker movements during active touch. Sensory-evoked signals in wS1 during active touch could evoke whisker retraction motor commands.Such a negative-feedback signal might help explain why whisker–object contacts typically occur at the most protracted point in the whisking cycle[52]. Active touch therefore seems to be governed by a ‘minimal impingement’ model with whiskers typically making light contact and ceasing to advance immediately after initial whisker–object touch[182], followed by later protraction giving rise to a ‘double-pump’[98].

The motor role of wS1 in driving whisker retraction does not depend on wM1, since it persists after pharmacological inactivation of wM1[109]. Moreover, the latency for evoking contralateral whisker movement by stimulating wS1 is shorter than that of stimulating wM1[109]. These data thus suggest a rather direct motor pathway from wS1. Anatomical tracing studies show that wS1 projects strongly to the spinal trigeminal nuclei, in a pathway that is apparently parallel to the projection from wM1 to the brainstem reticular (Rt) formation. Neurons in the spinal trigeminal interpolaris nucleus (Sp5i) directly innervate motor neurons in the facial nucleus (FN), which control the extrinsic muscles of the whisker pad that govern retraction movements[180]. The shortest circuit for wS1 to drive whisker retraction might therefore involve only three synapses: wS1→Sp5i→FN→muscle (see the figure, part **b**). This is similar to the main pathway by which wM1 is thought to evoke whisker protraction (wM1→IRt→FN→muscle)[183]. A ventral portion of IRt (vIRt) is thought to contain the oscillator for driving rhythmic whisker movements[183], with inhibitory premotor neurons in vIRt innervating the facial nucleus motor neurons of intrinsic muscles driving whisker protraction[184]. Interestingly, some neurons in wM1 also directly innervate FN[180,185]. Conversely, there are many other, more complex, synaptic circuits by which wM1 and wS1 can control whisker movements; for example, wS1 activity can evoke rhythmic whisker protraction at long latencies by recruiting wM1[107]. Finally, it is worth pointing out that many other brain

regions contribute to controlling whisker movements, including many other brainstem nuclei, cerebellum, and superior colliculus[98,180,186–189].

Although wS1 is clearly a primary sensory area that receives strong innervation from the primary somatosensory thalamus and is the first cortical area to respond to whisker deflection, it could also be viewed as a primary motor area that evokes whisker movements with a shorter latency than other cortical areas[109,181]. Interestingly, recent research has revealed that the parietal cortex in monkeys contains corticospinal neurons that directly contribute to hand movements[190], suggesting that motor control by 'sensory' cortex might be a common phenomenon.



Part a is adapted from Matyas et al., 2010 (Ref #109).

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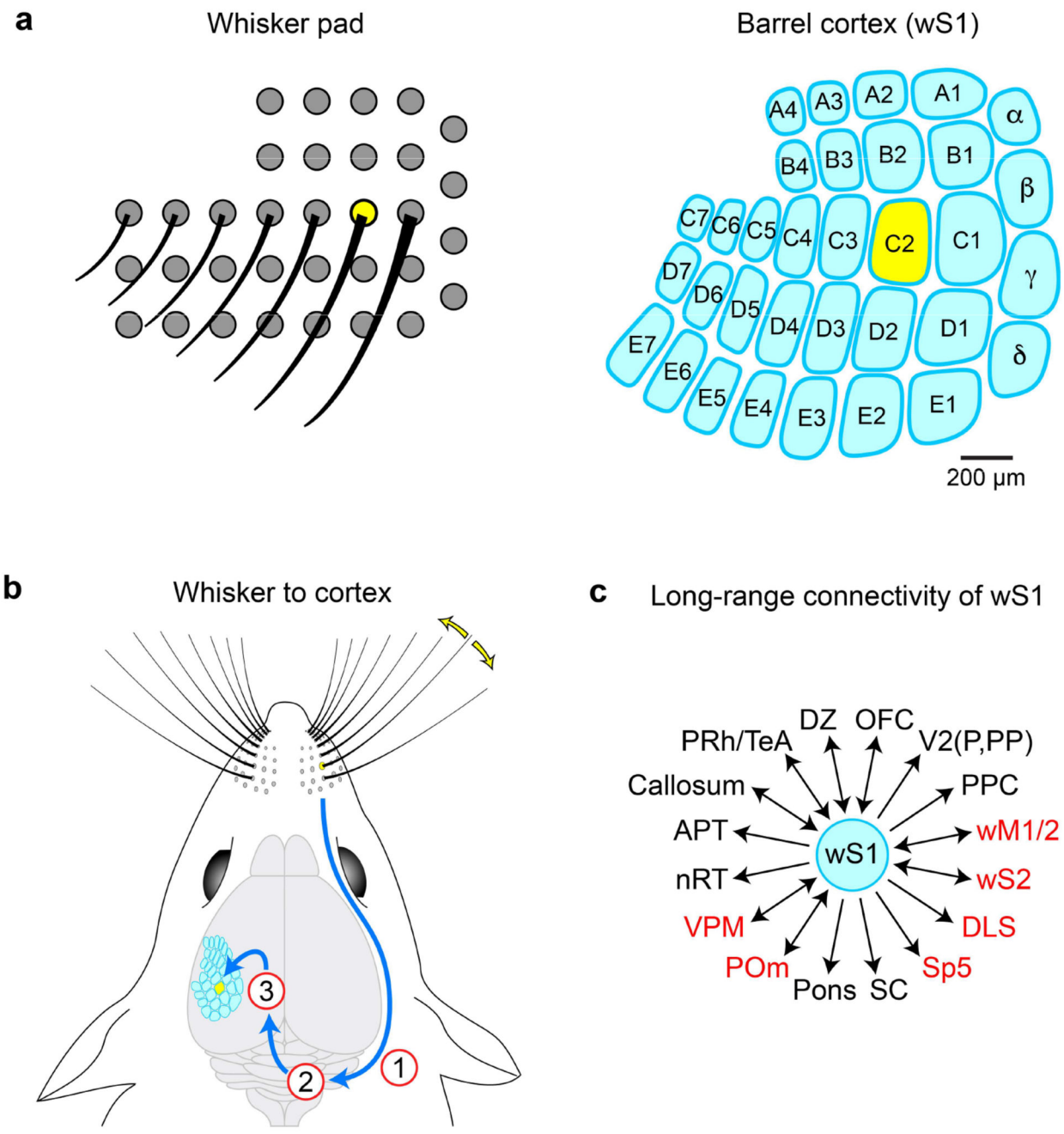

Fig. 1. Long-range connectivity of wS1 barrel cortex.

a | The primary somatosensory cortex of rats and mice contains obvious anatomical units called ‘barrels’ in layer 4 of wS1, which represent individual whiskers on the snout and are somatotopically organized[1]. **b** | Deflection of a mystacial whisker evokes sequential activity in: trigeminal ganglion primary sensory neurons (1); brainstem neurons (2); and thalamic neurons (3), before reaching wS1. **c** | A schematic representation of the long-range connectome of wS1[16–19]. Red font highlights strongly connected brain regions discussed further in this Review. APT, anterior pretectal nucleus; DLS, dorsolateral striatum; DZ,

dysgranular zone surrounding wS1; nRT, nucleus reticularis of the thalamus; OFC, orbitofrontal cortex; POm, posterior medial nucleus of the thalamus; PPC, posterior parietal cortex; PRh/TeA, perirhinal cortex or temporal association cortex; SC, superior colliculus; Sp5, spinal trigeminal nuclei; wM1/2, primary/secondary whisker motor cortex; wS1, primary whisker somatosensory barrel cortex; wS2, secondary whisker somatosensory cortex; VPM, ventral posterior medial nucleus of the thalamus; V2 (P, PP), secondary visual area, labelled in previous studies as area P or PP.

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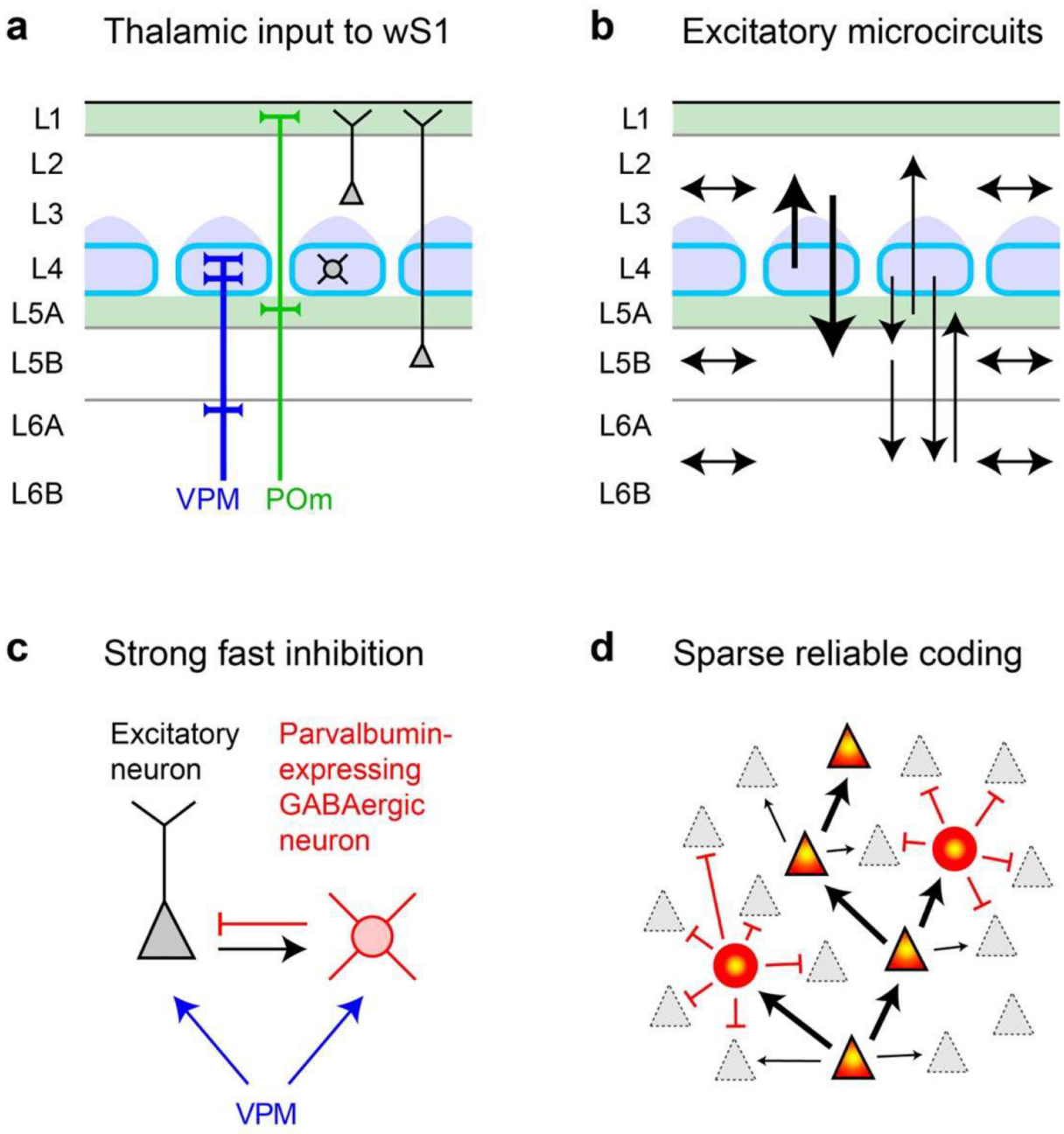

Fig. 2. Neural circuits for sparse reliable coding of touch in wS1.

a | Neurons in primary whisker somatosensory thalamus (VPM) signal whisker deflections primarily to L4 barrels (outlined in cyan). VPM axons (blue shading) extend into the L3 regions directly above the L4 barrels. Higher-order thalamic input from POm innervates L1 and L5A. **b** | Excitatory neuronal microcircuits of wS1 include the 'canonical' L4→L2/3→L5 pathway, as well as many other synaptic pathways including L4→L5, L4→L6, L5A→L2, L6→L5A and L5→L6. Extensive horizontal connectivity across barrel columns is prominent in L2/3 and L5/6. **c** | Fast-spiking inhibitory GABAergic neurons

expressing PV are strongly and reciprocally connected to nearby excitatory neurons and also receive thalamic input. PV^+ neurons provide feedforward, lateral and feedback inhibition. **d**| Sparse strong excitatory synaptic connectivity combined with strong dense inhibition could drive reliable, sparse activity in specifically wired excitatory neuronal circuits.

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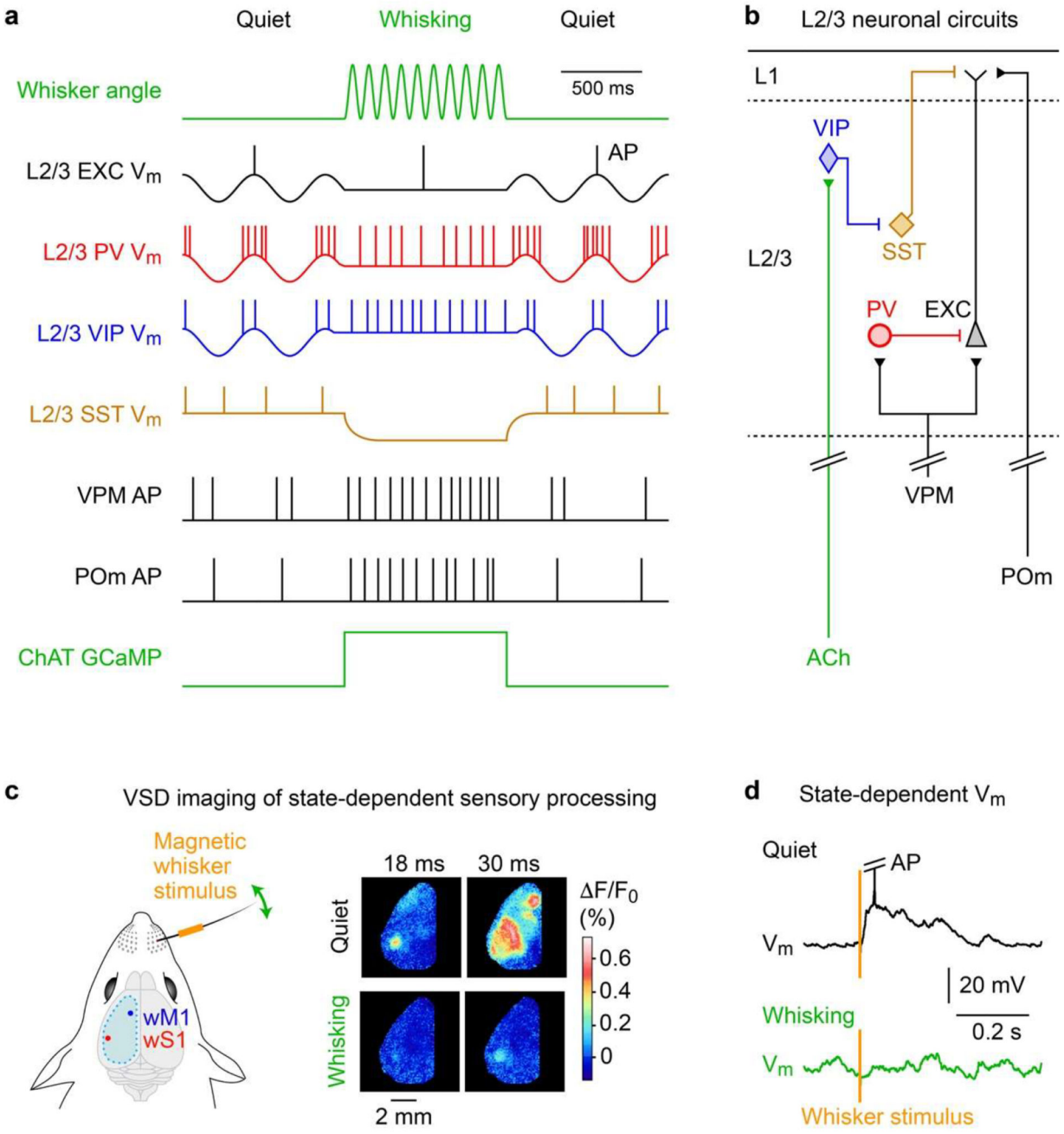

Fig. 3. Cell-type-specific modulation in wS1 during active whisking.

Schematic representation of the dynamics of whisker movements and cell-type-specific V_m fluctuations and action potential firing during quiet and whisking periods. During quiet periods, when the whiskers are not moving, slow synchronous V_m fluctuations are found in excitatory (EXC) neurons, PV^+ neurons and VIP^+ neurons in L2/3. SST^+ neurons show smaller V_m fluctuations that are less correlated to their neighbours. During whisking, thalamic action potential firing rates increase and cholinergic inputs (which are labelled in ChAT GCaMP mice) become more active. Slow cortical V_m fluctuations are suppressed

during whisking. VIP^+ neurons depolarize and increase firing rate, whereas SST^+ neurons hyperpolarize and decrease their action potential rate. **b** | Schematic synaptic circuitry contributing to state-dependent patterns of L2/3 activity. Cholinergic input might depolarize VIP^+ neurons, which express nicotinic acetylcholine receptors. VIP^+ neurons inhibit SST^+ neurons. Thalamic input (from the VPM or POm) to excitatory neurons and PV^+ neurons drives depolarized, desynchronized V_m fluctuations, with combined glutamatergic and GABAergic conductances reducing V_m variance in most cell-types.**c** | A brief whisker deflection evokes an excitatory neuronal response in wS1, which can subsequently propagate to other brain regions such as wM1, as visualized by voltage-sensitive dye (VSD) imaging[15]. Large, spreading sensory responses are evoked during quiet wakefulness, whereas the same whisker deflection evokes a smaller, more localized response if delivered during whisking. **d** | Single-trial examples of whole-cell V_m recording from a L4 spiny stellate neuron in wS1 showing the sensory response evoked by a whisker deflection during a period of quiet wakefulness and during whisking[12].

Panel c is from Ferezou et al., 2007. Ref #15.

Panel d is from Crochet & Petersen, 2006. Ref #12.

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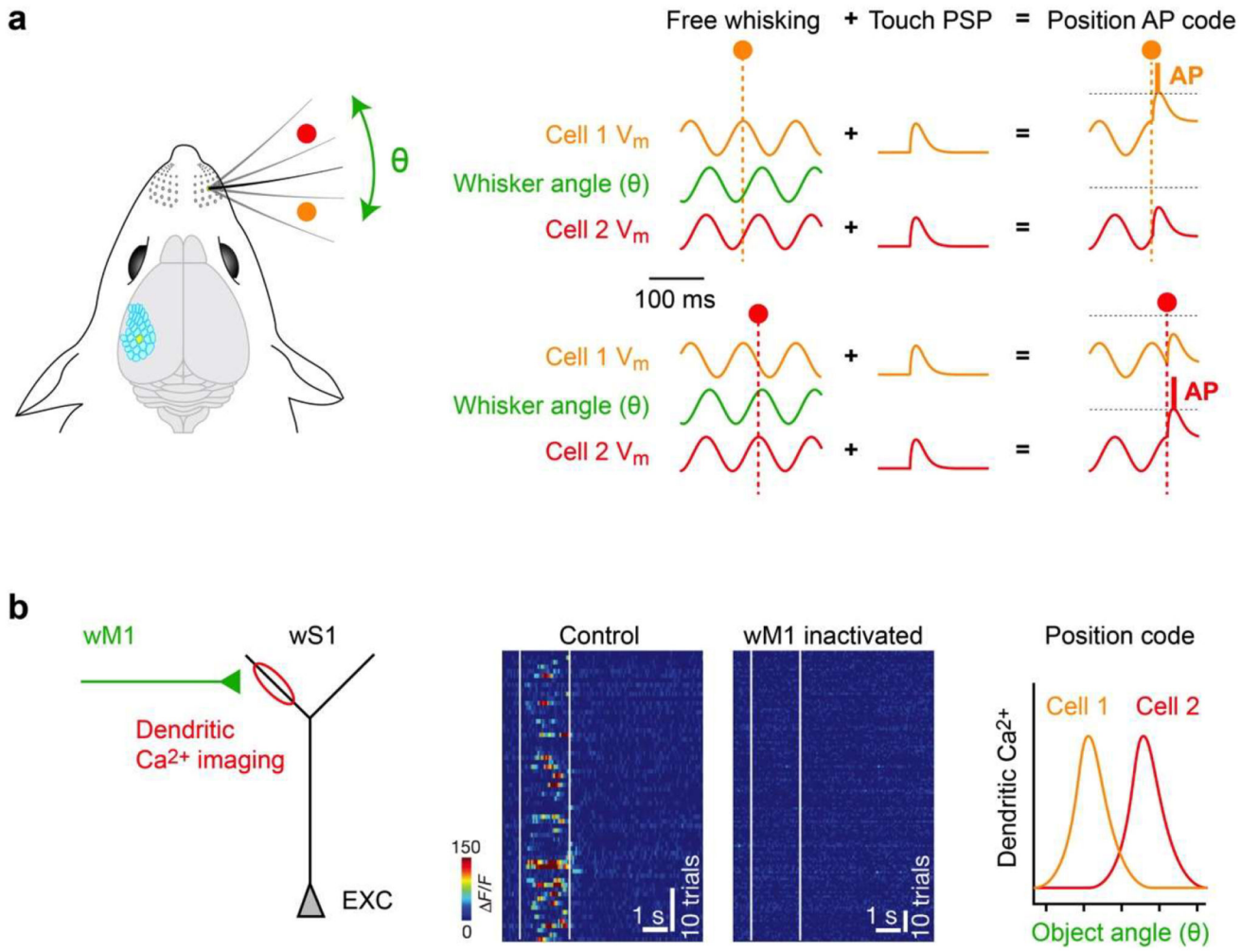

Fig. 4. Sensorimotor computations in wS1.

a |Rodents can localize objects with their whiskers, which requires integration of motor and sensory signals. Some neurons in wS1 exhibit rapid V_m fluctuations that are phase-locked to the whisking cycle. In the schematic example, during free whisking, cell 1 is most depolarized when the whisker is in a relatively retracted position, whereas cell 2 is most depolarized at a more protracted whisker position. Whisker–object contact evokes depolarizing sensory postsynaptic potentials (touch PSP). If touch occurs at a retracted phase of whisking, the V_m of cell 1 might cross the threshold required to fire an action potential. By contrast, if touch occurs at a protracted phase, cell 2 might be more likely to fire an action potential. **b** | Axons from wM1 innervate L1 of wS1. Calcium imaging of the L1 tuft dendrites of L5 pyramidal neurons reveals that active touch evokes signals that are suppressed by inactivation of wM1. The dendrites of different cells respond to different object locations[110].

Panel b is from Xu et al., 2012. Ref #110.

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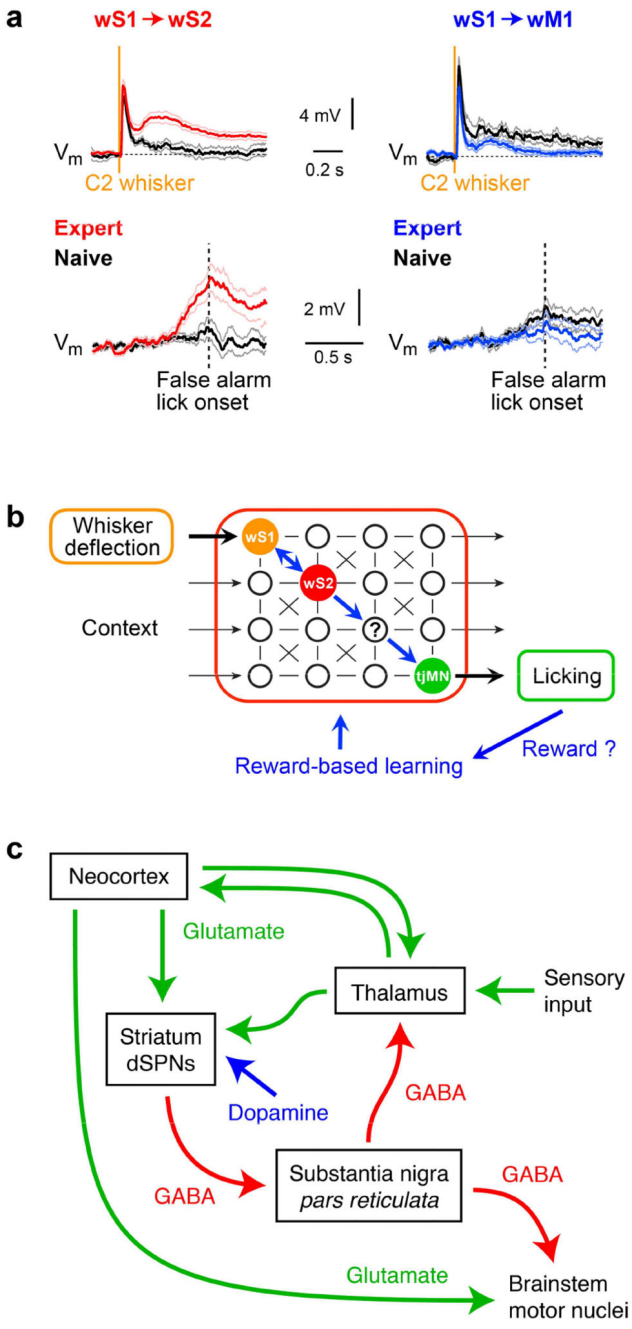

Fig. 5. Neural circuits for goal-directed sensorimotor transformation.

a Some neurons in L2/3 of wS1 project to wS2 (red) and other neurons project to wM1 (blue). Neurons in wS1 projecting to wS2 have a larger depolarizing response to whisker deflection in expert (trained) mice performing a whisker detection task than do naive mice. These neurons also depolarize immediately before ‘false alarm’ licking in expert mice but not naive mice. Neurons in wS1 that project to wS2 might therefore contribute to the transformation of sensory input into the motor command to initiate licking for reward. By contrast, neurons in wS1 that project to wM1 show no such training-dependent differences

in false-alarm-related activity[137].**b** | Schematic circuit diagram illustrating the hypothesis that reward-based learning of a simple whisker detection task might involve strengthening of reciprocal excitation between wS1 and wS2. How neuronal activity in wS1 and wS2 might ultimately signal to tongue- and jaw-related motor neurons (tjMN) to evoke licking is currently unknown, but presumably involves interactions with many other brain areas. **c** | Schematic drawing highlighting the potential role of dopamine acting on D1R-expressing direct pathway striatonigral projection neurons (dSPNs) to potentiate glutamatergic input from cortex and/or thalamus through reward-based learning. Enhanced sensory-evoked activity in dSPNs could contribute to evoke licking by disinhibition of brainstem motor nuclei and/or motor thalamus.

Panel a is from Yamashita & Petersen, 2016. Ref #137.

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