

## REVIEW

## Long-range cortical dynamics: a perspective from the mouse sensorimotor whisker system

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## Abstract

In the mammalian neocortex, the capacity to dynamically route and coordinate the exchange of information between areas is a critical feature of cognitive function, enabling processes such as higher-level sensory processing and sensorimotor integration. Despite the importance attributed to long-range connections between cortical areas, their exact operations and role in cortical function remain an open question. In recent years, progress has been made in understanding long-range cortical circuits through work focused on the mouse sensorimotor whisker system. In this review, we examine recent studies dissecting long-range circuits involved in whisker sensorimotor processing as an entry point for understanding the rules that govern long-range cortical circuit function.

## Introduction

The mammalian neocortex is parcellated into specialized cortical areas dedicated to specific functions. A single area does not operate in isolation but functions in a concerted manner with other cortical areas, integrating information from one set of areas, transforming it, and passing it along to other areas. The capacity to dynamically route and coordinate the exchange of information between areas is a critical feature of cognitive function (Buzsaki, 2010; Kopell *et al.*, 2014; Fries, 2015), enabling processes such as higher-level sensory processing and sensorimotor integration. The dynamic nature of long-range communication is also believed to be a key process that enables cognitive flexibility. Diminished cognitive flexibility measured as decreased performance in attention and working memory tasks have been associated with a range of neurological disorders including autism spectrum disorder, schizophrenia, and Alzheimer's disease as well as during aging (Friston & Frith, 1995; Festa *et al.*, 2005; Wen *et al.*, 2011). Disruptions in long-range connectivity between cortical areas such as a reduction in functional connectivity and disordered white matter distributions have also been observed under these conditions (Meyer-Lindenberg *et al.*, 2005; Sigurdsson *et al.*, 2010; Schipul *et al.*, 2011; Uhlhaas & Singer, 2012), suggesting a link between these two pathological hallmarks. Despite the

importance attributed to these long-range connections, their exact role in cortical function and the rules that govern their operations remain an open question. It is hypothesized that activity in lower sensory areas carries information about the environment in a 'feed-forward' manner to update higher areas driving decisions or actions, while activity in higher areas representing internal predictions can select for relevant stimulus information in lower areas through 'feedback' connections (Cauler, 1995; Hupe *et al.*, 1998; Gilbert & Sigmán, 2007; Larkum, 2013; Zhang *et al.*, 2014; Makino & Komiyama, 2015). To understand these circuits, it is necessary to disentangle how neuronal subpopulations, defined by both their functional properties and their specific connections, contribute to long-range communication under behaviorally relevant conditions.

In recent years, progress has been made in understanding long-range cortical circuits through work focused on the mouse sensorimotor whisker system. Mice use their whiskers to sense objects and navigate through the environment (Diamond *et al.*, 2008). The ability to train animals to sophisticated sensorimotor tasks and to exhaustively monitor sensory and motor variables has made the mouse whisker system an attractive model to study corticocortical connections under behaviorally relevant conditions. Integrative approaches combining molecular, genetic, anatomical, and functional techniques have been applied to investigate interactions between the major sensorimotor cortical areas: primary somatosensory cortex (S1), secondary somatosensory cortex (S2), and primary motor cortex (M1). This has enabled detailed dissections for how long-range circuits are involved in whisker sensorimotor processing. Here, we review recent studies as an entry point for understanding principles that govern long-range cortical circuit function. We will focus on how these circuits operate under the context of goal-directed behaviors involving stimulus detection, object localization, and texture discrimination.

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### Local and long-range connections across whisker sensorimotor cortex

S1 has long been an appealing model for investigating cortical function due to its sophisticated somatotopic sensory map. Each vibrissa is represented by cytoarchitecturally defined layer 4 (L4) neurons that forms ‘barrels’ (Woolsey & Van der Loos, 1970). Physical deflections of the vibrissa are transduced by mechanoreceptors in

the whisker follicle and ascend to somatosensory and motor cortices via the trigemino-thalamo-cortical pathway (Fig. 1). Two rodent thalamic nuclei, the dorsal-medial part of the ventral posteromedial nucleus (VPMdm) and posterior medial nucleus (POm), are early sensory gateways that transmit tactile information received from trigeminal nuclei of the brain stem to the cortex (Ahissar *et al.*, 2000; Yu *et al.*, 2006; Wimmer *et al.*, 2010). In S1, VPM

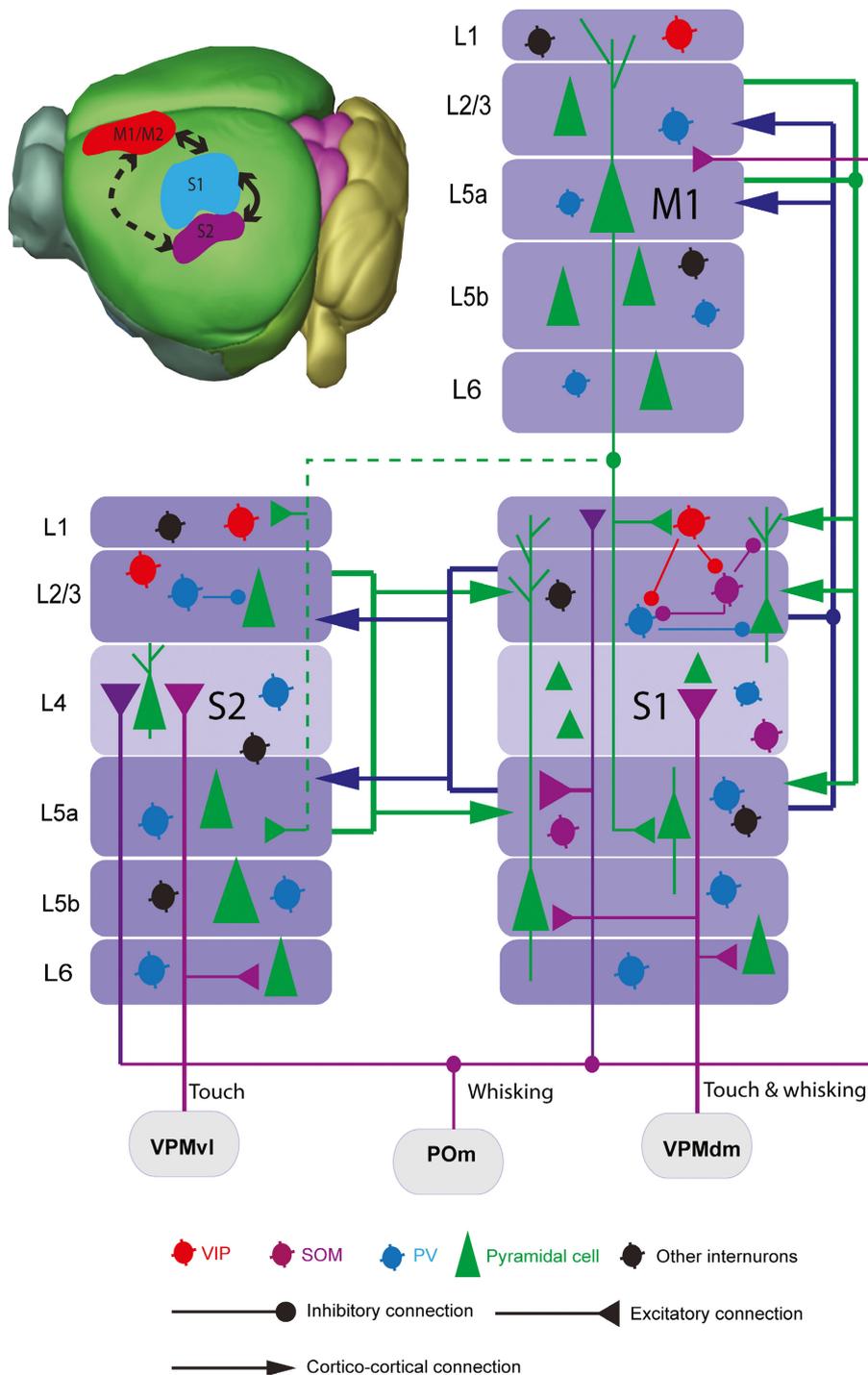


FIG. 1. Local and long-range connectivity in mouse sensorimotor cortex. M1/M2, primary/secondary motor cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; VPMvl, ventrolateral domain of ventral posterior medial nucleus (VPM); VPMdm, dorsal-medial part of VPM; POm, posterior medial nucleus. Projections to septa and dysgranular zones of S1 are not shown. Line thickness indicates connectivity strength. Green line, feedforward projections. Pink line, feedback projects. The 3D mouse brain volume model is adapted from Allen Institute for Brain Science.

predominantly innervate L4 and also weakly innervate L5B/L6A with mainly single-whisker input ('lemniscal pathway'; Killackey, 1973; Bureau *et al.*, 2006; Constantinople & Bruno, 2013), whereas the POm sends axons to all S1 layers but preferably targeting L5A and L1 with multiple-whisker input ('paralemniscal pathway'; Killackey, 1973; Koralek *et al.*, 1988; Deschenes *et al.*, 1998; Bureau *et al.*, 2006). In addition, some multiwhisker inputs are conveyed by the ventral lateral VPM (VPMv) to S1 ('extra-lemniscal pathway'; Pierret *et al.*, 2000).

The laminar organization in S1 has been implicated in segregation and integration of sensory information (Lubke & Feldmeyer, 2007). L2/3 receives major ascending input from intra-columnar L4 and L5A and trans-columnar L4 input from nearby barrel columns (Schubert *et al.*, 2007; Feldmeyer *et al.*, 2013). Connectivity from L4 to L3 is similarly as prominent as those from L2/3 to L5 (Hooks *et al.*, 2011). Connectivity between L2/3 excitatory pyramidal neurons is sparse and weak (Holmgren *et al.*, 2003; Schubert *et al.*, 2007; Lefort *et al.*, 2009; Petersen & Crochet, 2013), whereas connectivity between excitatory-inhibitory neurons and inhibitory-inhibitory neurons are relatively strong. L5A neurons receive major input from other intra-columnar and trans-columnar L5A neurons (Schubert *et al.*, 2006), which is complemented by contributions from L4 and supragranular layers. L5B neurons receive the strongest trans-columnar input from the nearby barrel column. Both VPM and POm receive feedback from corticothalamic projection neurons in layer 6 and strong disinhibitory inhibition from the reticular nucleus and zona incerta (Lin *et al.*, 1990).

S2, located posterolateral to S1, bears a less defined somatotopic organization (Carvell & Simons, 1986, 1987). POm targets L4 of S2 (Viaene *et al.*, 2011; Pouchelon *et al.*, 2014), whereas VPMv innervates L4 and L6 (Pierret *et al.*, 2000). The layers of S2 share similar cytoarchitectonic features with S1. In S2, the excitatory descending pathway from L2/3 to L5 is more prominent than connections from L4 to L3 (Hooks *et al.*, 2011). Infragranular S2 neurons target several subcortical and thalamus regions, forming collateral long-range corticostriatal and corticothalamic pathways (Levesque *et al.*, 1996).

The primary vibrissal motor cortex (M1), which is located in the posteromedial part of agranular frontal motor cortex, possesses almost no granular L4 but an expanded L5B and L6 (Brecht *et al.*, 2004a; Hooks *et al.*, 2011; Castro-Alamancos, 2013). Sensorimotor information is directly related to M1 via the sensory thalamic nucleus from POm, which innervates L2/3 and L5A, and via the motor thalamus (VA/VL thalamic nuclei), which targets L2/3 through L5B but avoids L6 (Hooks *et al.*, 2013). M1 also possesses three classes of long-range projection neurons: intra-telencephalic-type neurons which are cortex and striatum projecting; L5 pyramidal-tract-type neurons which are largely brain stem and spinal cord projecting; and L6 which are largely thalamus projecting. M1 disinhibits POm by innervating the zona incerta (Urbain & Deschenes, 2007).

S1, S2, and M1 exhibit prominent reciprocal connectivity (Miyashita *et al.*, 1994; Mao *et al.*, 2011; Suter & Shepherd, 2015). In S1, corticocortical neurons that project to M1 or S2 are largely non-overlapping subpopulations (Sato & Svoboda, 2010; Chen *et al.*, 2013; Yamashita *et al.*, 2013). Feedforward S1 neurons that project to M1 ( $S1_{M1}$ ) originate from L2/3 and L5A of S1 and preferentially innervate L2/3 and L5A of M1. In turn, M1 targets S1 ( $M1_{S1}$ ) in L2/3 and L5A (Mao *et al.*, 2011; Hooks *et al.*, 2013). A subpopulation of L6 regular spiking excitatory neurons in S1 also receive very strong M1 input (Kinnischtzke *et al.*, 2014). In addition to direct excitatory connections,  $M1_{S1}$  neurons innervating L2/3 also target vasoactive intestinal peptide-positive (VIP+) inhibitory neurons in

S1 which preferentially target somatostatin-positive (SOM+) inhibitory neurons that contact dendrites of L2/3 pyramidal neurons (Lee *et al.*, 2013). Feedforward and feedback connections between S2 and S1 largely originate from both supragranular and infragranular layers (Welker *et al.*, 1988; Aronoff *et al.*, 2010). Reciprocal connections between S2 and M1 have also been reported (Miyashita *et al.*, 1994; Suter & Shepherd, 2015). Corticospinal axons from both M1 and S2 partly converge on middle layers of the cervical spinal cord (Suter *et al.*, 2013; Suter & Shepherd, 2015).

## Functional properties of M1, S1, and S2 during behavior

Rodents are capable of collecting spatial and texture- and shape-related information from nearby objects using their whiskers. Several behavioral tasks have been developed to experimentally investigate how such sensory information is processed and utilized for goal-directed behavior (Fig. 2). One basic behavior is a tactile detection task in which mice are trained to report the deflection of a single whisker (Sachidhanandam *et al.*, 2013). For spatial information, mice have been trained to various tasks including bilateral-edge distance (Shuler *et al.*, 2001; Krupa *et al.*, 2004), gap width (Hutson & Masterton, 1986; Jenkinson & Glickstein, 2000), object localization (Knutsen *et al.*, 2006), and virtual wall tracking behaviors (Sofroniew *et al.*, 2014). During object localization, mice are able to report absolute azimuthal position of an object based on vibrissae with a precision of six azimuthal degrees (Mehta *et al.*, 2007; O'Connor *et al.*, 2010a). Texture discrimination tasks have been used to investigate how mice resolve object-related information based on fine-level kinematic features generated from whisker-object contact (Arabzadeh *et al.*, 2003, 2004; Moore, 2004; von Heimendahl *et al.*, 2007; Wolfe *et al.*, 2008). Rodents are able to discriminate different textures within three whisker sweeps across the textured surface (von Heimendahl *et al.*, 2007; Chen *et al.*, 2013).

### M1

Mice adjust their whisker motor strategies according to task conditions. During tactile detection, whisking prior to and during stimulation reduces task performance, suggesting that mice might refrain from whisking in order to increase stimulus detection (Kyriakatos *et al.*, 2017). In fact, facial nerve transection suggests that detection of passive deflection does not require whisker movement (Sachidhanandam *et al.*, 2013). In contrast, mice display prominent rhythmic whisking during texture discrimination (Chen *et al.*, 2013, 2015) and concerted whisker sweeps during object localization (O'Connor *et al.*, 2010a,b; Petreanu *et al.*, 2012). Concerted whisker sweeps during object localization serve to sample the proximal spatial environment. In contrast, rhythmic whisking during texture discrimination drives whisker kinematics that differs across textures such as the frequency of high-velocity, high-acceleration stick-slip events and curvature changes (Jadhav & Feldman, 2010; Chen *et al.*, 2013, 2015).

M1 is involved in the planning and execution of these whisker movements. M1 activity is modulated by whisker movements in both rats and mice (Ebbesen *et al.*, 2017). During whisking in air, M1 neurons are modulated by slow variations in the envelope of whisking, such as amplitude and mid-point values (Hill *et al.*, 2011; Friedman *et al.*, 2012), which is independent of proprioceptive sensory feedback. Larger proportions of L2/3 neurons exhibit fast modulations related to whisking phase than L5 neurons, while more L5 cells show modulation correlated to the whisking mid-point (Sreenivasan *et al.*, 2016).

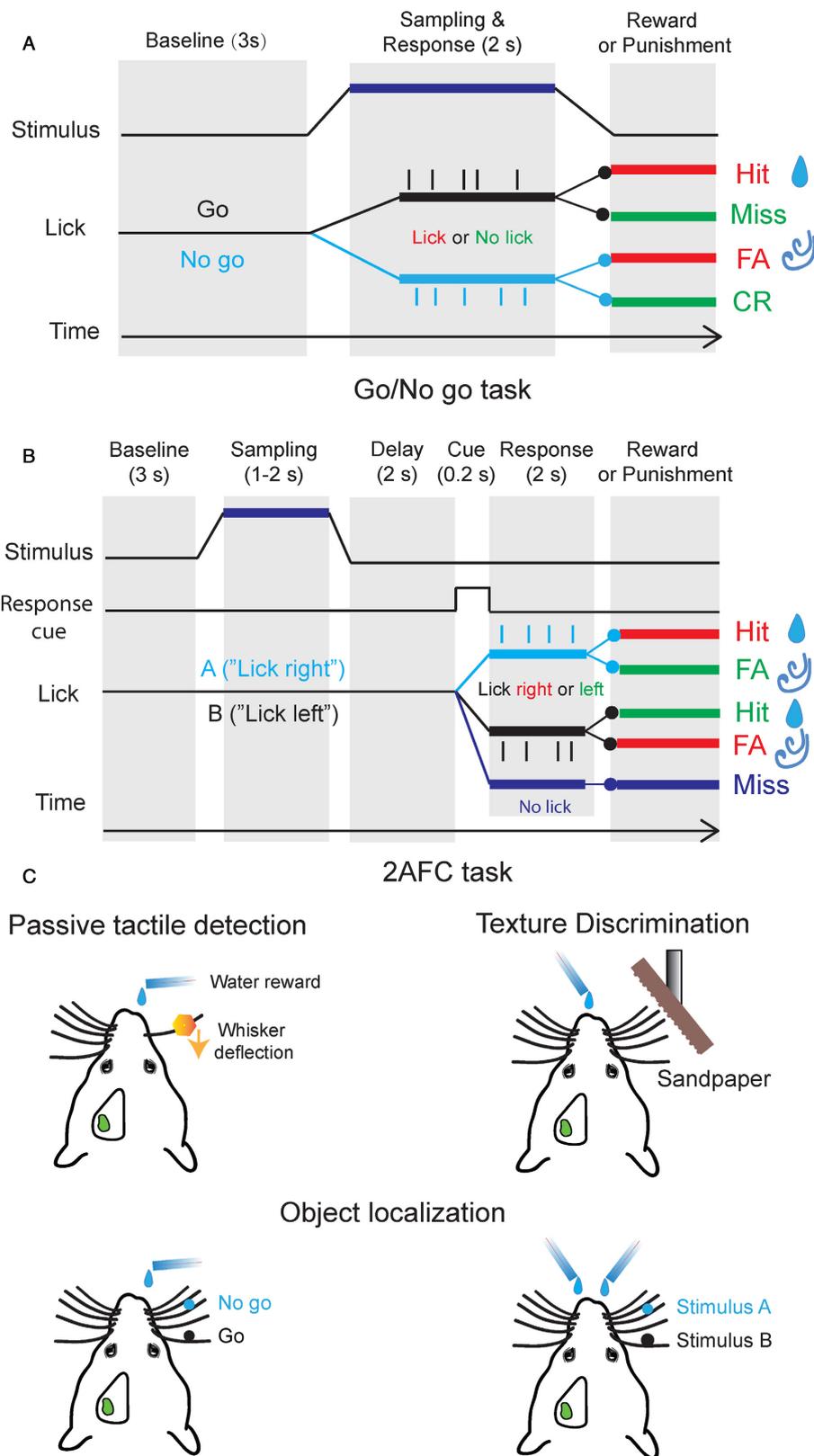


FIG. 2. Whisker-based behavioral paradigms. (A) Go/No Go task. Mice report the presentation of 'Go' stimulus by licking for reward ('Hit') and hold for 'No Go' stimulus ('CR'). Incorrect 'Go' and 'No Go' trials are denoted as 'miss' and 'false alarm,' respectively. (B) Two Alternative Forced Choice (2AFC) task. The mice report by licking the left or right water port for 'stimulus A' or 'stimulus B', respectively. A delay period can be introduced between sensory sampling period and response cue. (C) Representative whisker-based tasks. In a passive tactile detection task, mice are trained to detect and report the deflection of a single whisker. In a texture discrimination task, mice report differences in the coarseness of textures. In an object localization task, mice are trained to discriminate the location of presented poles presented along the anterior-posterior axis of the animal.

Intracortical microstimulation (ICMS) of M1 evokes contralateral rhythmic whisker retraction in a pattern similar to whisking in air (Berg & Kleinfeld, 2003; Brecht *et al.*, 2004b). Areas that drive whisker retraction are larger and more central compared to areas driving protraction (Haiss & Schwarz, 2005). Unilateral optogenetic inactivation of M1 leads to a significant decrease in whisking initiation (Sreenivasan *et al.*, 2016). In a separate study, ICMS elicited whisker retraction, whereas inactivation resulted in contralateral protraction and increased whisker movements (Ebbesen *et al.*, 2017). These seemingly contradictory findings suggest that distinct and dedicated circuits maybe devoted to the initiation and suppression of whisker movements.

## S1

Several inactivation experiments have demonstrated that S1 is necessary for behaviors involving tactile detection, object localization, and texture discrimination (O'Connor *et al.*, 2010a; Miyashita & Feldman, 2013; Sachidhanandam *et al.*, 2013; Guo *et al.*, 2014). During tactile detection, evoked responses in L2/3 pyramidal neurons were found to consist of two components: an early sensory response encoded in the form of a reversal potential and a later secondary depolarization that reflected the animal's choice. For L2/3 inhibitory neurons, whisker stimulus drove parvalbumin-positive (PV+) and VIP+ neurons, whereas SOM+ neurons fired at low rates. PV+ neurons also exhibited choice-related activity in the period between the early sensory response and when the animal reported their choice, suggesting that this cell type contributes to gating sensorimotor transformation after initial sensory processing (Sachidhanandam *et al.*, 2016). Calcium activity in the apical dendrites of L5 pyramidal neurons has also been identified to contribute to the sensory detection threshold during this task (Takahashi *et al.*, 2016).

During behaviors involving active touch, membrane potentials of L2/3 neurons show rapid, highly correlated large-amplitude responses (Crochet & Petersen, 2006; Ferezou *et al.*, 2007). During whisker movement, both S1 firing rate and subthreshold membrane potentials are better modulated by fast vibrissa phase cycles (Fee *et al.*, 1997; Crochet & Petersen, 2006), which is likely due to sensory reafference. Touch-evoked S1 responses are also modulated according to the whisking phase cycle (Curtis & Kleinfeld, 2009).

During object localization, differences in activity reflecting object location are already strongly observed in L4 (O'Connor *et al.*, 2010a). This selectivity in L4 excitatory neurons is facilitated by the suppression of whisker movement information from L4 PV+ inhibitory neurons (Yu *et al.*, 2016). While L5 also exhibits high levels of activity and discriminability, L2/3 excitatory neurons are the least active and show touch-related, whisking-related, and mixed responses (Chen *et al.*, 2013; Peron *et al.*, 2015). L2/3 neurons also showed strong direction tuning during object touch along the rostral-causal axis of the animal (Peron *et al.*, 2015). Despite this general survey of layer-specific representations across S1 during object localization, the specific computations occurring within and across layers during the task remain unclear.

During texture discrimination, texture information has been found to be encoded by both firing rate and spike timing in S1, where rougher textures typically drive higher firing rates than smoother textures in matched trial conditions (von Heimendahl *et al.*, 2007; Zuo *et al.*, 2015). Texture-related time-locked spike patterns are attributed to high-velocity and high-acceleration whisker slip-stick events, which occur more frequently in rough textures (Wolfe *et al.*, 2008; Jadhav *et al.*, 2009). Curvature changes related to whisker

'sticks' drive higher firing rates and are also stronger in rough textures (Chen *et al.*, 2015).

## S2

Across species, S2 mediates tactile sensation and many cognitive functions including learning, memory, multimodal processing, and decision-making (Sacco & Sacchetti, 2010; Romo & de Lafuente, 2013). In the rodent whisker system, the function of S2 has been less investigated. Tactile responses in S2 differ from S1. S2 exhibits more multiwhisker receptive field responses than S1 (Kleinfeld & Delaney, 1996). In anesthetized rats, S2 neuron responses are rapidly adapting and more selective for the angle of whisker deflection (Kwegyir-Afful & Keller, 2004). S2 neurons are more sensitive to differences in lower frequency whisker stimulation and are less time locked to such stimuli as compared to S1 (Melzer *et al.*, 2006). The extent to which these features are driven by POM vs. S1 is unclear. However, latency of responses in S2 to contralateral whisker stimulation is similar to that of S1, suggesting that POM is a major driver of sensory responses in S2 (Kwegyir-Afful & Keller, 2004; Megevand *et al.*, 2008). S2 also possesses strong interhemispheric callosal connections and bilateral responses suggesting that it may be involved in integration of bilateral sensory information (Debowska *et al.*, 2011). During texture discrimination, S2 can similarly encode texture information as S1 from firing rate and spiking timing codes (Zuo *et al.*, 2015). However, S2 exhibits more diverse, non-sensory responses than S1. More neurons in S2 were observed to respond to whisking and showed stronger choice-related responses compared neurons in S1 (Chen *et al.*, 2016; Kwon *et al.*, 2016).

## Functional interactions across S1 and M1

Studies investigating the nature of interactions between S1 and M1 suggest several potential functions (Fig. 3). Whole-cell recordings of S1<sub>M1</sub> neurons show that passive tactile stimulation evoke fast, large postsynaptic potentials (PSPs) as well as phasic action potential firing, whereas repetitive active touch evoked strongly depressing PSPs and only transient firing (Yamashita *et al.*, 2013). S1<sub>M1</sub> neurons reliably encode fine-level kinematic features such as whisker angle, curvature changes, and stick-slip events across animal training (Chen *et al.*, 2015). This suggests that S1<sub>M1</sub> neurons are well suited for stimulus detection as well as for reporting instantaneous stimulus information. Additionally, input from S1 to M1 can initiate whisker movement. S1 can directly drive whisker retraction (Matyas *et al.*, 2010). Optogenetic inhibition of S1 excitatory neurons causes hyperpolarization of membrane potential and reduced firing rate in M1, as well as reduced probability of whisking movement. In contrast, optogenetic activation of S1 rapidly depolarized M1 neurons and drove contralateral whisker retractions (Sreenivasan *et al.*, 2016). This suggests that feedforward pathways from S1 to M1 might be critical for initiating motor plans upon stimulus detection and potentially in response to specific stimulus features.

During object localization, calcium activity of M1<sub>S1</sub> neuron axons contains mixed information about whisker movement kinetics, object position, and touch. This information can provide S1 with both motor and sensory contexts during behavior (Petreanu *et al.*, 2012). The influence of these feedback signals onto local excitatory and inhibitory S1 neurons has been investigated. Direct projections from superficial M1 to output cells of subgranular S1 are thought to mediate whisker retraction (Matyas *et al.*, 2010).

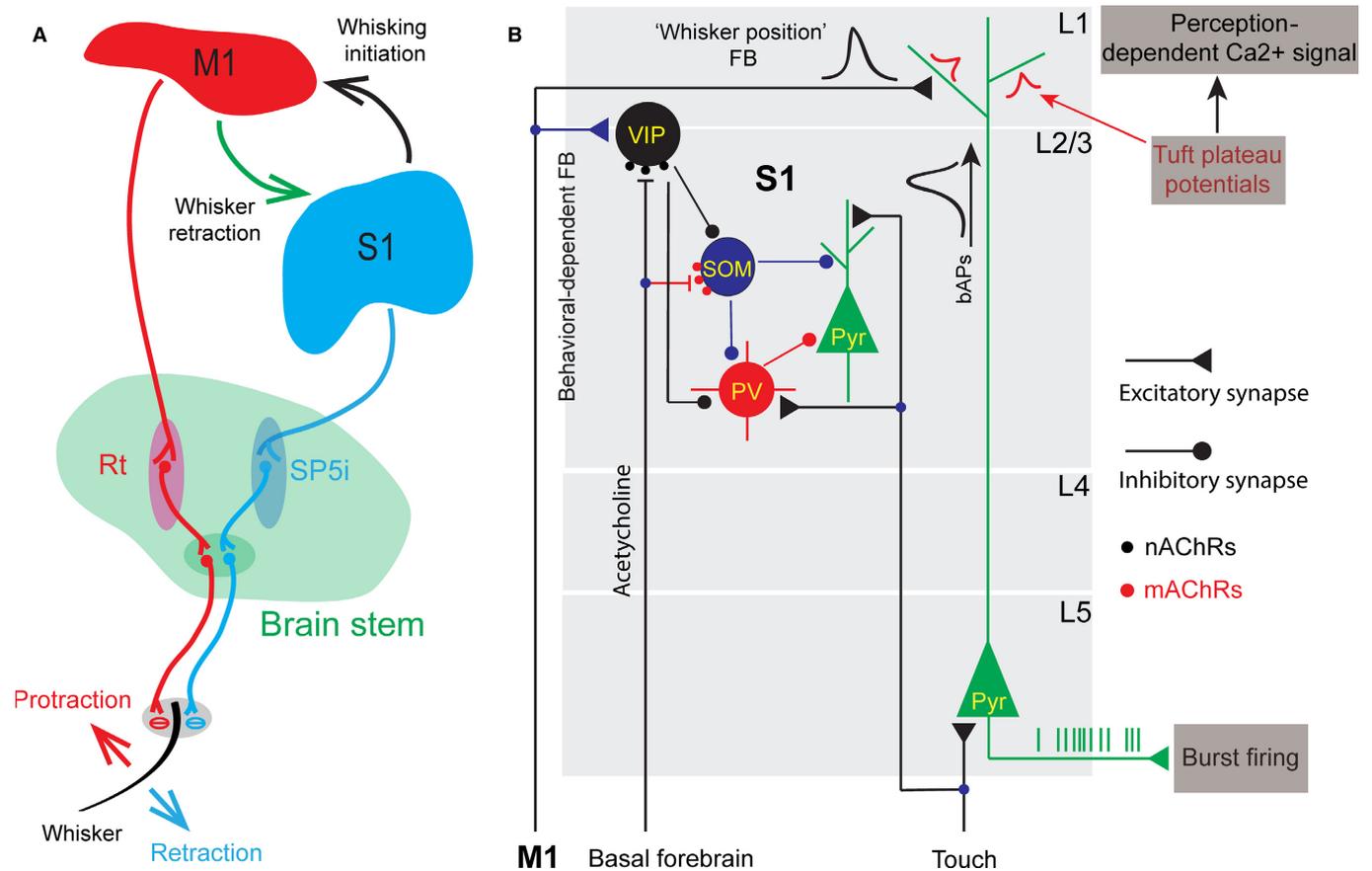


FIG. 3. Functional interaction across M1 and S1. (A) S1 is necessary for the initiation of M1-mediated rhythmic whisker protraction. M1 is necessary for S1 mediated whisker retraction. Rt, brain stem reticular nuclei; Sp5i, spinal trigeminal interpolaris nucleus. (B) M1 feedback modulates S1 responses and provides whisker position signal. Behavior-dependent response in S1 is mediated by a disinhibitory circuitry, which recruits VIP+ and SOM+ interneurons targeting PV+ interneurons and pyramidal neurons. In the object localization task, the coincidence of depolarization from M1 feedback input and back-propagation action potentials (bAPs) at L5 pyramidal neurons tuft dendrite generates tuft plateau potentials and perception-dependent dendritic calcium signals, which may trigger burst firing in L5 pyramidal cells.

Monosynaptic connections of M1 axons onto S1 L5 pyramidal neurons have also revealed a circuit computation for object localization that involves active input processing through pyramidal-neuron dendrites. Large-amplitude calcium signals along the apical tuft dendrites were observed when active touch occurred at particular object locations or whisker angles that require both vibrissal sensory input and primary motor cortex activity (Xu *et al.*, 2012). Thus, M1 feedback input to S1 facilitates whisker-based object localization and potentially other functions requiring sensorimotor integration.

While direct monosynaptic excitatory connections between S1 and M1 are involved in specific sensorimotor computations, indirect connections through local inhibitory interneurons may provide additional functions that depend on brain state (Castro-Alamancos, 2004; Ferezou *et al.*, 2006; Hentschke *et al.*, 2006; Poulet & Petersen, 2008; Fu *et al.*, 2014; Wester & McBain, 2014). Different mechanisms that influence brain state-related responses in S1 have been proposed such as thalamic control (Steriade *et al.*, 1993; Poulet *et al.*, 2012), neuromodulatory effect (Constantinople & Bruno, 2011; Lee & Dan, 2012; Marder, 2012; Wester & McBain, 2014), and corticocortical feedback (Gilbert & Sigman, 2007; Zhang *et al.*, 2014). Compared to quiet wakefulness, low-frequency, high-amplitude responses were suppressed while high-frequency, low-amplitude responses were enhanced during the active state. Optogenetic

activation of M1<sub>S1</sub> neuron axons exerts rapid and target-specific changes in S1 network state, leading to reduced low-frequency (1–5 Hz) local field potential (LFP) power and enhanced gamma band (30–50 Hz) LFP power. This change in network state results in more reliable sensory responses in S1 (Zagha *et al.*, 2013). This cortical feedback modulation of S1 responses occurs independently of thalamus, suggesting a direct long-range corticocortical effect in controlling brain state.

These state-dependent influences of M1 and S1 could occur through M1<sub>S1</sub> connections onto SOM+ and VIP+ interneurons. While fast-spiking GABAergic neurons dominate the non-whisking quiet wakefulness state, non-fast-spiking GABAergic neurons dominate the active whisking period (Gentet *et al.*, 2010). Whole-cell recording of SOM+ neurons showed hyperpolarized and reduced firing rate in response to both passive touch and active whisking (Gentet *et al.*, 2012). During whisking, M1<sub>S1</sub> neurons strongly recruit VIP+ neurons, which inhibit SOM+ neurons and disinhibit L2/3 excitatory pyramidal neurons in S1 (Lee *et al.*, 2013). Genetic ablation of cholinergic muscarinic M1 or M3 receptors in SOM+ neurons almost completely suppressed their activity across all layers, suggesting an important cholinergic source of excitatory drive to these whisking-activated subtypes (Munoz *et al.*, 2017). Thus, the influence of M1 onto S1 through inhibitory neurons and the neuromodulation of these cell types

might enable the dynamic regulation of long-range interactions related to sensorimotor integration according to different behavioral demands. In summary, interactions between S1 and M1 appear to function to extract positional information, initiate whisker movement, and adjust motor plans to better encode sensory information and carry out behavior.

### Functional interactions across S1 and S2

In contrast, interactions between S1 and S2 appear to underlie a different set of functions (Fig. 4). Under non-task conditions,  $S1_{S2}$  neurons contrast with  $S1_{M1}$  neurons in exhibiting sustained firing in response to passive whisker deflection and non-adapting responses to multiple active touches (Yamashita *et al.*, 2013). This suggests that  $S1_{S2}$  neurons might have the ability to integrate sensory information over time as needed to extract complex, high-order features of an object's identity. In line with this,  $S1_{S2}$  neurons are more prominently activated during texture discrimination and more accurately encode the identity of different textures.  $S1_{S2}$  neurons show stronger choice-related activity compared to other S1 neurons (Chen *et al.*, 2013). This choice-related activity is a learned feature that is specific to  $S1_{S2}$  neurons as  $S1_{M1}$  neurons faithfully represented basic sensory features throughout task learning (Chen *et al.*, 2015). During tactile detection, task learning also produced a licking-dependent depolarization in  $S1_{S2}$  neurons that correlated with the animal's choice (Yamashita & Petersen, 2016). Thus,  $S1_{S2}$  neurons have a unique capacity to acquire choice- or context-related responses during behavioral learning.

Choice-related responses in  $S1_{S2}$  neurons appear to be inherited from S2 (Chen *et al.*, 2016; Kwon *et al.*, 2016; Yang *et al.*, 2016). Imaging S2 feedback axons in S1 showed that touch and choice-related activity propagate in a loop such that S2 cortical feedback reinforces feedforward input from S1 (Kwon *et al.*, 2016). While S1 and S2 can be driven by both sensory- and motor-related variables, the exchange of sensory and choice information between S1 and S2 appears to be both highly coordinated and specific to corticocortical interactions between these two areas (Chen *et al.*, 2016). To summarize, interactions between S1 and S2 are involved in generating choice-related context to sensory information that arises in an experience-dependent manner.

### Conclusion and future directions

In conclusion, we have outlined several critical functions that long-range cortical networks across the mouse sensorimotor system play in behavior. Interactions between S1 and M1 as well as between S1 and S2 carry out multiple functions in order to cover a range of sensorimotor processing needs and behavioral demands. On one level, these two reciprocal pathways share striking homology to the 'where' and 'what' pathways described in the visual system (Goodale & Milner, 1992). Connections between S1 and M1 bear resemblance to the 'dorsal' visual stream involved in object localization while connections between S1 and S2 bear resemblance to the 'ventral' visual stream involved in the object recognition (Yamashita *et al.*, 2013). While this could be an overgeneralization, it establishes a phenomenological framework for which deeper investigations can be pursued in the future to dissect specific circuits and mechanisms that drive these long-range operations.

One area of future research is the extent to which neuronal oscillations play in coordinating and regulating information flow across cortical areas. Studies in the primate visual and somatosensory system have implicated the synchronization of activity across cortical areas through oscillations as means to facilitate information transfer between areas (Brovelli *et al.*, 2004; Fries, 2005; Haegens *et al.*, 2011; Ni *et al.*, 2016). Spiking activity in barrel cortex is strongly locked to beta and gamma band LFP (Vinck *et al.*, 2015). Inter-areal LFP coherence between S1 and remote areas such as perirhinal cortex, hippocampus CA1, and visual cortex peaked between theta-beta band, consistent with idea of low-frequency band neural oscillation serves as top-down communication channel (Wang, 2010; van Kerkoerle *et al.*, 2014; Bastos *et al.*, 2015). It remains to be seen how these oscillations may be involved in facilitating the interactions across M1, S1, and S2 during behavioral tasks.

The role that subcortical input from thalamic and neuromodulatory regions play in coordinating these long-range interactions also warrants further investigation. Similar to the pulvinar's role in coordinating inter-areal information in the visual system (Saalman *et al.*, 2012), higher order thalamic nuclei such as POM could play a role in coordinating inter-areal information in the whisker system (Chen *et al.*, 2016). Given the clear state-dependent effects that the cholinergic system has over S1 activity, it is also worth

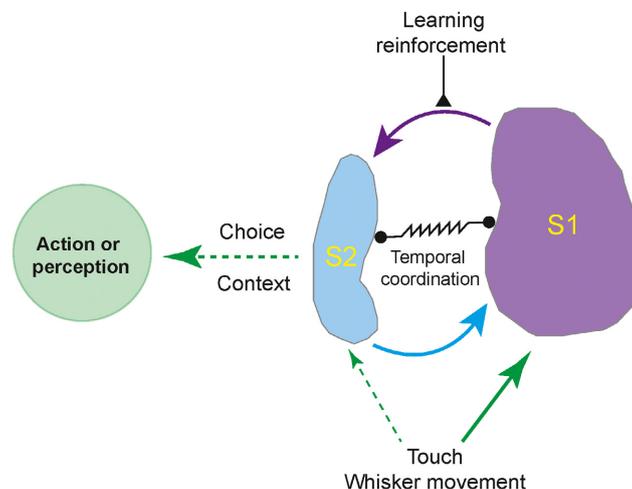


FIG. 4. Functional interaction across S1 and S2. The neuronal activity in S1 and S2 are temporally coordinated during texture discrimination task. During goal-directed behavior, choice and context information originates from S2 and propagates in a S1-S2 loop. Learning reinforces pathway-specific feedforward input from S1 to S2 encoding touch-related information.

considering how M1 and S2 are affected by such input and how that affects information flow between these areas. Considering these and other mechanisms will provide a broader perspective for inter-areal function during behavior and may reveal general principles for relationships between local and long-range circuit function across the brain.

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## Conflict of interest

The authors declare no competing financial interests with respect to authorship or the publication of this article.

## Author contributions

J. Ni and J.L. Chen prepared and wrote the manuscript.

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