contributes to nAChR agonist binding and desensitization kinetics (8), but also may respond to changes in network activity (34). Local regulation of Lynx1 levels may allow cholinergic activation to induce islands of plasticity while maintaining overall circuit stability. Visual attention tasks in fact preferentially modulate fastspiking inhibitory neurons (35, 36), consistent with a convergence of top-down influences upon local excitatory-inhibitory circuit balance.

References and Notes

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Supporting Online Material

www.sciencemag.org/cgi/content/full/science.1195320/DC1 Materials and Methods

Figs. S1 to S3

References

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100% co-localization with Lynx1 (%)

Motor Control by Sensory Cortex

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Classical studies of mammalian movement control define a prominent role for the primary motor cortex. Investigating the mouse whisker system, we found an additional and equally direct pathway for cortical motor control driven by the primary somatosensory cortex. Whereas activity in primary motor cortex directly evokes exploratory whisker projection, primary somatosensory cortex directly drives whisker retraction, providing a rapid negative feedback signal for somatosensory integration. Motor control by sensory cortex suggests the need to reevaluate the functional organization of cortical maps.

The remarkable findings of Penfield and Boldrey (1), which have been supported by many subsequent studies (2–11), emphasize a key role for motor cortex in mammalian movement control. Investigating the mouse whisker system (12–14), we found that primary somatosensory barrel cortex forms an equally direct and equally prominent motor cortex pathway, compared with that originating from the classical motor cortex.

We first functionally mapped the sensory activity evoked by a single brief deflection of the C2 whisker through wide-field voltage-sensitive dye (VSD) imaging of the contralateral somatosensory cortex in awake head-restrained mice (15, 16). The earliest cortical VSD response to C2 whisker deflection occurred at 7.4 ± 0.5 ms (n = 5 mice, mean ± SD) and was specifically localized to the C2 barrel column of primary somatosensory neocortex (S1s2) (Fig. 1A). Over the subsequent milliseconds, nearby cortical columns depolarized, with activity propagating in a wavelike manner.

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Fig. 1. Cortical sensorimotor interactions in the mouse whisker system. (A) VSD imaging reveals the spatiotemporal dynamics of the cortical sensory response evoked by a single brief deflection of the C2 whisker. (B) ICMS (gray shading) of S1C2 (red) and M1C2 (blue) evoked whisker retraction, whereas ICMS of M1Protract (green) drove whisker protraction. (C) Movement amplitude and latency evoked by ICMS of S1C2 (n = 26 mice), M1Retract (including M1C2, n = 31 mice), and M1Protract (n = 30 mice). (D and E) Sensory-evoked whisker retraction (yellow) was blocked by TTX inactivation of S1 (orange) (P < 0.01, n = 5 mice). Data presented as mean ± SD.

Fig. 2. Sensory cortex drives whisker retraction independently of motor cortex. (A and B) Inactivation of M1 by TTX, completely blocked movements evoked by intracortical microstimulation (ICMS) of M1Protract (green) and M1Retract (blue) but did not affect spontaneous whisker movement driven by ICMS of S1 (red) in the same mice (n = 7 mice). Note that spontaneous whisker movement can still occur following inactivation of M1 by TTX (see M1Protract trace). (C and D) Optogenetic stimulation of S1 in ChR2 transgenic mice evoked whisker retraction, which was unchanged by inactivation of M1 by TTX (n = 5 mice). (E and F) Whisker retraction evoked by optogenetic stimulation of S1 neurons expressing ChR2 from an adenoassociated viral vector (n = 8 mice). Data presented as mean ± SD.

At 6.5 ± 1.9 ms (n = 5 mice) after the first excitation of the C2 barrel column, a second localized region of depolarization was evoked in primary motor cortex (M1C2), which also spread over the next milliseconds (Fig. 1A). These imaging experiments defined two spatially localized initiation sites (S1C2 and M1C2) for cortical sensory processing associated with the C2 whisker. To gain insight into their functional contributions to whisker behavior, we targeted intracortical microstimulation (ICMS) to these two cortical regions, finding that stimulation of either S1C2 or M1C2 evoked short-latency retraction of the C2 whisker (n = 5 mice) (Fig. 1B). Stimulation of a more medial region of motor cortex (M1Protract) drove rhythmic whisker protraction (Fig. 1B). Additional mapping experiments based on stereotaxic coordinates revealed this motor map to be well defined, with M1C2 localized within the motor cortex whisker retraction area, M1Retract (figs. S1 and S2) (8, 15). Quantified across all experiments (Fig. 1C), ICMS of S1C2 drove whisker retraction of −10.3° ± 3.9° with a latency of 14.8 ± 2.8 ms (n = 26, stimulation sites across 26 mice); ICMS of M1Protract drove whisker retraction of −18.0° ± 8.8° with a latency of 21.1 ± 5.8 ms (n = 116, across 31 mice); and ICMS of M1Retract drove whisker retraction of 17.1° ± 9.0° with a latency of 35.3 ± 12.1 ms (n = 86, across 30 mice). Latencies for evoking whisker movements were shorter for ICMS of S1 compared with those of M1 (P < 0.001).
Thus, the cortical regions involved in the initial processing of C2 whisker sensory input (S1C2 and M1C2) both drove whisker retraction. To test for behavioral relevance of the retraction motor response from sensory cortex, we attached metal particles to the C2 whisker and evoked a train of brief whisker deflections by a pulsed magnetic field. Mice retracted the C2 whisker in response to this sensory stimulus by $-2.8° \pm 1.4°$ ($n = 5$ mice), but, if the S1 barrel cortex was inactivated by tetrodotoxin (TTX), then the mice failed to respond (whisker movement of $0.3° \pm 1.2°$, $n = 5$ mice, $P < 0.01$) (Fig. 1, D and E). Inactivation of motor cortex by TTX did not affect the sensory-evoked whisker retraction (fig. S3).

These results suggest that S1 might drive movement without the participation of M1. We tested this hypothesis by investigating the effect of TTX application to M1 on ICMS-evoked movements. Although complete blockade of motor cortex was verified by the absence of movements evoked by ICMS of M1, the whisker retraction evoked by ICMS of S1 was unaffected by TTX application to M1 (control amplitude of $-11.0° \pm 3.4°$, TTXM1 amplitude of $-12.9° \pm 2.1°$; control latency 13.0 ± 1.5 ms, TTXM1 latency 12.9 ± 1.6 ms; $n = 7$ mice) (Fig. 2, A and B).

ICMS evokes widespread activity under some experimental conditions (15, 17, 18). We therefore tested for S1-evoked movements by using a second independent method that involved optogenetic stimulation of neurons expressing ChR2. In Thy1-ChR2 transgenic mice (21, 22), robust whisker retraction could be evoked by blue light stimulation of S1 barrel cortex (Fig. 2C).

Application of TTX to motor cortex completely blocked movements evoked by optogenetic stimulation of motor cortex, but it had no effect upon S1-evoked optogenetic whisker retraction (S1 control amplitude $-15.5° \pm 2.7°$, S1 TTXM1 amplitude $-12.7° \pm 0.9°$, S1 control latency 13.7 ± 0.9 ms, S1 TTXM1 latency 14.3 ± 0.9 ms; $n = 5$ mice) (Fig. 2, C and D, and movie S1). To achieve the highest specificity for optogenetic stimulation, we used an adeno-associated viral (AAV) vector to locally express ChR2 in S1 barrel cortex (Fig. 2E). Blue light stimulation of these S1 neurons drove a robust short-latency whisker retraction in 8 out of 11 mice (amplitude $-10.8° \pm 3.2°$, latency 16.1 ± 1.8 ms, $n = 8$ mice) (Fig. 2, E and F).

We next began to question whether the movements evoked by stimulation of S1 were driven directly by motor cortex or whether the evoked whisker retraction might actually be relayed via S1.

Whisker protraction driven by ICMS of M1Retract was enhanced by TTX inactivation of S1 ($n = 13$ mice) (Fig. 3, A and B). However, the whisker retraction evoked under control conditions by ICMS of M1Retract was reversed after TTX application to S1 and was replaced by rhythmic protraction (control amplitude $-18.0° \pm 5.6°$, TTXS1 amplitude 21.6° ± 9.9°; $n = 14$ mice) (Fig. 3, A and B). Similarly, the retraction evoked by optogenetic stimulation of M1Retract in Thy1-ChR2 mice was also reversed into protraction by TTX application to S1 ($n = 5$ mice) (Fig. 3, C and D, and movie S2). In a separate set of experiments, applying 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and 2-amino-5-phosphononovaleric acid (APV) to S1 [to block AMPA and N-methyl-D-aspartate (NMDA) types of ionotropic glutamate receptors, respectively], we determined that the whisker retraction evoked by optogenetic stimulation of M1Retract is mediated by a glutamatergic synapse in S1, whereas neither the protraction evoked by stimulation of M1Protract nor the retraction evoked by stimulation of S1 required glutamatergic synaptic transmission in S1 (Fig. 3, E and F). These results reveal that the direct action of whisker primary motor cortex neurons (both M1Retract and M1Protract) is to drive whisker protraction. The whisker retraction evoked by stimulation of motor cortex area M1Retract is in fact driven indirectly, but reliably, via synaptic activation of S1.

Having defined different functional motor roles for M1 (whisker protraction) and S1 (whisker retraction), we next investigated the downstream signaling pathways. Consistent with a major feedforward pathway for sensory information from S1 to M1 visualized with VSD (Fig. 1), we found a high-density column of axons from S1C2 in the
Fig. 4. Motor signaling pathways from S1 and M1. (A) Lentivirus-labeled axonal projection into M1 by neurons located in the C2 barrel column of S1 (red). Biotinylated dextran amine (BDA) was injected into this region of M1 (green). In the overlay, colocalization appears in yellow. (B) The lentiviral injection site in S1 barrel field (S1-BF) of the same mouse is strongly labeled along with the axonal projection to S2 (red). The BDA-labeled axonal projections into S1 from M1 (green) arborize primarily in layers 1, 5, and 6 of the barrel field (S1-BF) and the surrounding dysgranular zone (S1-DZ). (C) M1 (green) projects to the brainstem reticular formation (RF), and S1 (red) projects to spinal trigeminal nuclei (SP5) of the same mouse. Schematic drawing (left) adapted from Paxinos and Franklin (33). (D) Microstimulation of RF evoked whisker protraction, whereas microstimulation of S5 drove whisker retraction. Microstimulation locations were marked with lesions, and fixed sections were cytochrome oxidase stained. (E) Amplitudes and latencies for whisker movement evoked by microstimulation of S5 (n = 4 mice) and RF (n = 3 mice) (mean ± SD). (F) Schematic drawing of two parallel whisker motor pathways from the cortex to the motor neurons located in the facial nucleus (FN).

Given the importance of sensorimotor interactions during any form of active sensing, one should next examine whether reliable anddirect motor control by sensory cortex is a general feature or whether it is a specialization of the mouse whisker sensorimotor system. Interestingly, previous investigations found overlapping sensory and motor representations of the rodent hindlimb (2). Furthermore, in the monkey, corticospinal neurons are present in S1 (30), and retrograde trans-synaptic tracing from finger muscles labels neurons in S1 (37). In this context, it is also interesting to note that early motor mapping studies in monkeys (32) and humans (1) describe movements evoked by stimulation of primary somatosensory cortex in addition to motor cortex. Motor control by sensory cortex, as demonstrated by our experiments in the mouse whisker system, might therefore also be relevant to the functional organization of human cortex.

References and Notes

16. Materials and methods are available as supporting material on Science Online.
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