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Gain control in the sensorimotor system

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Coordinated movement depends on constant interaction between neural circuits that produce motor output and those that report sensory consequences. Fundamental to this process are mechanisms for controlling the influence that sensory signals have on motor pathways—for example, reducing feedback gains when they are disruptive and increasing gains when advantageous. Sensory gain control comes in many forms and serves diverse purposes—in some cases sensory input is attenuated to maintain movement stability and filter out irrelevant or self-generated signals, or enhanced to facilitate salient signals for improved movement execution and adaptation. The ubiquitous presence of sensory gain control across species at multiple levels of the nervous system reflects the importance of tuning the impact that feedback information has on behavioral output.

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Introduction

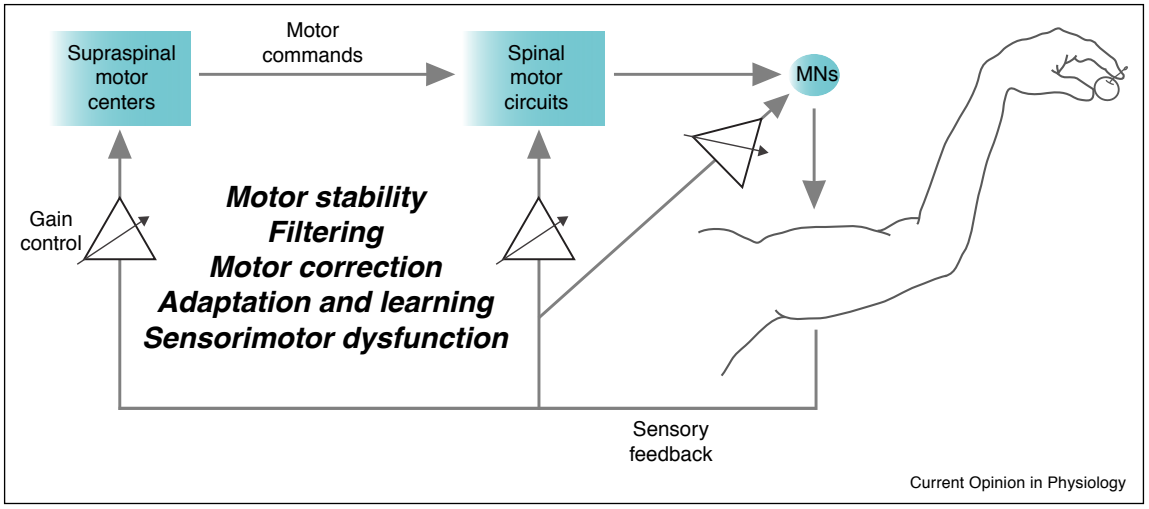
A fundamental feature of movement across species and the diverse behavioral repertoires they exhibit is the dynamic interplay between sensory feedback and motor output. Sensory afferents – for example, somatosensory, visual, auditory, and olfactory – convey many discrete types of information critical for effective interaction with the environment. In the absence of somatosensory feedback information, muscle contraction can be elicited, but coordination across muscles for smooth execution of purposeful movement is lost [1]. Yet the simple transmission of raw feedback signals alone is not sufficient to explain the many ways motor output is continuously adjusted and refined. Rather, sensory feedback gains, defined broadly as the ratio between the output from and the sensory input to a given system, are modulated with impressive spatiotemporal flexibility. A useful entry point for thinking about gain control is to examine cases when feedback gains are reliably decreased or increased, as we describe below. That said, it is important to keep in mind that gain control can manifest in many nuanced ways; from an optimal control theory perspective, gains are dynamically adjusted throughout a behavior to achieve task success, and whether a feedback signal is attenuated or amplified can depend on whether that information contributes to or distracts from attaining a goal. Thus, how feedback gains are adjusted can vary widely, depending on behavioral context and the state of the body and the environment. To explore the organization and function of gain control mechanisms in the nervous system, we examine this phenomenon broadly, from the regulation of monosynaptic reflex arcs that connect sensory afferents to motor neurons, to modulation of higher-order circuits that reside synapses away from the periphery (Figure 1).

Several recent reviews describe the functional organization of sensory feedback pathways and the ways in which they interact with motor circuits to govern movement [2–6]. Here, we describe recent studies across a variety of species that explore the organization of neural circuits that influence sensory feedback gains and how this feedback modulation affects behavioral output. Perhaps unsurprisingly, the adjustment of sensory gains can serve many purposes (Figure 1). We outline illustrative cases in which sensory gain control is used to: 1) maintain stability and reduce variability of motor neuron activity; 2) gate out disruptive and self-generated feedback; 3) improve online motor control by increasing the influence of relevant feedback channels; and 4) facilitate longer-term changes in the motor system as it adapts to new conditions and learns new tasks. Finally, we conclude by discussing recent studies showing the clinical relevance of feedback gain control and the consequences of dysfunction in these systems.

Stability and fidelity of motor neuron output

The motor system is plagued by sources of variability and disruption, including noise in motor and sensory pathways and inherent delays in peripheral feedback that can cause instability. If left unchecked, reflex pathways meant to protect muscles and stabilize motor output can, instead, interfere with ongoing movement [7]. One of the more direct ways to modulate sensory gain and maintain stability is at the monosynaptic

Figure 1



Sensory gain control in the nervous system.
Sensory gain, defined broadly as the ratio between the output from and the sensory input to a given system, is subject to many forms of modulation serving diverse behavioral functions. For example, during limb movement the strength of sensory feedback is regulated at the output of sensory afferents onto spinal motor neurons and interneurons, as well as in supraspinal regions that can be many synapses downstream of peripheral afferent input. As highlighted in this review, sensory feedback from the limb can be attenuated to maintain movement stability and filter out disruptive or self-generated signals. Conversely specific feedback channels can be enhanced to facilitate online corrections within a movement as well as longer-term adaptation to changing environmental conditions or novel task demands. Ultimately, the adjustment of feedback gains is complex and time-varying, and how sensory gain is modulated depends on behavioral goals and the state of the body and the environment. Given the wide range of mechanisms and roles for sensory gain control, dysfunction can cause a diversity of sensorimotor deficits and pathologies.

connection between proprioceptive afferents and motor neurons to ensure that disruptive or delayed inputs are not translated into muscle activity. A conserved mechanism for reducing the impact of sensory afferent activity is through a specialized class of presynaptic inhibitory neurons that target primary afferent terminals and reduce feedback gain at the proprioceptor-motor neuron synapse [8,9]. Loss of these neurons in the cervical spinal cord produces severe forelimb oscillations during reaching, suggesting that delayed proprioceptive feedback can drive forelimb movement instability when the direct recruitment of motor neurons is not inhibited [10]. This phenomenon extends throughout the rostro-caudal axis of the spinal cord—a recent study found that a population of spinal presynaptic inhibitory neurons in the lumbar spinal cord that express the RORβ orphan nuclear receptor gate sensory afferent transmission during locomotion, and their inactivation results in excessive flexion and perturbed gait [11•].

In addition to presynaptic modulation of their inputs, motor neurons themselves have intrinsic gain control properties that govern their output. A rhythmic hindlimb scratching preparation in the turtle was used to show that motor neuron gain is rapidly modulated by adjusting the mean membrane potential, ensuring that the relative variability of motor neuron firing remains stable across different forces [12]. Similarly, modeling studies show that nonlinearities in the motor neuron input–output function can be driven by persistent inward currents, and that these currents are affected by neuromodulatory and inhibitory inputs to drive large changes in motor neuron gain [13]. These findings are reminiscent of experiments showing that fast motor neuron responses to muscle stretch are larger with greater background muscle activity, a process called automatic gain scaling; at longer latencies after muscle stretch, the motor system eventually overcomes this gain scaling in order to make appropriate adjustments regardless of the initial activity of the muscle [14]. In some species, groups of motor neurons can directly interact with each other to control the gain of motor output; in *Caenorhabditis elegans* a class of GABAergic motor neurons are functionally coupled to cholinergic motor neurons to inhibit bending of the head, establishing a gain control system to optimize undulatory head movements during forward locomotion [15]. Thus, motor neurons and their direct sensory inputs are subject to diverse mechanisms of gain control. At its most basic, these mechanisms serve the need for decreasing motor variability and increasing movement stability. These modulatory mechanisms can also be recruited by upstream pathways, raising the question of how sensory gain control might be used for more sophisticated tuning of behavioral output.

Gating irrelevant, disruptive, and self-generated feedback

Much of the information that bombards sensory systems is irrelevant or redundant, if not disruptive, for motor output, suggesting that one fundamental role for sensory gain control is to ensure that only relevant feedback is processed by spinal and supraspinal motor centers. Where and how does this filtering occur?

Spinal cord

Beyond the proprioceptor-motor neuron synapse discussed above, presynaptic inhibition exerts an influence on a variety of feedback modalities. Recordings from the spinal cord of monkeys producing wrist movements have revealed that cutaneous feedback gains are reduced by presynaptic inhibition, and this gain modulation is driven by descending pathways [16]. Moreover, this suppression of cutaneous feedback in the spinal cord translates to reduced tactile responses across multiple neocortical areas during movement, with the motor cortex also showing reduced feedback gains during movement preparation [17]. More recently, these experimental approaches revealed a striking divergence in how different sensory modalities are modulated in the spinal cord during active movement (Figure 2). In contrast to a reduction in cutaneous feedback gains, proprioceptive gains are selectively amplified during wrist movement, suggesting that while tactile feedback might be disruptive to ongoing movement, certain proprioceptive signals could be advantageous [18••]. That said, during object manipulation cutaneous signals from the hand can be quite acute, suggesting the existence of high tactile feedback gains when relevant to task performance [19]. Together, these studies reveal that descending pathways that are active during limb movement dynamically adjust feedback gains in the spinal cord to regulate which types of peripheral information gain access to supraspinal centers [7].

Brainstem and olfactory bulb

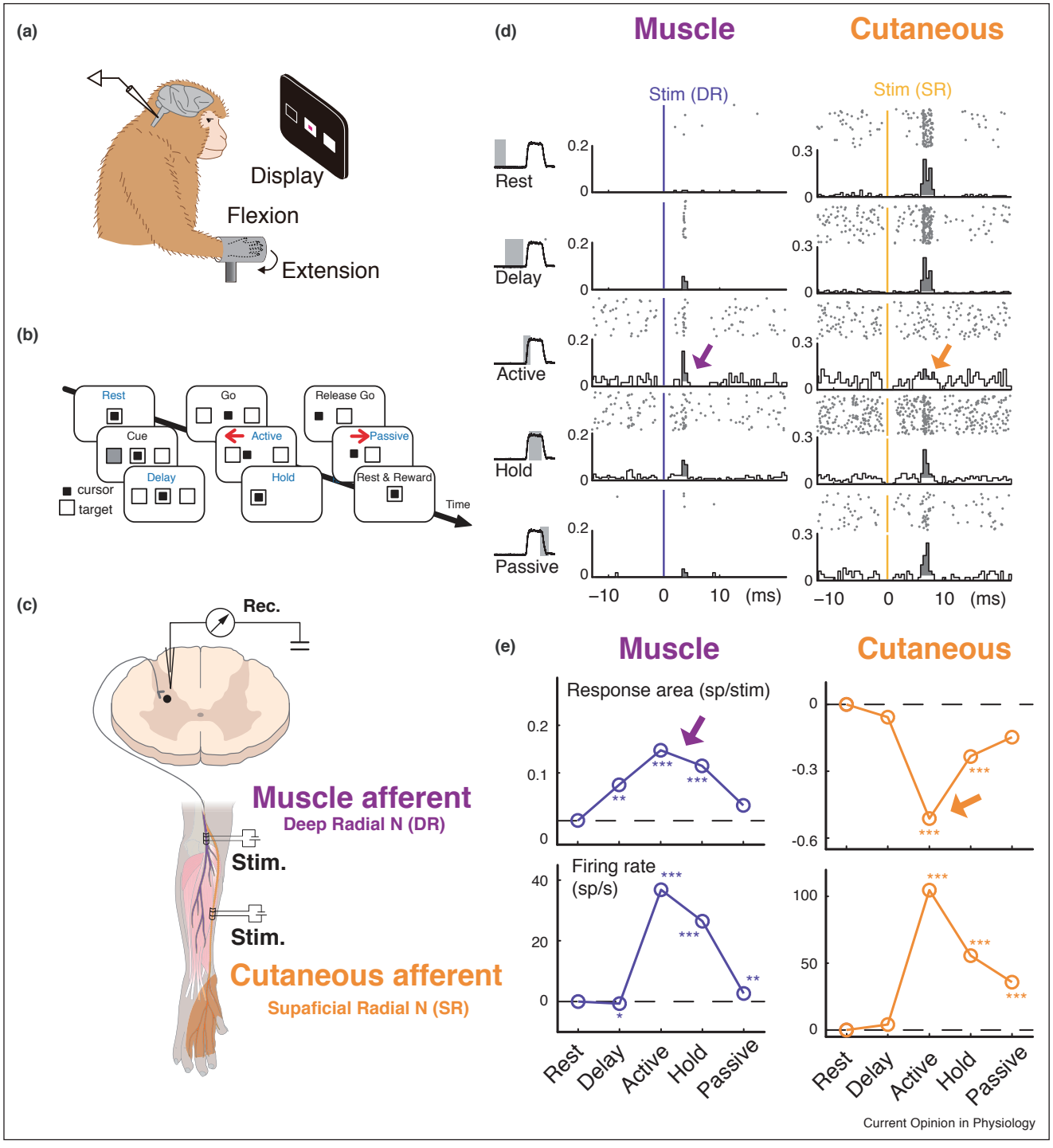
Inhibition of sensory transmission need not be confined to the spinal cord. Rodents use their whiskers to sample the environment, with vibrissae on the snout conveying tactile information via the trigeminal nerve into the brainstem. Descending projections from sensory cortex have recently been shown to gate the transmission of this tactile information at the first synapse in the central nervous system, suggesting that top–down signals are responsible for filtering feedback during active sensing of the environment [20•]. Auditory feedback can also be gated; small populations of genetically defined neurons in the brainstem of zebrafish exert presynaptic inhibition on auditory afferents, reducing the impact of auditory feedback on the startle response [21]. Olfactory cues also trigger strong behavioral responses in a variety of species, suggesting that this sensory modality is also subject to context-dependent gain control. Indeed, a recent study identified inhibitory neurons in the lamprey olfactory bulb that can modulate hard-wired feedback pathways, providing a potential explanation for how the same olfactory-cues can produce divergent sex-specific and life-stage-specific locomotor responses [22]. Together, these studies further support the idea that inhibition of incoming signals provides a conserved means across species and sensory modalities for ensuring that disruptive feedback does not aberrantly influence motor output.

Cerebral cortex

The demonstration that feedback signals can be gated in the spinal cord and brainstem would suggest that the effects of this modulation would also appear in sensorimotor feedback pathways transmitted through the neocortex. Recent studies in humans support the idea that sensory-evoked responses in the cortex are inhibited in a context-dependent manner. Magnetoencephalographic brain imaging during median nerve stimulation has shown that cortical oscillatory activity is gated when stimulation is coupled to haptic exploration as compared to a passive condition [23]. Moreover, shaping of sensory input might be task dependent, with greater inhibition in somatosensory cortex emerging during gross versus fine hand movements [24]. Further evidence that behavioral context influences gating of cortical tactile sensitivity was provided by a study exploring how tactile responses in primary motor cortical cells are modulated when animals are asked to report different types of stimulation. Tactile selectivity of motor cortical cells decreased when animals were asked to report differences in stimuli using the ipsilateral limb, suggesting that a top–down mechanism can gate irrelevant stimuli in motor cortex during action [25]. These findings raise the question, why bother modulating sensory-evoked responses in cortex?

Gating of cortical responses to sensory input provides a potential mechanism for suppressing inappropriate motor output. Inhibition of cortical activity during the preparatory phase of movement has been widely reported, and a recent study suggests that broad inhibition of corticospinal pathways that control both task-relevant and task-irrelevant muscles during movement preparation could serve to decrease background noise while increasing the gain of pathways that control appropriate motor output when the movement is ultimately initiated [26]. Inhibitory gating of cortical activity, however, may not be the only way to suppress undesired movements in response to sensory input. A recent study used a brain-machine interface approach to explore why sensory-evoked responses do not elicit premature or inappropriate motor output. These experiments found that initial cortical population activity is organized in output-null space, meaning it does not change downstream activity, and only gradually enters output-potent dimensions in which downstream effectors are recruited [27]. A related study using a recurrent neural network model of primary motor cortex suggests that small amounts of incoming

Figure 2



Differential modulation of cutaneous and proprioceptive feedback gains during wrist movement.
(a) Recording setup. Cervical spinal neuron activity was recorded while monkeys performed a wrist flexion-extension task with an instructed delay controlled by a manipulandum. **(b)** Task sequence. The black filled squares represent a moving cursor, the solid empty squares represent central and peripheral targets, and the gray filled square represents the peripheral cue. Red arrows illustrate either active or passive movement direction. During flexion trials, the active movement and hold epochs required a wrist flexion movement, and the passive movement involved a wrist extension (and vice-versa for extension trials). **(c)** Identification of first-order spinal neurons. Nerve cuff electrodes were chronically implanted on peripheral nerves of the arm: the deep branch of the radial nerve (DR, purple) and the superficial branch of the radial nerve (SR, orange). Note that DR mostly projects to extensor muscles in the forearm (proprioceptive muscle afferent). SR exclusively innervates a patch of skin on the dorsal, radial aspect of the hand (cutaneous afferent). Concurrent with nerve stimulation, the activity of spinal neurons was recorded extracellularly using

modulation that adjust cortical input–output gains can shift high-dimensional network activity and adjust downstream outputs, providing a means for eliciting desired movements and even generating novel ones [28]. Together, these findings suggest that cortical neurons can undergo broad changes in input–output gains that are subject to neuromodulation and will only produce desired output once appropriate population activity patterns emerge.

Self-generated feedback

One major function of these spinal, brainstem, and cortical mechanisms for sensory gain control is to discriminate feedback generated by one's own movements (reafference) from feedback generated by the environment (exafference) [29]. Recent studies highlight how reafference might be gated in auditory, somatosensory, and visual systems, focusing in particular on how efference copies of motor output might be used to modify feedback gains in anticipation of the predicted sensory consequences of self-generated movement.

An fMRI study of humans performing sound-producing actions found that output from primary motor and supplementary motor cortex modulates auditory cortex during the perception of self-generated sounds, potentially by conveying an intracortical efference copy [30]. However, another study using magnetoencephalography during a similar task argues that predictive attenuation of sensory signals in auditory cortex occurs in parallel to the production of motor output, but before efference copies can be transmitted, suggesting additional mechanisms for gating reafference [31]. Experiments in mice have provided circuit-level insight into the pathways by which motor cortex can attenuate feedback gains in auditory cortex (Figure 3). Animals were trained in an acoustic virtual reality system to associate specific tone frequencies to their locomotor speed. After learning this reafference association, auditory cortical responses to the frequency generated by locomotion were specifically suppressed via secondary motor cortex recruitment of inhibitory neurons in auditory cortex. Moreover, mice simultaneously acquired an improved ability to detect tones not linked to their movement speed, suggesting that sensory gain control filters out self-generated feedback while enhancing sensitivity to exafference [32••].

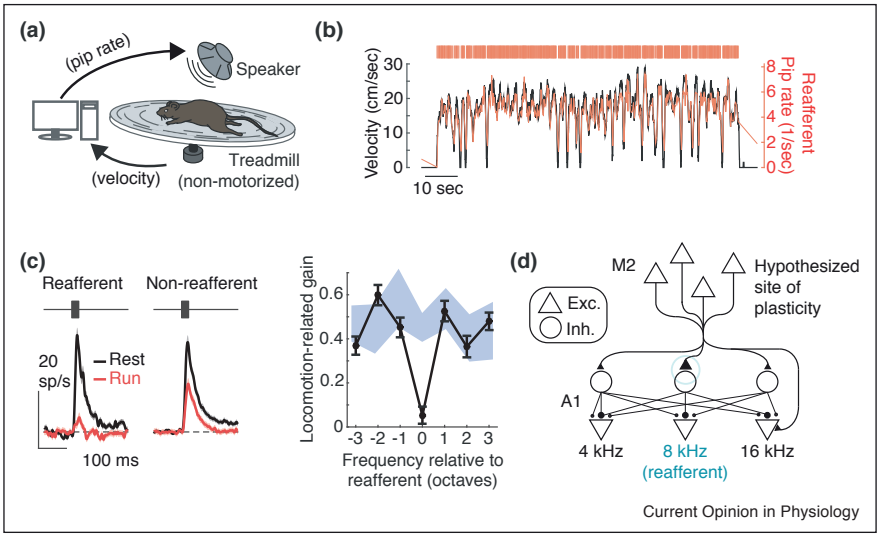
Reafferent filtering is not specific to auditory feedback. Proprioceptive feedback from the limbs, some of which is transmitted to the external cuneate nucleus, is also subject to efference copy-mediated suppression during limb movement. Interestingly, this sensory gain modulation was observed during awake movements, but not during twitching in sleeping neonatal rats, suggesting that some forms of self-generated movement are not subject to the same gating in the developing brain [33]. Moreover, work from the same group found that efference copies during sleep-related twitches are conveyed by other pre-cerebellar structures, the lateral reticular nucleus and the inferior olive, demonstrating that the developing cerebellum receives a variety of efference copy and reafferent signals during active sleep that might be involved in training the nervous system to distinguish self-generated feedback [34]. Tactile reafference is also subject to movement-related gating, and recent work in the mouse vibrissal system shows that cortico-thalamic neurons in layer VI of primary motor cortex are involved in suppressing tactile responses in somatosensory cortex [35].

Active visual sensing is performed with rapid eye movements, termed micro-saccades and saccades, and these self-generated ballistic movements are subject to reafferent filtering [36,37]. Analogous to saccades for active visual sensing, weakly electric fish perform active sensing by producing small body movements relative to the environment. A recent study artificially manipulated reafferent feedback and found that fish upregulate or downregulate active sensing movements based on feedback gains, suggesting a closed-loop system in which the gain of incoming sensory signals directly translates to the amplitude of motor output [38].

Control of reafferent feedback gains might even extend into the realm of the imaginary; the perceived strength of an external touch on the left hand is attenuated if subjects are told to imagine that they themselves are producing the touch with their right hand, indicating that even unexecuted movements can modulate the level of tactile perception [39]. Similarly, modulation of presynaptic

(Figure 2 Legend Continued) single metal electrodes. **(d)** Example of evoked response and firing rate modulation in spinal neurons. Raster plot and peristimulus time histogram (PSTH) of two spinal neurons divided into five behavioral epochs (rows). Examples of wrist extension are shown. Colored vertical lines indicate the timing of stimulation. The peak area corresponds to the gray zone in the PSTH (the white part at the bottom of the peak represents the baseline mean firing rate preceding the stimulation pulse). The *x*-axis represents time in milliseconds (ms), and the *y*-axis represents spiking probability. The PSTH bin size is 0.5 ms. During active wrist extension the response to cutaneous afferent stimulation (SR) was attenuated (orange arrow), while the response to muscle afferent stimulation (DR) was facilitated (purple arrow). **(e)** Attenuation of cutaneous and facilitation of proprioceptive responses. Difference in peak area (top; spikes per stimulation above baseline) and mean firing rate (bottom; spikes per second) between rest and the four behavioral epochs, corresponding to the spinal neurons shown in (d). (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. Peak area: binomial test; Firing rate: Mann–Whitney U test). Note that while the modulation of mean firing rate was comparable between the two neurons, modulation of the peak response area diverges, suggesting that sensory gain modulation is specific to a given afferent input. Moreover, modulation of the response area began during the instructed delay period, suggesting a descending origin for proprioceptive and cutaneous gain control. Adapted from Confais *et al.* [18••].

Figure 3



Attenuation of auditory reafference by cortical circuits.
(a) Acoustic virtual reality behavioral setup. Head-fixed mice ran on a treadmill and heard tones whose frequency corresponded to running speed. As they acclimated to the task, mice learned an auditory reafference associated with their locomotion. **(b)** Association of locomotor output and auditory feedback. Black traces represent locomotion speed and red traces represent tone frequency aligned to motor output. **(c)** Extracellular recordings from neurons in auditory cortex reveal attenuation of reafferent auditory feedback. Left plots show population PSTH to reafferent and non-reafferent tones after acclimation to the task. *y*-axis shows spikes per second. During running, auditory cortical responses to reafferent tones were suppressed relative to non-reafferent tones (red traces). Right plot shows average locomotion-related suppression of auditory cortical neurons across mice. Center of plot represents the expected reafferent tone frequency. *y*-axis represents locomotion-related gain, defined as the ratio of the neuronal response strength during running versus rest. Suppression was greatest for the reafferent tone relative to tones of different octaves. Black bars show standard error and blue shading shows 95% confidence bounds. **(d)** Motor cortical modulation of reafferent auditory gains. Data from this study support a model in which secondary motor cortex (M2) recruits inhibitory neurons in auditory cortex that locally inhibit excitatory neurons. During acclimation to the task, M2 inputs onto inhibitory neurons that are tuned to the reafferent frequency are strengthened, providing a mechanism for selective gating of self-generated auditory feedback by motor cortex. Adapted from Schneider *et al.* [32••].

inhibition on primary afferent inputs to the spinal cord can be observed when subjects are told to only imagine a movement, suggesting that overt motor output is not a perquisite for efference copy-mediated reafferent suppression [40].

Modulating salient signals for improved control

Sensory gain control need not be limited to filtering unwanted input—the impact of signals that are particularly useful can also be increased to enhance sensitivity and facilitate task execution, and several recent studies identify circuits that might be responsible. For example, feedback amplification can be mediated by connectivity across cortical areas. In mice, tactile feedback from the paw to somatosensory cortex is subject to top–down modulation by secondary motor cortex. These intracortical projections increase dendritic spiking and burst firing in layer V pyramidal neurons in sensory cortex, and inactivation of this pathway perturbs tactile perception, suggesting that top–down modulation is involved in enhancing tactile feedback gains for accurate perception and feedback control [41]. Feedback gains can also be enhanced locally within the somatosensory cortex by intralaminar communication. A recent study found that layer II/III pyramidal neurons can enhance whisker-evoked sensory responses in layer V, amplifying the gain of cortical output [42].

Sensory gains can also be facilitated in subcortical structures. Neurons in the optic tectum of the barn owl involved in gaze control and spatial attention receive midbrain cholinergic input that can increase visual feedback gains [43]. In the mammalian spinal cord, descending corticospinal neurons from somatosensory cortex facilitate light-touch evoked activity in dorsal horn interneurons, revealing a top–down pathway for amplifying spinal tactile transmission to the brain (also see discussion of top–down pain modulation below) [44••]. Invertebrates also rely on the rapid amplification of salient feedback signals. Dragonflies pursue prey that produce only a small input to the retina. A pair of recent studies found that the gain of target-detecting neurons in the optic lobe is increased in a predictive way, augmenting sensitivity ahead of the target's path and minimizing variability in neuronal response to noisy inputs in order to

improve pursuit [45,46]. Thus, pathways for amplifying sensory feedback gains are present across the hierarchy of sensorimotor circuits. What are some of the behavioral roles for increasing sensory gain?

Online motor correction

One major function of enhancing the gain of relevant feedback is to keep the motor system informed of error, for example due to noise or external perturbation, in order to facilitate appropriate online corrections [2–5]. In the laboratory, these corrections are often probed by inducing a visual shift in the target or in a cursor representing the hand during a goal-directed reaching movement and measuring visuomotor feedback gains—that is the amplitude of rapid corrections relative to a visual perturbation. A recent study asked how the sensorimotor system specifies appropriate visuomotor feedback gains when the subject is directed to reach for a wide target, where feedback gains are low and more error can be tolerated, or, conversely, to a narrow target, when feedback gains are set high to increase sensitivity to perturbations and improve performance. When subjects were informed of the correct target only after initiation of the reach, visuomotor feedback gains were set to the average of what would be expected for the wide or narrow target alone. These findings suggest that the motor system simultaneously determines multiple feedback gains when presented with task uncertainty [47•]. Similarly, when subjects are asked to reach to two different targets with each hand, visuomotor feedback gains appear to be set in parallel for each hand [48]. In addition to visual perturbation of the target or hand position, visual background motion caused by one's own body movement can also induce online corrections in the direction of visual motion, a phenomenon called the manual following response. A recent study probed the visuomotor gains of these manual following responses during a mid-reach saccadic eye movement, finding that gain modulation occurs rapidly during the saccade to coordinate gaze and reach in a predictive manner [49].

Somatosensory feedback is critically important for online control, and a wide variety of studies use mechanical perturbation, of the limb for example, to probe how somatosensory signals are modulated during movement. As discussed above, there has been much exploration of how gain is reduced in sensory and motor cortices, raising the question of whether cortex also plays a role in enhancing relevant somatosensory feedback gains for online motor correction. Previous work has implicated primary motor cortex (M1) in rapid corrections during limb movements following a mechanical perturbation, finding that single neurons in monkey M1 integrate sensory information from multiple joints into signals that can be used to appropriately counter a limb perturbation within approximately 50 ms [50]. More recently, the same group found that the regions of the cerebral cortex that are recruited and the order with which they respond to sensory feedback following a limb perturbation depends on context, namely whether the monkey is engaged in keeping the hand on the same target versus selecting a new target [51]. Moreover, a recent study provides evidence that feedback gains are set in motor cortex before the initiation of the movement, and these gains reflect recent experience with the environment and predict the speed of the impending reach [52]. These findings reveal that the ways in which sensory gains are modulated and the cortical areas they recruit in response to a mechanical perturbation are complex, varying dynamically with changing behavioral goals and experience.

Motor cortex is likely involved in executing a corrective response to a perturbation. In a locomotor task in which mice navigate a virtual corridor and experience unexpected shifts in corridor direction, inhibition of motor cortex affects the initiation of corrective turns after visual perturbation, but not the execution of spontaneous turns, suggesting an important role for motor cortex in coordinating salient visual cues with movement correction [53]. Key to defining how cortex influences motor correction is the identification of subcortical motor circuits that are recruited by descending cortical projections. A recent anatomical and functional study in mice found that the motor cortex directly innervates pre-motor interneurons in the spinal cord, while the sensory cortex largely avoids these last-order interneurons. Moreover, perturbation of motor cortex and sensory cortex and their respective interneuron targets in the spinal cord produces distinct deficits during forelimb movements, suggesting different roles for these cortical regions in the online adjustment of forelimb motor output [54].

Adaptation and learning

In addition to online corrections within a movement, the adjustment of feedback gains plays a prominent role in long term adaptation to changing environmental conditions. The state of our bodies and the environment is continuously changing, and one way the nervous system adapts to these changes is by adjusting feedback gains in a selective and flexible fashion. A recent study measured visuomotor feedback gains after human subjects adapt to a variety of novel dynamics generated by a robotic manipulandum, finding that gain modulation is not general for all perturbations, but rather is selective to the direction of perturbation and tuned to the dynamics of the environment [55]. Primary somatosensory cortex may be essential for 'storing' learned changes in feedback gains. Much like in primates, mice trained in a joystick task adapt their motor output to force field perturbations. When the forelimb area of somatosensory cortex is inhibited, motor adaptation is diminished but basic motor kinematics and reward-based learning are spared, suggesting that sensory cortex is critically involved in

updating sensorimotor feedback gains during changing environmental conditions [56].

Changes in feedback gains due to sensorimotor adaptation can also affect reflexive responses to perturbation. Using a robotic manipulandum, a recent study altered forelimb intersegmental dynamics in human subjects, by either restricting the shoulder joint or leaving it free to move, and measured how shoulder muscle recruitment adapts to mechanical perturbation. Feedforward control (shoulder muscle activity) changed together with feedback control (the size of the reflex response to perturbation) during adaptation in a manner that reflected the altered intersegmental dynamics. These results suggest that voluntary and reflexive movements use the same internal model of the limb to adjust gains based on the state of the body, and thus feedforward and feedback control may not be distinct in a meaningful way [57••]. In addition, the same group found evidence that these sophisticated corrections of limb motor output can emerge surprisingly rapidly, through fast spinal feedback pathways [58]. Together, these findings reveal how sensory feedback gains are dynamically adjusted based on the state of the limb, and show that this gain modulation may not occur exclusively in the cerebral cortex, but also in subcortical reflex arcs within the spinal cord.

Beyond adapting an existing motor program to new conditions, learning an entirely new motor task also takes advantage of flexible modulation of sensory feedback gains. In a recent study, mice were trained to discriminate two textures while the activity in two groups of primary somatosensory cortical neurons was recorded—one group projecting to primary motor cortex and another group projecting to higher-order sensory cortex (S2). Two different forms of sensory gain regulation in the two groups of neurons were observed while learning the task; the motor cortex-projecting neurons increased discrimination performance by recruiting previously inactive neurons, while the S2-projecting neurons did so by shifting texture tuning across the population, but not at a single neuron level [59]. These findings suggest that there are diverse means by which task-relevant sensory gains are modulated in different cortical areas when learning a new motor task.

Sensory gain control in health and disease

Motor disorders

Because sensory gain modulation is tightly linked to the control of ongoing behavior, dysfunction in gain control circuits would be expected to result in movement deficits. It has been well documented that sensory input gains can be attenuated just before movement onset. A recent study explored whether sensory attenuation is altered in patients with bradykinesia, a primary motor sign of Parkinson's disease, since patients typically have difficulty initiating movement. No sensory gating was observed at movement onset in these patients, while sensory attenuation could be recovered with medication [60]. These findings suggest that sensory gating is important for suppressing sensory feedback in advance of a volitional movement, and loss of sensory attenuation could contribute to the pathophysiology of bradykinesia. Similarly, there is increasing evidence that the basal ganglia, the primary site of pathology in Parkinson's disease, functions to control the gain of descending motor commands, and thus movement kinematics, in a dopamine-dependent manner [61].

Another example of pathology linked to deficits in gain control can be found in spinal reflexes. The gain of a spinal reflex (e.g. the cutaneo-muscular reflex) is well known to change dynamically according to the phase of locomotion. This phenomenon is typically examined by stimulating peripheral cutaneous afferents during a specific phase of locomotion and examining the size and latency of the evoked response in muscle. A recent study modified this approach by having subjects push a handheld button that triggers the electrical stimulation at specific times during locomotion, and this self-induced afferent stimulation was compared with conventional externally generated stimulation. In healthy subjects, the reflex responses evoked by self-generated simulation were smaller than those that were externally triggered, indicative of sensory gating during locomotion; however, patients with focal cerebellar lesions showed less sensory attenuation, suggesting that the cerebellum is involved in attenuating self-induced reflex responses by predicting the sensory consequences of ongoing behavior [62]. These studies highlight the ways in which deficits in sensory gain modulation could be used as a biomarker to measure the onset and progress of motor pathophysiology.

Pain

Pain can have profound effects on movement, and aberrant gain control is implicated in many aspects of pathological pain. Since its introduction in 1965, gate control theory has had an enduring influence on experiments exploring how the gain of nociceptive input can be modulated [63]. Briefly, the theory proposes that innocuous mechanical stimuli transmitted by Aβ fibers recruits feedforward inhibition in the spinal cord that attenuates input to pain transmission neurons, and this inhibitory gate can be inactivated by strong Aδ and C fiber input. A recent study sheds some mechanistic light onto this theory, finding that glutamate receptor kinetics and filtering by potassium channels are responsible for ensuring appropriate timing of gate control [64]. Other modulatory mechanisms can modulate nociceptive gain; for example dopamine can elicit presynaptic inhibition of primary nociceptive inputs to projection neurons in lamina I of the spinal cord, providing a potential mechanism for the amelioration of chronic inflammatory pain [65]. Moreover, the descending corticospinal pathway

from somatosensory cortex that facilitates tactile transmission that we discussed earlier [44••] can also contribute to aberrant pain transmission. In a mouse model of peripheral neuropathic pain, corticospinal input to spinal laminae III–V elicits tactile allodynia, facilitating the activation of ascending pain pathways by what are normally innocuous tactile stimuli [44••]. Together, these studies reveal circuit mechanisms by which spinal and supraspinal pathways normally involved in sensorimotor control can also contribute to aberrant transmission of nociceptive inputs.

Conclusions

Given the diversity of gain control mechanisms across sensorimotor hierarchies of the central nervous system, it is not surprising that sensory gain control is used to achieve a variety of functions. Across species and behaviors, gain control serves to reduce the impact of undesired or disruptive sensory input, while selectively amplifying feedback useful for adjusting ongoing movements and shaping motor output to match changing environmental demands. Thus, regulation of sensory feedback is a fundamental motif of the sensorimotor system that is applied flexibly to a diversity of circuits to facilitate the successful execution of movement. And it is becoming increasingly clear that dysfunctional gain control can manifest as many forms of pathology, from tremor to pain. Hand-in-hand with steadily improving tools for dissecting the function of gain control circuits in behaving animals will be greater insight into the many ways in which sensory feedback impacts movement, and better strategies for therapeutic intervention to restore balance when gain control goes awry.

Conflict of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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