OPINION

Motor cortex — to act or not to act?

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Abstract | The motor cortex is a large frontal structure in the cerebral cortex of eutherian mammals. A vast array of evidence implicates the motor cortex in the volitional control of motor output, but how does the motor cortex exert this 'control'? Historically, ideas regarding motor cortex function have been shaped by the discovery of cortical 'motor maps' — that is, ordered representations of stimulation-evoked movements in anaesthetized animals. Volitional control, however, entails the initiation of movements and the ability to suppress undesired movements. In this article, we highlight classic and recent findings that emphasize that motor cortex neurons have a role in both processes.

In the late 1860s, two young physicians conducted an experiment that would have a major influence on our thinking about brain function and about motor control. Fritsch and Hitzig used electrodes to evoke a tickling sensation in their own tongues and then applied the same currents to specific sites in the frontal cortex of their experimental animals, dogs. They found that these currents evoked movements of the experimental animals, whereby the type of evoked movement varied with the cortical location of the stimulation site[1] (FIG. 1a). The discovery of this 'motor map' paved the way for modern thinking about the cerebral cortex. Soon afterwards, Ferrier identified a similar cortical motor map in monkeys[2], and after years of careful experiments, it became clear that the cortical motor representation is highly somatotopic, comprising a fine-grained 2D map of the external body[3]. In later work, it became clear that long, intense stimulation trains can activate complex motor patterns[4]. Moreover, although early experiments demonstrated that surgically lesioning the frontal 'motor sites' did not abolish movements[1], these experiments indicated that a prime role of this cortical area must be movement generation; hence, it was named motor cortex.

A major advance in our understanding of the motor cortex came when cortical mapping experiments were conducted in humans. The Canadian neurosurgeons Penfield and Rasmussen[5] mapped the cortex in awake patients during surgeries. This approach had an enormous advantage over the experiments carried out on anaesthetized animals: the experimenter could ask the patient how the cortical stimulation felt. These experiments yielded two insights: first, they confirmed that the human motor cortex contains a somatotopic map of the body, a motor 'homunculus' (FIG. 1b), and second, the patients often reported that motor cortex stimulation led to movement inhibition and muscle relaxation. On stimulation of motor cortex sites, patients commonly felt a sense of paralysis and numbness focal to specific body parts (FIG. 1b). The Penfield and Rasmussen experiments indicated that the human motor cortex is not a pure 'motor map' (REF. 6); it is also a map of movement suppression[5].

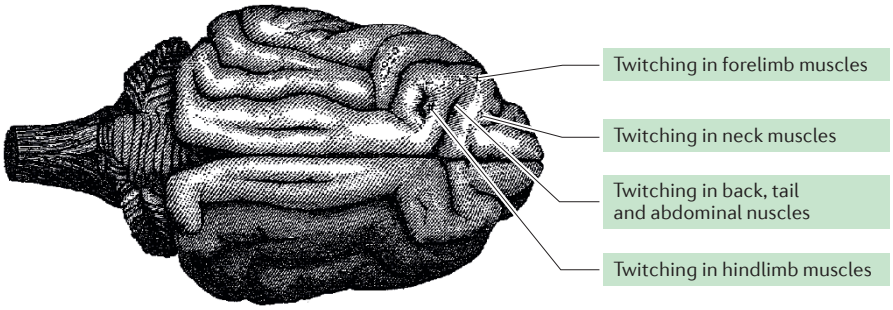
Several subsequent studies have made similar observations and shown that so-called negative motor areas (cortical areas where stimulation inhibits movement) are widespread across the motor cortex[7–10] and the premotor cortices[11]. Such movement-suppressive effects of motor cortex stimulation are impossible to discover in experiments on anaesthetized animals, in which only 'positive' motor effects can be evaluated. Interestingly, we know from animal experiments that many motor cortex stimulation sites produce no movements at all[12–14], but the motor maps observed from stimulating motor cortex in anaesthetized animals have dominated our thinking about motor cortex function[15]. A further complicating factor in determining the role of the motor cortex in movement is that stimulation of negative motor areas can be made to elicit positive movements (that is, muscle twitches) with an increase in stimulation current[10] and may thus be misclassified as non-responsive or high-threshold sites if only positive effects of stimulation are evaluated[11].

The stimulation-evoked movements observed by Fritsch and Hitzig suggest that motor cortex is a structure for movement generation, whereas the stimulation effects observed by Penfield and Rasmussen point to a role of motor cortex in movement suppression. In this Opinion article, we discuss these opposite views of motor cortex function and argue that the motor cortex is involved in both processes.

From motor cortex to muscle

What do we mean by the term 'motor cortex'? The motor cortex is a large frontal structure in eutherian mammals (FIG. 2a). There are a number of ways to delineate motor cortex. As described above, the classic, physiological definition of motor cortex (primary motor cortex) is the largest frontal area where, for example, electrical[1,2,5,12,16] or optogenetic[14,17] stimulation elicits somatotopically organized movements at low stimulation thresholds. In higher mammals, this 'body map' of movements is adjacent to and is a mirror image of the body map in the primary somatosensory cortex[12,16,18–21]. We suggest therefore that these four criteria — low stimulation thresholds for movements, full body topography, adjacency to the primary somatosensory cortex, and mirror-image topography of the primary somatosensory cortex — define a homologous area — that is, the primary motor cortex — in eutherian mammals. By this definition, marsupials (which can be found on an early branch of the mammalian tree) have a large somatosensory representation but no motor cortex[21–23] (FIG. 2a). Conversely, in rodents, the primary motor cortex is large and indeed takes

a Motor cortex as a 'motor map'



b Motor cortex as a movement-suppression map

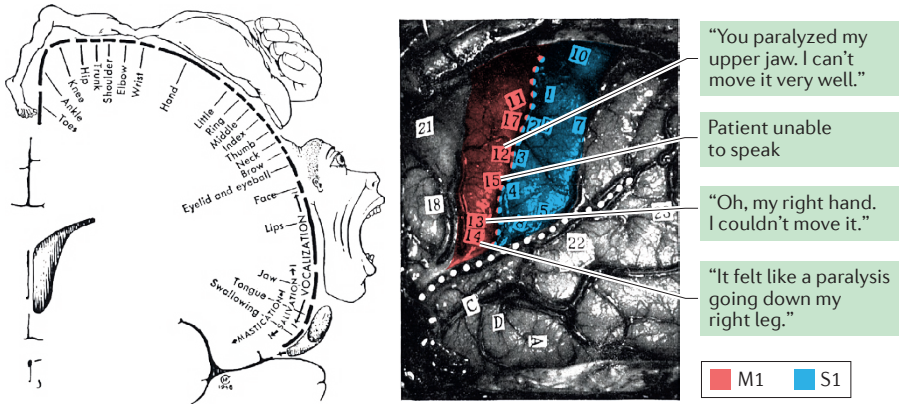


Figure 1 | **Two opposing views of the motor cortex. a** | Through use of anaesthetized dogs, Fritsch and Hitzig discovered that the motor cortex seems to act as a motor map. The panel depicts the dog brain and indications of the evoked movements they observed following stimulation at various sites of the dog motor cortex[1]. **b** | Penfield and Rasmussen performed stimulation experiments in patients and discovered a similar motor map in humans, the famous motor homunculus[5] (left). Although stimulation-evoked movements in anaesthetized animals suggest that motor cortex is a structure for movement generation, Penfield and Rasmussen observed that stimulation of motor cortex in awake patients often led to movement suppression. The right panel shows an intra-operative photograph and reports made by a patient during stimulation of motor cortical sites (the primary motor cortex (M1) is in red, and primary somatosensory cortex (S1) is in blue; the white dots indicate the Rolandic and Sylvian fissures)[5]. Part **a** is adapted from REF. 1. Part **b** (left panel) is from Penfield/Rasmussen. *The Cerebral Cortex Of Man*. ©1950 Gale, a part of Cengage, Inc. Reproduced by permission www.cengage.com/permissions (REF. 5). Part **b** (right panel) is from REF. 5, The Macmillan Company.

up almost all of the frontal cortex[12,16,24,25] (FIG. 2a). In primates, the frontal cortex contains several specialized premotor and prefrontal structures, and the primary motor cortex takes up (in relative terms) a much smaller area; it is a thin strip anterior to the Rolandic fissure[2,3,6] (FIG. 2a).

Other definitions of the primary motor cortex rely on anatomical markers such as the presence of a thick cortical layer 5b and a near-absent cortical layer 4 (REFS 26,27), the frontal area that is the origin of corticospinal projections[28,29] or the frontal area that receives dense corticocortical innervation from primary somatosensory cortex[30,31]. Finally, some definitions are based on mixed criteria[32] and often rely on comparative anatomy to name motor structures in, for example, the rodent brain after their putative corresponding primate homologues[18,20,21,32]. The precise correspondence between primate and rodent motor cortices (and other premotor areas) is largely unknown, and different ways of delineating the motor cortex sometimes suggest conflicting naming schemes[33]. For example, the area of rat cortex that the physiological approach designates as primary vibrissa motor cortex[12,16,17,19] is referred to as the secondary motor cortex (a putative homologue of primate supplementary motor areas) by the rat brain atlas[32] and some publications[34–39] and as the frontal orientation field (a putative homologue of the primate frontal eye field) by others[40–43].

Pathways from the motor cortex to motor neurons. Neurons in the motor cortex do not innervate muscles directly. The most 'direct' pathways from the motor cortex to muscles involve so-called pyramidal-tract-type neurons, which have their somata in layer 5 of the motor cortex and send their axons through the pyramidal tract to target neurons in the spine and brainstem. Some pyramidal tract neurons form synapses directly onto motor neurons that innervate muscles. This provides a straightforward circuit for motor control: if pyramidal tract neurons spike, downstream motor neurons depolarize and spike, which elicits muscle contraction[44]. In mammals, however, this direct wiring pattern appears to be the exception rather than the norm. In rodents[45–49] and primates[44,50], most corticobulbar and corticospinal neurons emanating from the motor cortex project to brainstem and spinal interneurons, many of which have inhibitory connections with motor neurons[44,51] (FIG. 2b). The monosynaptic projections from the motor cortex to motor neurons in primates constitute a specialization of primate distal limb muscles, which seems to have evolved for dexterous and fractionated digit movements[50,52–54] (FIG. 2b).

Anatomical loops via other motor centres. In addition to direct corticospinal projections from the motor cortex, there are major projections from the motor cortex to other cortical and subcortical motor structures, such as the somatosensory cortex, the basal ganglia, the motor thalamus, the brainstem and the cerebellum[55–57]. Like the motor cortex, the somatosensory cortex also directly innervates spinal and brainstem motor centres and can directly modulate muscle output[5,12,17,47]. Many motor cortical and pyramidal tract neurons send axon collaterals through the striatum and target neurons in the subcortical nuclei of the basal ganglia, which also contains circuits for both facilitation and suppression of muscle output. The basal ganglia circuitry is complex and not sharply dichotomous[58–61], but in the classic model, this circuitry is separated into the so-called direct and indirect pathways[58,62]. The net effect of exciting striatal neurons through the direct pathway is a disinhibition of spinal motor centres, whereas the net effect of exciting neurons through the indirect pathway is an increase in inhibitory drive from the basal ganglia to downstream spinal motor centres[58,62].

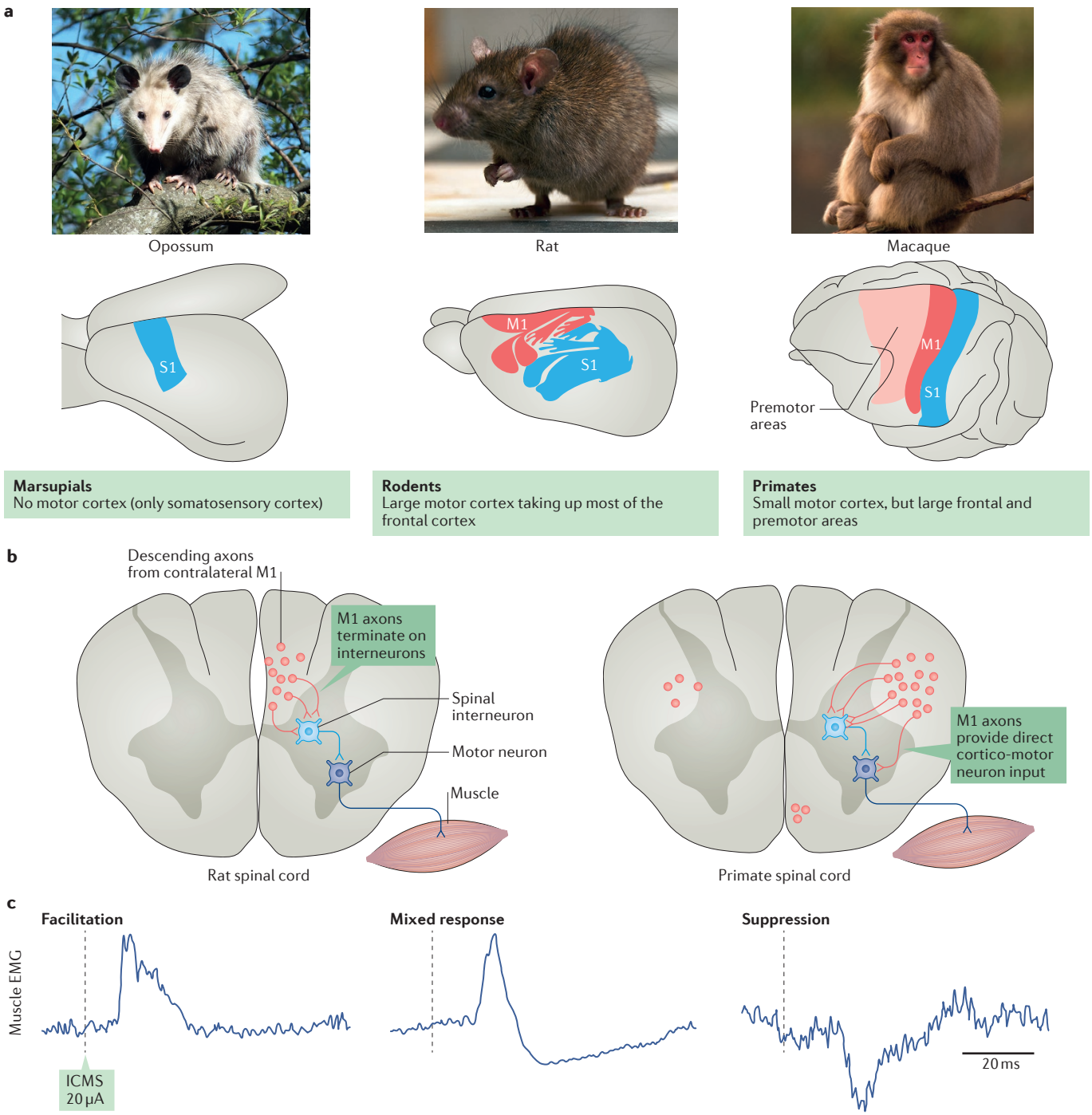


Figure 2 | **From motor cortex to muscle output: anatomy and functional connectivity. a** | The motor cortex is a large frontal structure in eutherian mammals. Marsupials, rats and primates all have a large somatosensory representation (the primary somatosensory cortex (S1) is shown in blue) but different motor representations in cortex. Marsupials have no motor cortex, whereas in rodents, the primary motor cortex (M1; red region) takes up almost all of the frontal cortex, and in primates, the frontal cortex is compartmentalized into specialized premotor subfields (pale red regions), and M1 is comparatively small. **b** | In most mammals, motor cortex axons terminate on spinal interneurons, not directly on motor neurons (left panel; the red dots indicate descending axons from M1, but only some of the connections from these axons to their downstream targets are depicted). In certain cases (for example, in the context of distal limbs in primates and the larynx in humans), some motor cortex axons terminate directly onto motor neurons[44,52] (right panel). This direct corticomotor neuronal connection is evolutionarily more recent[44,50,52]. **c** | Focal intracortical microstimulation has revealed that motor cortex activity can have facilitative, mixed or, most commonly, suppressive effects on muscular activity (vertical lines indicate stimulation; the mean electromyogram (EMG) of 250 trials is shown in each panel; from left to right, the EMGs of a forearm flexor muscle and two intrinsic hand abductor muscles are shown)[64]. In part **a**, the image of the opossum is reproduced with permission of Silvia Frigerio/EyeEm/Getty, the image of the rat is reproduced with permission of Alexander W. Helin/Getty and the image of the macaque is reproduced with permission of Vince Burton/Alamy Stock Photo. Part **a** (lower-left panel) is adapted with permission from REF. 21, Wiley. Part **a** (lower-centre panel) is adapted with permission from REF. 33, Elsevier. Part **a** (lower-right panel) is adapted with permission from REF. 33, Elsevier. Part **b** is adapted with permission from REF. 44, Annual Reviews. Part **c** is adapted with permission from REF. 64, Springer.

Facilitation and suppression of muscle activity by the motor cortex. Parallel anatomical loops exist — through direct projections from the motor cortex to spinal neurons and through indirect projections via other motor centres — by which motor cortex activity might potentially facilitate or suppress muscle activity. Spike-triggered averaging of muscle electromyography (EMG) signals reveals that spikes of single motor cortical pyramidal tract neurons can predict both EMG peaks and EMG troughs[44,63–65]. In primates, monosynaptic excitatory connections between motor cortex neurons and spinal motor neurons are abundant, and net inhibitory connections to motor neurons are multisynaptic, occurring via spinal interneuron microcircuits. Accordingly, peaks in the spike-triggered EMG (indicating muscle facilitation) are abundant (~24% of neurons) and large and have a short latency. Troughs in the spike-triggered EMG, by contrast, appear to be fewer in number (~2% of neurons) and are smaller, presumably owing to the temporal noise induced by the many synapses between motor cortical spike and muscle contraction. This higher noise makes it likely that spike-triggered averaging underestimates the functional connectivity of motor cortex neurons that mediate net suppressive effects[63–65]. More generally, spike-triggered averaging techniques are only well suited to reveal oligosynaptic connections from the motor cortex to motor neurons. During active behaviour, it is possible that the motor cortex may initiate[30] or suppress[66] motor programmes initiated reflexively from subcortical circuits, including the basal ganglia and brainstem[49,67,68].

An alternative way of revealing the impact of motor cortex activity on muscle output is to relate EMG signals to intracortical microstimulation. Motor cortex microstimulation also causes increases and decreases in EMG signals and in the membrane potential of spinal motor neurons[64,65,69–71] (FIG. 2c). In microstimulation experiments using brief stimulation trains (lasting a few milliseconds), net EMG suppression is much more common than net EMG facilitation[64,65], thus implicating motor cortex neurons in the suppression of muscular activity. In microstimulation experiments using longer stimulation trains (lasting several hundred milliseconds), it is possible to elicit coordinated sequences of muscle activation and inhibition towards a variety of body postures[4,72].

Clearly, analysing the relationship between motor cortex activity and muscle activity either by spike-triggered averaging techniques or by cortical microstimulation leads to different conclusions. It should be noted that intracortical microstimulation induces neural activity that is very different from 'natural' physiological patterns[73–75]. Thus, findings from investigations of the functional connectivity from the motor cortex to muscles, which suggest that motor cortex activity has a substantial role in movement suppression, might be viewed simply as artificial effects that interfere with natural motor programmes and have little physiological relevance. There is also evidence to suggest that the relationship between motor cortex and muscle activity is highly dynamic[71], which further complicates the interpretation. In addition, even though the effects of microstimulation point to a substantial role of motor cortical activity in the suppression of muscle activity, suppression of muscle activity is not necessarily suppression of motor output. Initiation of most motor actions, such as reaching, involves both muscle excitation and muscle inhibition. In the limb motor system, there are agonist and antagonist muscles that span the various joints that must be coordinated to make a movement[65,76].

The physiology of action

In this section, we review motor cortex activity patterns that are associated with action. Here, it is important to emphasize the immense diversity of motor cortex discharge patterns. Such response diversity might contribute to behavioural flexibility, but it limits the validity of general statements about motor cortex activity. In the motor cortex — much like in other cortices — cellular responses vary greatly between cortical layers and cell types, and it is increasingly recognized that there is a need for cell-specific readouts and unbiased population analysis to study this brain region.

Distal limb movements in monkeys. A major share of what we know about how motor cortex activity correlates with movement has come from single-cell recordings in primates while they performed reaching movements or hand manipulations. Just as with the interpretation of stimulation effects, changes in spike rate must be interpreted with the caveat that an increase in motor cortical activity can be seen as facilitating movement in reference to the excitation of agonist muscles but also as inhibition in reference to the antagonists. However, even though some motor cortex neurons decrease their activity during such movements, the activity of the majority of motor cortex and pyramidal tract neurons correlates positively with movement and force[77–82] (FIG. 3a). Motor cortex recordings during arm movements in monkeys displayed peak firing rates just before movement onset and a cessation of activity before movement completion, suggesting a role for the motor cortex in movement initiation[77].

Complex activity patterns during limb movements in non-primates. In mammals other than primates, the relationship of motor cortical firing rates with limb movements is complex. In cats, for example, there is no overall modulation of motor cortex activity during locomotion versus rest[83,84]. However, motor cortex activity increases with the 'difficulty' of the locomotion, when the animal must make precise, controlled steps, such as over obstacles or onto narrow steps of a ladder[84–86]. Most motor cortex neurons progressively increase their firing rate when a cat walks progressively more slowly to take smaller steps between barriers[87]. Motor cortex activity in cats is also related to phases of the step cycle, with more spiking during the swing phase (in which the foot is not touching the ground) than during the stance phase (in which the foot is applying force against the ground)[84–87].

With current techniques, it is now possible to investigate the relationship between motor cortex activity and motor output with high fidelity in rodents[88]. In contrast to the archetypal increase in motor cortex activity with movement that has been observed in most studies of primate motor cortex[77–82], a surprising predominance of suppression of motor cortex activity during movement has been reported across several recent rodent studies. For example, a recent study used extracellular recordings to investigate activity in deep layers of the motor cortex in mice running freely on a treadmill. During locomotion, the average spike rate of neurons in these layers decreased by 30%, and single units that discharged fewer spikes during locomotion (66% of neurons) were much more common than neurons that increased their firing rate during locomotion (34% of neurons)[89]. Furthermore, the reduction in spike rate correlated with the spike width, such that units with wider spikes (that is, putative principal cells[90], barring some exceptions[91–93]) showed the strongest suppression of activity[89].

In a similar study, the activity of layer 5b neurons in the mouse motor cortex during locomotion was investigated with intracellular recordings[94]. In this study, there was also an unusual abundance of layer 5b motor cortical neurons that decreased their spike rate during locomotion (FIG. 3b). Overall, during locomotion, there was no modulation of motor cortex firing, but at the single-cell level, more layer 5b neurons were activated (53%) than suppressed (38%)[94].

Vibrissa motor cortex activity during whisking. In the rodent whisker system, movements can be easily quantified. Similar to locomotion, but different from grasping and reaching, whisking movements are mediated by a subcortical central pattern generator[95,96]. The whisker motor plan is laid out for highly controlled whisker protraction[97], which the animal uses to palpate objects in front of the nose[98,99]. The vibrissa motor cortex is very large (FIG. 2a) and makes up approximately 6.5% of the whole cortical sheet[12,16,19,24,25]. Several studies have examined the relationship between vibrissa motor cortex activity and whisking kinematics[67,100–102], and the relationship between vibrissa motor cortex activity and whisker movement is still debated. An early study examined the relationship between vibrissa motor cortex activity and whisker pad EMG[100] and did not find "any obvious correlation" between the two[103]. Several subsequent studies made similar observations and found no overall modulation of vibrissa motor cortex population activity by whisking[67,100–102], but this view has been challenged by two recent publications[30,66]. One investigation found that during whisking in head-fixed mice, there was a decrease in the firing rate of layer 2/3 neurons and a more mixed response pattern in layer 5 neurons in the motor cortex[30]. Specifically, there was a small increase in layer 5 activity around the onset of whisking, and single cells in this layer displayed both firing rate decreases and increases during whisking[30]. Similar to earlier conclusions from monkey motor cortex studies, such findings might indicate a role for the vibrissa motor cortex in whisking initiation[30]. Another study also investigated activity in layer 5 of vibrissa motor cortex, but this time in freely moving rats during various forms of more naturalistic whisking behaviours. Exploratory whisking in the air, whisking to palpate objects and social whisking during facial interactions with conspecifics[66] were associated with an ~21% overall decrease in spike rates in layer 5 of the vibrissa motor cortex (FIG. 3c). Furthermore, intracellular recordings from layer 5 vibrissa motor cortex neurons in socially interacting rats revealed that social whisking was associated with reduced cellular excitability and membrane hyperpolarization[66].

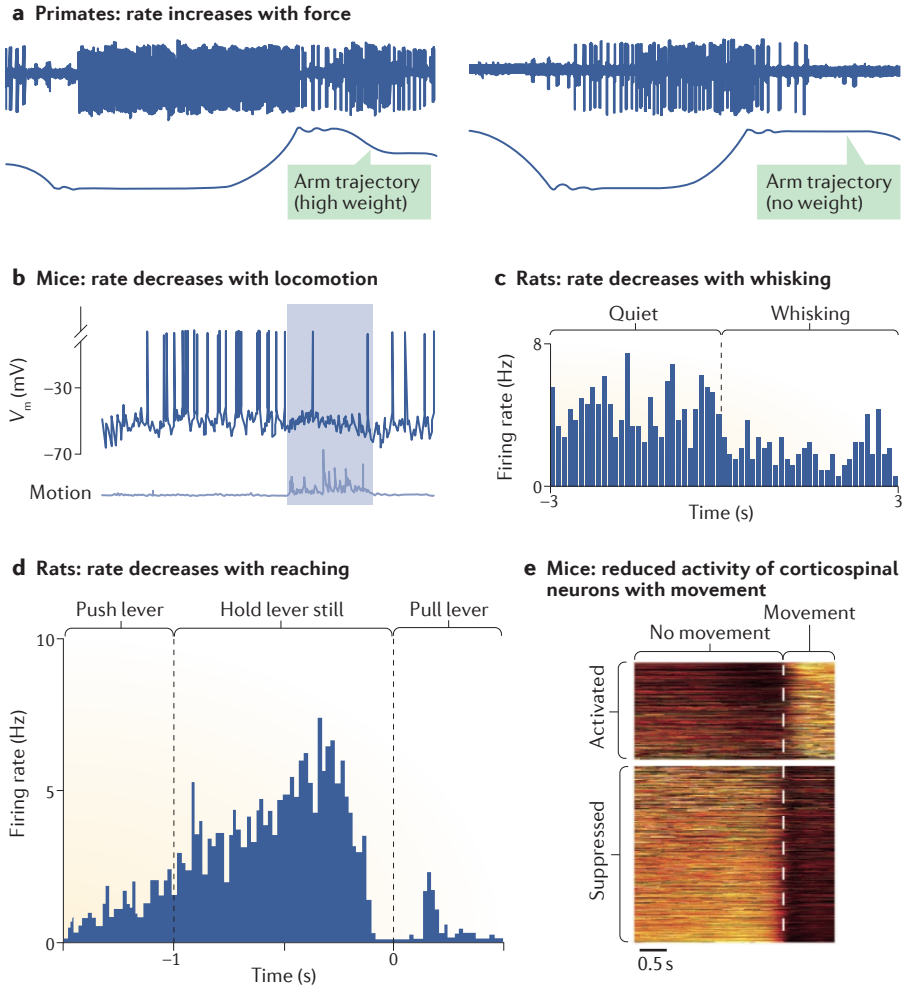


Figure 3 | **Motor cortex activity during movement.** Various studies in primates and rodents have revealed a relationship between movement and activity in the motor cortex. **a** | In a classic experiment[79], a monkey was trained to move a lever connected to a weight to receive a reward. Extracellular recording of motor cortical activity and arm trajectory when the monkey lifted a heavy weight (left) or no weight (right) revealed that motor cortical neuron firing rates increase with arm movements and force in primates. **b** | Motor cortex activity decreases with locomotion in mice[89,94], as can be seen from an intracellular recording from a layer 5b motor cortex neuron, which is suppressed during locomotion[94]. **c** | In rats, motor cortex activity decreases with whisking. The panels shows a peri-stimulus time histogram of an extracellularly recorded single unit in layer 5 of rat vibrissa motor cortex, aligned to the beginning of whisking[66]. **d** | Similarly, in rats, motor cortical activity commonly decreases with reaching movements[104]. Here, the activity of a neuron in layer 5b of the motor cortex is suppressed during reaching[104]. **e** | Calcium imaging during a lever-manipulation task revealed that two-thirds of corticospinal neurons in mouse motor cortex decrease their activity during movements. The panel shows normalized $\Delta F/F$ of all movement-related neurons, aligned to the beginning of movement; the darker colour reflects lower activity. Part **a** is adapted with permission from REF. 79, The American Physiological Society. Part **b** is from REF. 66, Macmillan Publishers Limited. Part **c** is adapted with permission from REF. 94, Elsevier. Part **d** is from REF. 104, Macmillan Pubishers Limited. Part **e** is from REF. 112, Macmillan Pubishers Limited.

Motor cortical inhibition during reaching movements. Through use of a forelimb task, in which head-fixed rats must push and pull a lever to receive a reward, various studies have revealed suppressed motor cortical activity during forelimb movement[104,105]. In one study, involving extracellular unit recordings across all layers, 43% of task-related neurons were active during

movement, whereas 57% were active during non-movement[104] (FIG. 3d). Juxtacellular recordings targeted to deep-layer neurons (>900 µm from the cortical surface) yielded a more mixed picture, with equal proportions of task-related neurons firing during movement and during non-movement. Interestingly, however, the vast majority (94%) of fast-spiking interneurons in the motor cortex fired during the movement phase, suggesting that phases of forelimb movement are associated with greatly increased motor cortical inhibition[104].

Another study investigated motor cortical activity in mouse motor cortex during reaches, which were cued by a vibrotactile stimulus to the paw[105]. The response of regular-spiking units during reaches was mixed, with 20% of regular-spiking units showing decreased spike rates and 39% of such units showing increased spike rates. In agreement with the high levels of motor cortical inhibition noted above, almost all parvalbumin-positive interneurons increased their firing rates[105].

In primates, attempts have also been made to investigate how motor cortex activity patterns during reaching map onto principal and inhibitory cell types. One study used spike width to identify putative inhibitory interneurons in the motor cortex and found that in this subpopulation, firing rates tended to massively increase during movement, whereas the responses in putative principal neurons were more mixed and showed a smaller increase in firing rates on movement[82]. It should be noted, however, that some pyramidal cells in macaque motor cortex have very narrow spikes[106] and that a large subset of interneurons in monkey motor cortex have surprisingly wide spikes[107]; thus, identifying interneurons in motor cortex by spike shape has some caveats[92].

Corticospinal activity in the rodent motor cortex during movement. We know relatively little about the activity patterns of corticospinal neurons in the rodent motor cortex during movement. Studies involving recording from identified neurons during motor behaviour and using immunohistochemistry techniques to assign projection targets to recovered cells yielded only fairly low numbers of cells for which there was physiological and anatomical information[66,94]. Using retrograde labelling techniques combined with extracellular recordings[108] and calcium imaging[109], two studies investigated the activity of pyramidal-tract-projecting neurons in mouse anterior-lateral motor cortex (a premotor structure involved in licking[110,111]) and primary motor cortex during tongue movements. The activity of pyramidal-tract-projecting neurons displayed complex temporal patterns in relation to tongue movements, showing both increases and decreases with movement and during a delay period[108,109]. These studies focused on differences in firing rate between tongue movements in the ipsilateral and contralateral directions. Although the population of pyramidal tract neurons in the anterior-lateral motor cortex as a whole (across all firing patterns) showed a contralateral firing rate bias during movement[108,109], pyramidal tract neurons in motor cortex showed no contralateral preference; instead, they exhibited strong somatosensory responses[109]. Instead of comparing motor cortical activity during ipsilateral and contralateral trials, another recent study used calcium imaging to investigate how activity of corticospinal neurons in mouse motor cortex relates to movement. In this study, a calcium sensor was selectively expressed in corticospinal neurons of the motor cortex, and the dendritic trees of these neurons were imaged while the mice performed forelimb movements to solve a lever-press task (FIG. 3e). These data revealed that two-thirds of movement-related corticospinal neurons showed decreased activity during movement[112].

Acting without motor cortex

Movement patterns after motor cortex inactivation. Even the first experiments by Fritsch and Hitzig demonstrated that surgically lesioning the motor cortex did alter, but not abolish, movements in their experimental animals[1]. In most mammals, the behavioural effects of motor cortical lesions are remarkably subtle[113]. Many simple behaviours (for example, locomotion) persist even after total decortication[114,115] owing to the fact that many complete neural circuits from sensory input to motor output are fully contained within the spinal cord[116–118]. For example, because locomotion is regulated by intrinsic pattern generators in the spinal cord[116,117], a decorticate cat can display a wide range of natural gait patterns when walking on a treadmill[119,120].

Symptoms of motor cortical lesions in primates. Motor cortical lesions are associated with performance deficits in several movement-related tasks. The motor effects of motor cortical lesions greatly change over time and, hence, are not easily categorized. For example, although the acute effects of motor cortex lesions in primates and human patients (muscle weakness and reduced, slowed-down movement) suggest that motor cortex contributes positively to intact movement patterns, the chronic effects (spasticity, clonus and hypertonia) point to a net loss of inhibitory control of motor neurons[121–123]. A prominent effect of motor cortical lesions in primates is a loss of fractionated movements and the ability to independently move one body part without others: attempts at individuated movements of a given body part are accompanied by excessive, unintended motion of contiguous body parts[121,124–126]. These effects of motor cortex inactivation also suggest that the prime role for descending motor cortex activity may be to 'control' — that is, suppress and inhibit — undesirable movements.

Non-primates: loss of movement suppression dominates. In many mammals, motor cortex inactivation leads to increases in movement. For example, as perhaps suggested by the surprising abundance of motor cortical suppression during whisking, locomotion and reaching (FIG. 3b–d), the patterns of whisking and limb movements after motor cortical inactivation reveal surprising deficits in movement suppression and motor control, which we review below.

In line with the suppression of motor cortical activity during whisker movements[30,66] (FIG. 3b), unilateral lesioning[127] and unilateral inactivation[66] of the rat vibrissa motor cortex leads to protraction of the contralateral whiskers and increases the whisking power contralaterally (FIG. 4a). Moreover, in correspondence with the suppression of motor cortex activity in some cells during mouse locomotion on a treadmill[89,94] (FIG. 3c), forelimb motor cortex lesions can disinhibit limb movements. For example, swimming rats normally hold their forelimbs still and swim with only their hindlimbs, but after a unilateral forelimb motor cortex lesion, they start swimming with the contralateral forelimb as well[128] (FIG. 4b). After motor cortex lesions, cats[129,130] and rats[131,132] perform poorly in tasks requiring reaching and gripping food rewards. In line with the prevalence of suppressed neurons during forelimb reaching tasks[104,105,112] (FIG. 3d), these deficits do not arise because the animals move too little but because they lose individual digit movements (all digits move together instead) or because they cannot control their forelimb movements and 'over-reach' far past their intended targets (FIG. 4c).

Clearly, the interpretation of lesion-induced changes in behaviour is complex. Several recent studies have used optogenetic techniques to inactivate motor cortex rapidly and reversibly during motor behaviour, yielding mixed observations, which do not always align with lesion studies. For example, in contrast to observations made after lesioning[127] or pharmacological inactivation of the vibrissa motor cortex[66], optogenetic activation of inhibitory interneurons in the motor cortex did not affect whisker set angle and reduced whisking amplitudes[30]. Similarly, in contrast to the over-reaching induced by pharmacological inactivation of the motor cortex in cats and rats[129–132], optogenetic activation of inhibitory interneurons in the mouse motor cortex blocked the initiation and froze the execution of reaches during a trained reaching task, but it left untrained forelimb movements unaffected and had no effect on initiation or execution of tongue movements[133]. Perhaps the discrepancies between the apparent effects of motor cortex lesions and transient optogenetic inhibition can be at least partly explained by acute effects stemming from the rapid perturbation of homeostasis[134], but this remains an open question[135].

Together, studies have shown that motor cortex lesions lead to impaired performance in several movement-related tasks. In many mammals, these deficits are due not to an inability to generate movement but to a lack of controlled movements and compromised movement inhibition.

Motor cortex — not to act?

The physiology of action suppression. Motor cortex neurons have usually been studied during motor performance. However, a few recent studies have investigated the activity of motor cortical neurons in animals performing tasks in which withholding movement was required.

Several studies have investigated motor cortex activity using head-fixed experimental paradigms, in which mice were trained to respond to sensory stimulation by tongue movements in a go–no-go paradigm; that is, the animal must lick in response to the stimulus ('hit') and withhold licking to other stimuli ('correct rejection')[136,137] (FIG. 5a). In trials in which the mouse licked after the stimulus (hit trials), some layer 5 motor cortical neurons (41%; the so-called enhanced neurons, which had high baseline firing rates) increased their firing rate during licking, whereas others decreased their firing rate (20%; the so-called suppressed neurons, which had lower baseline firing rates) (FIG. 5a). However, in trials in which the mouse did not lick after the sensory stimulation (miss trials), enhanced neurons still increased their firing rate, but there was no modulation of suppressed-neuron activity[136] (FIG. 5a). The responses of enhanced neurons were highly correlated with the sensory stimulation, and only 500 ms after presentation of the stimulus (that is, after or near the reaction time of the mouse), there was also a small difference between 'hit' and 'miss' trials in the enhanced neurons[136]. In other words, changes in the suppressed neuron activity but not in the enhanced neuron activity in layer 5b of the motor cortex were strongly predictive of licking behaviour (the actual motor output). It remains an open question why enhanced neuron activity relates so weakly to the actual movement output in such a go–no-go task, whereas suppressed neuron activity shows a tight correlation with movement. It may be that enhanced neurons in the motor cortex largely represent a sensory signal[109,136,137], as a late component of such a sensory signal has been shown to correlate with perception[138].

Motor cortex inactivation and action suppression. In the sensorimotor go–no-go tasks described above, inactivation of sensory cortices leads to a degradation of task performance because the licking hit rate in go trials is reduced. The animal correctly does not lick to the no-go cue, but it also stops licking to the go cue (when it should lick), as if it does not perceive the sensory stimulus. When motor cortex is inactivated, the hit-rate licking remains high (the animal keeps licking to the go cue), but the animal also starts licking in no-go trials, in which licking is supposed to

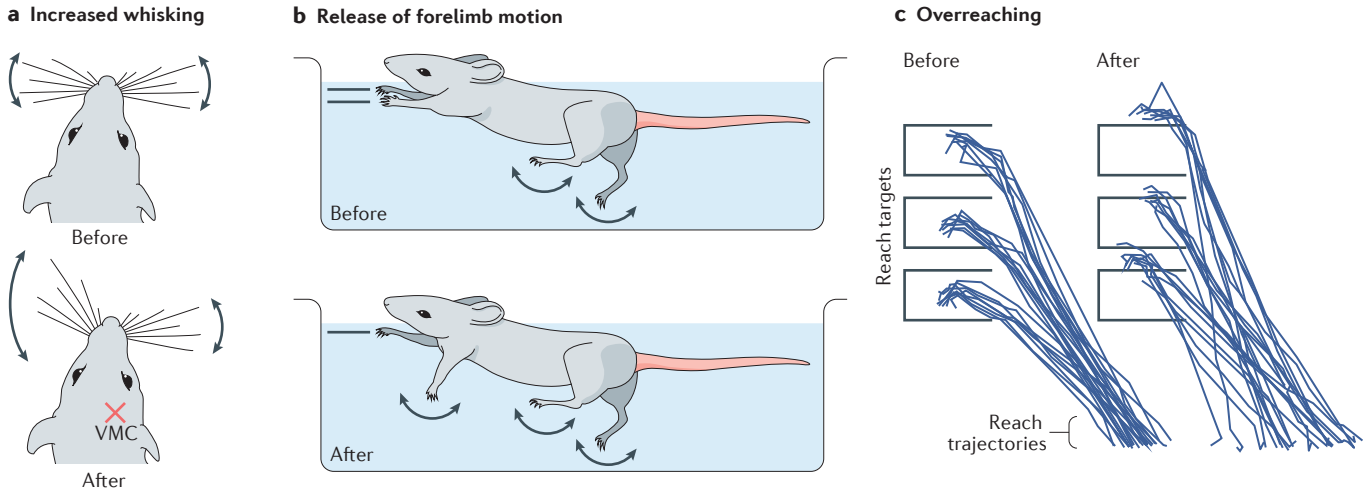


Figure 4 | **Movement patterns after motor cortex inactivation.** Inactivation of motor cortex interferes with but does not abolish movement and is often associated with impaired movement suppression. **a** | In intact rats, whisking is similar on both sides. However, after unilateral vibrissa motor cortex (VMC) blockade (as indicated by the cross), contralateral whiskers move forward and their whisking power increases[66,127]. **b** | Swimming rats normally hold their forelimbs still and swim with only their hindlimbs, but after a unilateral forelimb lesion in the primary motor cortex (M1), rats also use the contralateral forelimb to swim[128]. **c** | Intact cats can be trained to reach for morsels of food inside small reaching targets. After forelimb motor cortex inactivation, cats fail to receive the rewards because they move too much and over-reach past the targets[129]. Part **a** is from REF. 66, Macmillan Publishers Limited. Part **b** is adapted with permission from REF. 128, Elsevier. Part **c** is reproduced with permission from REF. 129, Elsevier.

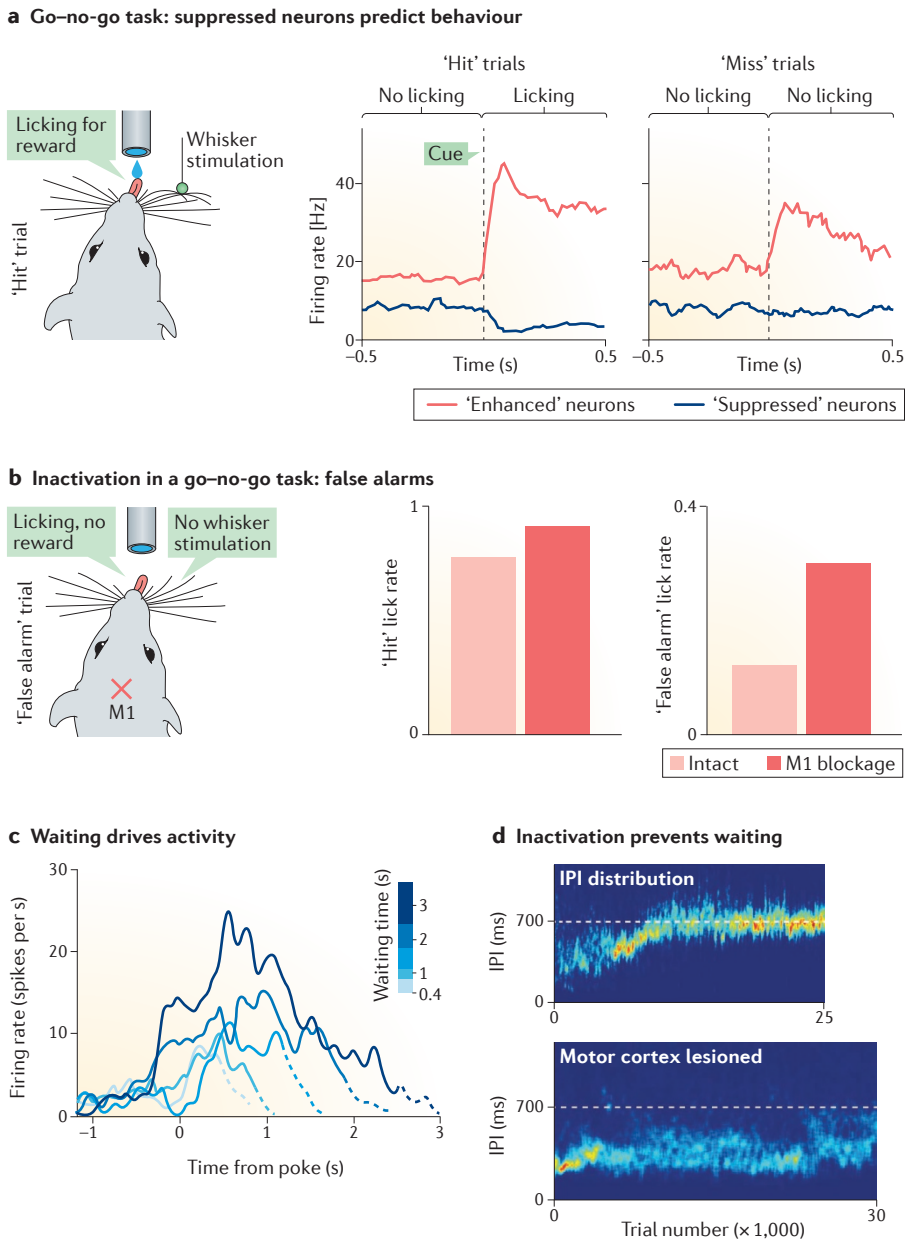


Figure 5 | **The neurophysiology of not moving.** Historically, there has been a focus on elucidating the role of motor cortex in movement generation, but several recent studies also implicate motor cortex in the withholding of disadvantageous motor output. **a** | In a sensorimotor go–no-go task, 'hit' trials, in which after a whisker stimulation, the mouse licks for a reward, are associated with an increase in the firing rate of some motor cortex neurons ('enhanced neurons') and a decrease in the firing rate of some other motor cortex neurons ('suppressed neurons'). In 'miss' trials, in which whiskers are stimulated but the mouse does not lick, the population of enhanced neurons responds nearly identically, but there is no response in the population of suppressed neurons. **b** | In a 'false alarm' trial in a sensorimotor go–no-go task, the mouse licks in the absence of whisker stimulation and is punished by a time-out period. Motor cortex inactivation does not affect the hit rate (when the mouse must lick) in this task, but it massively increases the false alarm rate (when a lick must be withheld)[136,137]. **c** | In a waiting task, in which a rat waits for a reward that arrives after a random time delay, longer waiting times are associated with higher motor cortical activity[35,36]. **d** | Both intact rats and rats with motor cortex lesions can learn to solve a task in which they must press a lever twice to receive a reward. Intact rats can learn to postpone the second lever press to receive a larger reward, but rats with motor cortex lesions cannot learn to postpone[144]. IPI, inter-press interval; M1, primary motor cortex. Part **a** is adapted with permission from REF. 136, Elsevier. Part **b** is adapted with permission from REF. 136, Elsevier. Part **c** is from REF. 35, Macmillan Publishers Limited. Part **d** is adapted with permission from REF. 144, Elsevier.

be suppressed and is punished by time-out periods[136,137] (FIG. 5b). The behavioural performance in such go–no-go paradigms is often quantified by a sensitivity index, *d'*, where $d' = Z(\text{Hit rate}) - Z(\text{False alarm rate})$ and $Z(\cdot)$ is the z-score, and the hit and false alarm rates are the rates of licking in go- and no-go trials, respectively. Thus, the inactivation of either the motor cortex or the sensory cortex leads to a reduced 'task performance', but for opposite reasons.

The effect of optogenetic activation of inhibitory interneurons in the motor cortex mirrors the effects of the pharmacological blockade of the brain region in go–no-go tasks. One study found that optogenetic inactivation of the motor cortex did not stop lick initiation or execution in a cued-licking task[133], and another study found that such inactivation of this brain region spared the hit rate but increased the false-alarm lick rate in a go–no-go task[136].

The fact that motor cortex inactivation does not reduce hit-rate licking but disinhibits disadvantageous licking suggests that a major role of motor cortex in such a task may not be the generation of licking but, rather, the withholding of tongue movements.

Withholding movement and waiting for rewards. Rats can learn to solve a task in which they must initiate trials by poking in a nose port and then wait for a reward, which arrives after a random time period[35,36] (FIG. 5c). When the time to reward is long, some rats will break the trial early and fail to receive the reward because of their 'impatience'. Recordings from motor cortex in rats performing such a waiting task revealed that more neurons suppressed their firing rate than enhanced it when the animals moved away from the nose port[35]. Furthermore, a large fraction (18%) of the motor cortex neurons showed activity just before or during the delay period, and the level of this activity was significantly related to the time that the rat decided to spend waiting for rewards. Although the activity patterns of single neurons were diverse, the majority of waiting-time-related neurons showed positive correlations between firing rate and waiting time, such that higher motor cortical firing predicted longer waiting[35] (FIG. 5c). It should be added, however, that many motor cortex cells showing delay activity also burst before movement onset, suggesting a possible role in movement initiation. A follow-up investigation used demixed principal component analysis to interrogate motor cortex activity for signals that might have

been hidden in the 'mixed' population response. Across the population, the pattern was the same: just before and during the waiting period, the principal components of the population activity were positively correlated with waiting time[36]. Motor cortex inactivation disrupted performance in the waiting task for two major reasons. First, most rats became 'impatient' during nose-poke trials and were not able to wait long enough to receive the reward. Second, the rats spent more time moving and less time receiving the reward[36].

It is a well-established finding across humans, monkeys and rodents that prefrontal and frontal cortical lesions are associated with deficits in behavioural inhibition[113,139–141], which manifests itself in impulsivity and "unrestrained and tactless" (REF. 142) behaviour. In one rodent study, the authors examined how motor cortical activity is modulated when behavioural inhibition is impaired owing to inactivation of the frontal cortex[143]. Rats were trained to perform a task in which they had to press a lever, hold it down for a delay period of 1 second, and then release it to receive a reward. Pharmacological inactivation of dorsomedial prefrontal cortex impaired the task performance: there was a large increase in 'premature responding' (that is, the rats released the lever too early and failed to receive the reward). Interestingly, recordings from the motor cortex revealed that the premature responding was not associated with an increase in motor cortex activity during the delay period. Rather, the inability to wait during the delay was associated with a decrease in motor cortex activity[143], suggesting that such activity might be important for the suppression of premature lever presses.

The interpretation that motor cortex has an important role in the suppression of disadvantageous lever presses is supported by findings from a recent study that investigated the effects of motor cortex inactivation in rats that were trained to press a lever twice to receive a reward[144] (FIG. 5d). Both intact rats and rats with motor cortex lesions could learn to solve the task by pressing the lever twice. Intact rats could learn to postpone the second lever press to obtain a larger reward, and once this had been learned, motor cortex ablation did not affect the stereotyped, learned motor sequence, which the rats used to time their lever pressing. Rats with motor cortex lesions, however, could not learn to postpone the second lever press and continued to receive only small rewards by pressing the lever in rapid succession[144] (FIG. 5d).

Conclusions and outlook

We have reviewed findings suggesting that, in addition to movement generation, motor cortex might contribute to movement suppression. We have discussed evidence indicating that, first, the famous motor homunculus by Penfield and Rasmussen is frequently presented as a movement map, but the observed stimulation effects indicate a somatotopic organization of movement suppression (FIG. 1). Second, motor cortex pyramidal tract neurons are often presented as heavily innervating spinal motor neurons, but this clear 'movement circuit' is an exceptional wiring pattern in mammals (FIG. 2). Third, in some preparations, motor cortex activity increases with movement, but movement is also accompanied by a surprising prevalence of principal neuron suppression and increased motor cortex inhibition (FIG. 3). Fourth, motor cortex lesions interfere with, but do not abolish, movement and are often associated with impaired movement suppression (FIG. 4). Last, motor cortex has mainly been investigated as a structure for movement generation, but several studies implicate motor cortex in the withholding of disadvantageous motor output (FIG. 5).

A purely movement-centred or action-centred perspective does not capture motor cortex function. The activity patterns of motor cortex neurons during ongoing behaviour are highly diverse. In addition to a (dynamic[112,145,146]) relationship with movement[30,66,67,76,89,94,100,102,104], neurons in the primary motor cortex have been implicated in choice, working memory and preparation of upcoming motor decisions[40–43]; in decision making in relation to rewards and upcoming motor strategies[34–39]; in 'mirror neuron'-like representations of actions[147–150]; and in the representation of visual[151] and somatosensory[31,109,137,152] stimuli. This diversity is probably important[109,137,153], and it emphasizes the need for unbiased analysis of neural activity. Thus, rather than 'searching' for single cells with a priori expected response patterns (for example, a positive correlation between cell activity and limb movement), we must also focus on analysis of, for example, multi-electrode or imaging data to determine if systematic population responses exist and how archetypical activity patterns map onto specific cell types and projection patterns.

Motor-suppressive functions of the motor cortex have received much less attention than the role of this cortical region in movement generation, but these negative motor phenomena[11] deserve broader attention. Movement is often associated with decreases in activity of principal neurons, increases in activity of fast-spiking neurons and large amounts of movement-related inhibition. This is an unexpected response pattern for a primary cortical area dedicated to movement, as cortical neurons most commonly respond to relevant stimuli with increased activity. This is the case for sensory cortices[154,155] and has been proposed as a general principle for the flow of cortical information[156]. Thus, although there are many ways to reconcile decreases in activity with a primarily movement-promoting function of motor cortical activity[76,81,157], the firing-rate decreases in response to relevant stimuli (that is, movement) observed in motor cortex constitute an unusual cortical response pattern that deserves more attention.

Numerous animal studies[113,158] and classic neuropsychological work[159,160] point to a major role of frontal and prefrontal cortex in the inhibitory control of behaviour[113,139–141]. The frontal cortices are relatively large in primates, although the primary motor cortex is comparatively small[2,3,6]. By contrast, in rodents, the frontal cortex is almost entirely primary motor cortex[12,16,19,24,25]. In primates, several premotor structures have been shown to perform movement-suppressive functions in the executive control of behaviour. For example, the primate frontal and cingulate cortex responses arising in the context of countermanding oculomotor movement and antisaccades have been described[161,162]. Similarly, both nonhuman primate studies and observations in humans point to a major role of the supplementary motor area in movement inhibition[163–165], and lesions to this area evoke involuntary, 'alien' movements[166].

We wonder whether rodent motor cortex might be involved in more generalized behavioural inhibition and be more 'frontal-like' than the potentially more movement-specialized primate motor cortex. Thus, although both the activity patterns during movement and the movement patterns after cortical blockade let it appear likely that rodent motor cortex plays a major role in movement suppression, whether this is an archetypical feature of motor cortex must be checked by comparative analysis. For example, it would be interesting to see how marsupials perform on tasks of behavioural inhibition, such as the classic marshmallow test[167].

Volitional control of motor output means deciding when to move and when not to move. Freud's notion of Überich[168] was based on a correct intuition about behaviour:

sometimes, it is very important to repress the urge to act on immediate desires. Action suppression is critical to the strategic planning of motor behaviours, but we still know little about how motor cortex contributes to this important cognitive capacity. We need to get away from a 'movement' perspective and further investigate motor cortex from a 'behavioural strategy' perspective. We propose that future investigations of motor cortex function should study both movement and movement suppression to elucidate how motor cortex allows mammals to behave in non-reflexive ways.

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The authors declare no competing interests.