

Feature Review

Physiological Markers of Motor Inhibition during Human Behavior

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Transcranial magnetic stimulation (TMS) studies in humans have shown that many behaviors engage processes that suppress excitability within the corticospinal tract. Inhibition of the motor output pathway has been extensively studied in the context of action stopping, where a planned movement needs to be abruptly aborted. Recent TMS work has also revealed markers of motor inhibition during the preparation of movement. Here, we review the evidence for motor inhibition during action stopping and action preparation, focusing on studies that have used TMS to monitor changes in the excitability of the corticospinal pathway. We discuss how these physiological results have motivated theoretical models of how the brain selects actions, regulates movement initiation and execution, and switches from one state to another.

Multiple Forms of Motor Inhibition during Human Behavior

Behaving in a goal-directed manner often requires suppressing inappropriate movement tendencies [1–3]. As such, many daily-life situations demand that humans refrain from acting in an automatic, stimulus-driven manner, subjugate internal desires that interfere with long-term plans (e.g., eating unhealthy food or drinking too much alcohol), or interrupt ongoing actions that are no longer appropriate (e.g., aborting a foot movement towards the accelerator when a pedestrian suddenly runs into the street). Without the efficient operation of inhibitory control, behavior becomes maladaptive, as evidenced in a range of psychiatric disorders [4,5].

Many studies have investigated the neural substrates of behavioral inhibition by using laboratory tasks that require stopping a planned action [6–10]. Under such conditions, rapid suppression of activity can be observed at various levels of the motor pathway, likely reflecting a pause in motor output [11,12]. Intriguingly, recent studies have revealed that the motor output pathway also shows profound inhibitory changes during action preparation, even during the planning of simple finger movements [13–18]. Hence, the motor system is inhibited not only when a movement needs to be aborted, but also when it is in the process of specifying a future action. The function(s) served by such inhibition as part of action preparation, and the extent to which it may support behavioral inhibition, have been the focus of considerable research over the past decade.

Here, we review and evaluate recent work that has explored physiological markers of motor inhibition in conditions requiring action stopping or action preparation. We focus on studies that have used TMS in humans to monitor changes in the excitability of the corticospinal pathway. Using this procedure, single-pulse TMS applied over the primary motor cortex (M1) elicits motor-evoked potentials (MEPs) in targeted contralateral muscles (Box 1 and Figure 1),

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Many aspects of behavior result in inhibition of the corticospinal motor output pathway.

The state of excitability of the corticospinal pathway can be assessed with single-pulse transcranial magnetic stimulation (TMS) over primary motor cortex (M1). The pulse elicits a temporally precise motor evoked potential (MEP) in the electromyography (EMG) recording from the targeted muscle. To measure the dynamics of excitability, MEPs are measured at various stages of task performance and compared in amplitude with MEPs measured at baseline (e.g., during the intertrial interval). Inhibition is evident when the MEPs are lower relative to baseline.

Motor inhibition is found when an ongoing or planned action needs to be aborted following a stop signal (reactive inhibition). In this context, behavioral inhibition is associated with a fast and global decrease in corticospinal excitability. This reactive inhibition is thought to rely on corticobasal ganglia loops via hyperdirect projections from the frontal cortex to the subthalamic nucleus (STN), providing a mechanism to generically brake the motor output.

Inhibition of the motor system is also evident in anticipation of a stop signal. Proactive inhibition has been characterized using selective stop tasks, where only part of an ongoing action needs to be interrupted. In this context, inhibition operates in a more focal manner, raising the hypothesis that separate basal ganglia pathways are recruited during behavioral inhibition,

Box 1. Electrophysiological Signatures of Motor Inhibition

Motor-Evoked Potentials to Transcranial Magnetic Stimulation

TMS is a non-invasive technique that can induce short (~250 μ s) electrical currents in the human cortex [132]. When the stimulating coil is placed over the primary motor cortex (M1), TMS elicits descending volleys in the corticospinal fibers. These fibers synapse on spinal motoneurons that innervate peripheral muscles contralateral to the stimulation site (Figure 1, main text). The evoked response, the MEP, can be easily recorded using surface electromyography (EMG). The amplitude of the MEP provides an assay of corticospinal (CS) excitability for the targeted muscle at the time of stimulation [2,19].

The MEP measured with surface EMG is a signal resulting from a complex series of waves that descend through the CS tract (D-waves and I-waves [133]). TMS over M1 can directly activate CS neurons. However, the TMS pulse also excites other fibers that, in turn, project onto CS neurons. These fibers may originate in M1, linking up with CS cells through intracortical circuits. They may also come from other cortical areas, such as premotor, somatosensory, and parietal regions, or from subcortical structures, such as the thalamus. Given that CS cells synapse onto motoneurons in the spinal cord before reaching their targeted muscle, the MEPs also depend on the excitability of the spinal circuitry. Importantly, these intracortical, transcortical, subcortical, and spinal inputs provide routes through which different inhibitory control processes can influence MEP amplitudes during action stopping and action preparation.

Sophisticated TMS protocols have been developed to provide probes on specific circuits. For example, paired-pulse protocols [134] apply a low intensity subthreshold conditioning TMS pulse, and measure its impact on the MEP response elicited by a subsequent suprathreshold test pulse generated in the same coil. The two TMS pulses are applied over M1, not only at specific intensities, but also at specific times. Conditioning pulses applied between 2 and 5 ms or between 50 and 200 ms before the test pulse are thought to probe GABAergic intracortical inhibitory circuits that act at corresponding intrinsic latencies, thus providing an assay to link inhibitory neurotransmission with motor behavior [84,133,135].

Other protocols use two separate stimulation coils to investigate transcortical influences on M1. These double-coil protocols measure the impact of a suprathreshold conditioning pulse over a cortical region assumed to generate a transcortical signal on the MEP elicited by a test pulse delivered through a coil placed over M1 [136]. TMS protocols have revealed the existence of inhibitory interactions between M1 in the two hemispheres as well as inhibitory projections from several frontal areas to M1 and the cerebellum to M1 (see, for example, [137–139]). A double-coil procedure in which two coils are used to stimulate M1 at a nearly simultaneous time (1-ms delay) was introduced recently as a new method to probe preparatory inhibition in both hands concurrently [85].

Other Electrophysiological Signatures of Motor Inhibition

Several attempts have been made to link specific electrophysiological signatures to inhibitory mechanisms (reviewed in [10,140]). The initiation of voluntary movements is associated with desynchronization of activity in the beta frequency band (13–30 Hz) in electrocorticography (ECoG) and scalp electroencephalography (EEG) recordings over motor cortex [141–143]. Consequently, beta activity has been associated with the ‘idling’ of the motor system, and a decrease in beta activity with a change from the ‘status quo’ of the motor state. Beta activity within M1 may reflect the operation of intracortical inhibitory mechanisms [144]. Notably, bursts of beta activity are observed before and after the movement-related beta desynchronization [145].

EEG studies of reactive stopping report a consistent increase in beta activity over right frontal regions for successful stopping compared to failed stopping [51,146]. Moreover, excessive beta synchrony throughout cortico-basal ganglia circuits coincides with increased bradykinesia in Parkinson’s disease [147,148] and with response inhibition during the stopping of actions [120]. Reactive stopping has been hypothesized to involve the recruitment of a mechanism that rapidly increases beta activity to suppress ongoing movement. Event-related potential (ERP) EEG signatures have also been linked to reactive inhibitory control. Greater amplitudes and shorter latencies of the N2/P3 complex have been associated with successful response inhibition [146]. Recently, it was shown that the latency of the P3 onset correlates with the speed of stopping [149].

Hence, TMS, ECoG, and EEG protocols provide a rich arsenal of methods for selectively probing circuits involved in generating inhibitory influences on the human motor system during action stopping and action preparation.

providing a temporally precise and muscle-specific assay of the state of excitability of the motor output pathway [2,19–21]. Other methods can also be used to track changes in motor excitability in humans. This includes the analysis of specific electroencephalography (EEG) waves (see Box 1 for a short overview) or fMRI signals that can provide a window into

exerting broad or focal inhibitory influences depending on task demands.

Several markers of motor inhibition can be observed during the period preceding a voluntary movement (preparatory inhibition). These markers are modulated by various task variables, suggesting a role for inhibition in response selection and response initiation.

The functional role of preparatory inhibition has been the subject of considerable debate. One hypothesis is that preparatory inhibition serves to assist action selection through a competitive process, whereby excitation of selected action representations is associated with the suppression of unwanted (inappropriate) action representations. Another hypothesis has focused on the regulation of response initiation, with inhibition serving to prevent premature movement, while preparatory activity unfolds across the cortex. A third view is that preparatory inhibition may serve to modulate the gain of the motor system. A reduction in background motor activity could facilitate movement onset by increasing the signal:noise ratio. This last hypothesis shifts the emphasis away from inhibition as a way to suppress unwanted or nonselected movements, to one in which preparatory inhibition promotes rapid action selection and implementation.

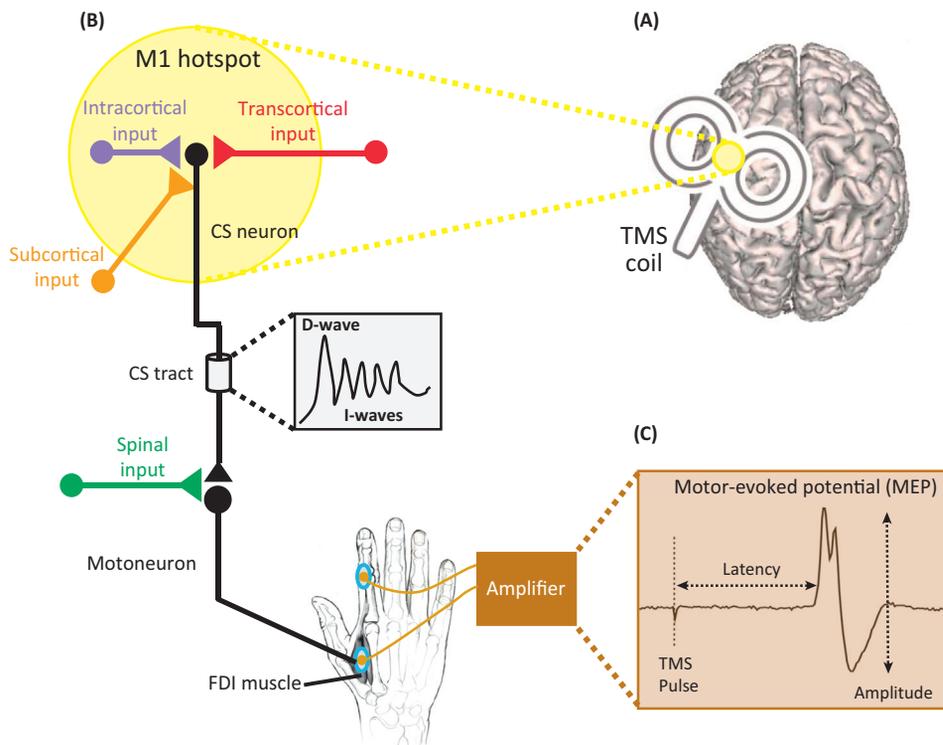
The relationship in terms of psychological function and neural mechanisms between reactive, proactive, and preparatory inhibition is an important challenge for future research.

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Figure 1. Transcranial Magnetic Stimulation (TMS) as a Probe of Corticospinal Excitability. (A) The TMS coil is placed over primary motor cortex (M1) at the ‘hotspot’ (depicted in yellow), the position at which the largest motor-evoked potentials (MEPs) can be recorded in the electromyograph (EMG) signal from a targeted muscle. (B) TMS over M1 activates corticospinal (CS) neurons directly or indirectly via the stimulation of intracortical circuits that project to CS neurons. Transcortical inputs from premotor, prefrontal, and parietal cortices, as well as axons of subcortical cells projecting onto M1, are also activated by TMS over M1. Depending on the position and intensity of stimulation, a series of descending volleys (D-wave and I-wave) are transmitted from M1 to the motoneurons in the spinal cord. These signals are further influenced by inputs at the spinal level before they jointly give rise to an MEP in the targeted, contralateral muscle [first dorsal interosseus (FDI) in the present example]. (C) The MEP is a bi-phasic response recorded from a targeted muscle via electrodes placed on the surface of the skin. It has a latency of approximately 18 ms after the TMS pulse when elicited in hand muscles. While the latency is relatively invariant, the peak-to-peak amplitude fluctuates, reflecting the sum of cortical, subcortical, and spinal contributions to the descending signals to the muscle.

larger-scale networks for inhibitory control (reviewed in [22–24]). Here, we only briefly refer to these other works because the TMS literature offers by itself a fertile ground for the discussion of mechanisms underlying action stopping and action preparation in humans. We discuss, in an integrated manner, the varied hypotheses concerning the role of motor system inhibition in shaping human behavior.

Motor Inhibition Associated with Action Stopping

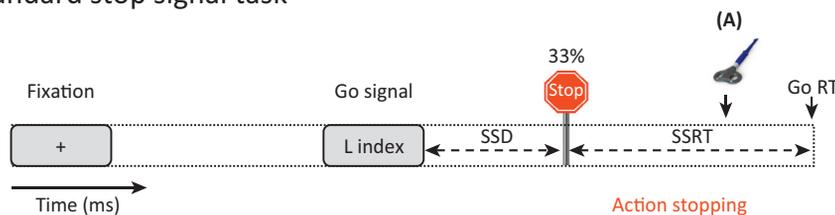
We frequently encounter situations in which a motor action, once initiated, becomes unnecessary or inappropriate. Imagine sitting in your car at an intersection and the traffic light has just turned green. You begin to shift your foot from the brake to the accelerator when, suddenly, a pedestrian runs into the street. Fortunately, you are able to quickly update your action plan, aborting the movement towards the accelerator. While this may be an extreme example of the importance of inhibitory control, our everyday behavior is replete with such changes of intent, elicited by unexpected variations in the environment.

Experimentally, the psychological processes and neural mechanisms underlying action stopping have been extensively studied with versions of the stop signal task [11,25]. This task has

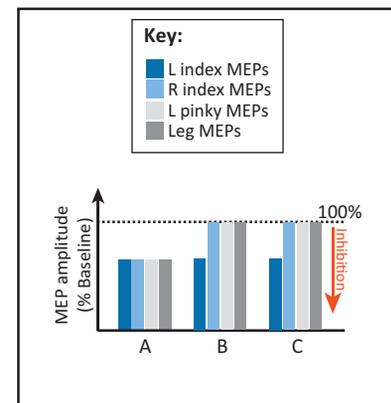
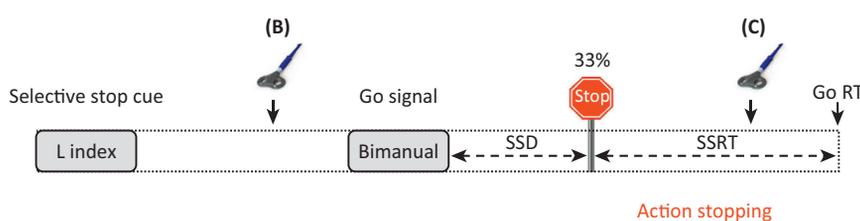
been used to explore a range of psychological questions, such as the relationship between response initiation and inhibition [26,27], and the characteristics of inhibitory control [28–31]. The stop signal task has also proved useful for characterizing deficits in behavioral inhibition in Parkinson's disease [32], schizophrenia [33], attention deficit hyperactivity disorder (ADHD) [34], and individuals with alcohol and drug dependencies [35,36].

In the standard form of the stop signal task (Figure 2, upper left panel), the participant is engaged in a reaction time (RT) task, with the emphasis on speeded responses. In a subset of trials (e.g., 33%), a stop signal stimulus is presented shortly after the go signal. Participants are instructed to attempt to cancel the initiated response as soon as they detect the stop signal. The time delay between the go and stop signal (stop signal delay, SSD) can be adjusted in a dynamic manner, such that participants only succeed in aborting the response at some specified criterion level (e.g., 50%). Action stopping has also been studied in an adapted version of the stop signal task, where bimanual responses are initiated, but the stop signal is relevant for only one of the responses (Figure 2, lower left panel). For example, if a go signal cues the participant to respond with synchronized button presses with the two index fingers, the stop signal here indicates that one finger should be stopped while the other finger should continue (e.g., stopping the left but not the right index finger response). This selective stop signal task provides a method to explore the impact of stopping one component of an ongoing action on the continuing piece of response. Below, we review evidence for the contribution of motor inhibitory mechanisms to standard and selective stopping.

Standard stop signal task



Selective stop signal task



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Figure 2. Study of Motor Inhibition during Action Stopping. The standard stop task (upper panel) often requires subjects to choose between left (L) and right (R) finger responses (L index finger trial in this example) occasionally interrupted by a stop signal (~33% of trials). The time between the go signal and the stop signal, or stop signal delay (SSD), is adjusted so that participants succeed in stopping on a targeted proportion of trials (usually 50%). When transcranial magnetic stimulation (TMS) is applied after the stop signal (A), motor evoked potentials (MEPs; expressed as a percentage of baseline) elicited in selected (L index), nonselected (R index), and irrelevant (L pinky or leg) muscles are globally suppressed, reflecting widespread reactive inhibition. In selective tasks (lower panel), subjects make bimanual movements (e.g., with index fingers); a cue is presented at the beginning of each trial, indicating the hand that may have to be stopped if a stop signal occurs (L index stop trial in this example). In this task, MEPs measured after the stop signal (C) are suppressed in only the agonist muscle that was cued for stopping, reflecting selective reactive inhibition. When TMS is applied before the stop signal in this type of selective stop task (B), MEPs are also only suppressed in the muscle that may have to be stopped, indicating selective proactive inhibition in anticipation of the stop signal.

Standard Stopping

Formal psychological models suggest that performance in the standard version of the stop signal task involves a race between two independent processes, one associated with response execution (GO) and the other with the cancellation of the planned response (STOP) [25]. This race model provides an analytic tool to estimate the duration of the covert STOP process, referred to as the Stop Signal RT (SSRT) [37]. The SSRT can be estimated by subtracting the SSD that yields a 50% stopping success rate from the average GO RT (Figure 2) (but see also [38]).

Electromyography (EMG) studies have shown that motor responses can be stopped at multiple stages of execution, including after the responding muscles are engaged [150]. Brain stimulation and electrophysiological methods have been used to identify the time course of corticospinal excitability changes during reactive stopping. A consistent finding has been that the presentation of a stop signal produces rapid suppression of MEP amplitudes, reflecting a marked drop in corticospinal excitability [39–42]. The fact that MEP amplitudes become smaller relative to baseline measurements obtained during the intertrial interval provides compelling evidence that successful stopping is not the result of a delay in the initiation of action preparation processes, but rather entails the active suppression of corticospinal excitability. Consistent with this idea, paired-pulse TMS protocols reveal a strengthening of GABAergic intracortical inhibition in M1 on stop trials [43]. Moreover, electrodes over M1, recording cortical activity during electrocorticography (ECoG), show a reduction of alpha–beta desynchronization (i.e., a relative increase of synchronization) in stop trials [44]. Other converging lines of evidence indicate that the suppression in motor activity entails not only cortical increases in inhibition, but also a reduction in excitatory input from the thalamus to M1. For example, electrophysiological studies in rats suggest that the stop process involves two stages, with a pause process followed by a later cancellation process both occurring at different levels within the basal ganglia [45,46], with subsequent effects on M1 [47]. Taken as a whole, the available data suggest that the presentation of the stop signal is not merely associated with terminating motor commands that produce excitation in M1, but with the recruitment of one or more active inhibitory mechanisms that suppress the motor command.

Neuroimaging and neuropsychological studies have identified a corticobasal ganglia network engaged during reactive stopping in the standard stop signal task, with key nodes including the right inferior frontal cortex (rIFC), the dorsomedial frontal cortex (especially the presupplementary motor area, preSMA), and the basal ganglia (reviewed in [12,48–50], see also [45]). Of particular interest has been the hyperdirect pathway between the frontal cortex and subthalamic nucleus (STN) of the basal ganglia [11,51–53]. A prominent hypothesis centers on the idea that the direct engagement of the STN by the cortex provides a mechanism to rapidly shut down motor output. The STN sends diffuse excitatory projections to the internal segment of the globus pallidus pars interna (GPi) [12,54–57], which in turn sends inhibitory output to the motor thalamus, decreasing the excitatory drive to the motor cortex (but also see [58] for an involvement of the basal forebrain). This neural architecture has been directly implicated in stopping and is thought to inhibit the motor system in a global manner [8,12,59].

Consistent with this hypothesis, single-pulse TMS studies underscore that reactive stopping is not limited to inhibition of the selected (to-be-stopped) response representation, but has a global suppressive effect on the motor system, bringing the activity of action representations below resting levels in a nonselective manner. That is, successful stopping reduces MEPs not only in the task-relevant agonist muscle, but also in task-irrelevant muscles (Figure 2A, right panel). For example, when the relevant effector is the left index finger, MEP suppression is observed in other muscles of the responding hand [39] or homologous muscles in the non-responding hand [43]. Furthermore, this spread extends beyond the upper extremities.

Aborting a hand response produces a reduction of MEPs elicited in leg muscles [40,42], while aborting speech or a saccade produces inhibition in hand muscles [41,60]. Thus, there appears to be a diffuse suppressive effect when a planned action is suddenly aborted in the standard stop signal task. It is noteworthy that the inhibition of task-irrelevant muscles provides additional evidence that stopping not only involves termination of ongoing excitatory commands, but also engages an active inhibitory process. Moreover, this nonselective inhibition of the motor system is consistent with the idea that the hyperdirect projection from the cortex to STN can result in broad inhibition of the motor system [11,12,59,61].

Selective Stopping

When only part of a compound response has to be stopped, humans exhibit interference, with reaction times for the nonstopped (continuing) component being slower on stop trials compared with go trials [62,63]. To illustrate this point, let us go back to the driving example mentioned above: imagine you were manipulating the radio button when a pedestrian stepped into the road. While the situation demands that you immediately abort your movement towards the accelerator, you are also likely to stop tuning the radio. This observation has been understood in the light of the operation of a global stopping command, one that affects both targeted and nontargeted actions. Following this, the remaining response (e.g., tuning the radio) must be reprogrammed, resulting in a RT cost [64].

Although the driving situation may demand a complete shift of attention to avoid hitting the pedestrian, it is somewhat puzzling that interference can be profound in experimental tasks, given the everyday observation that we are often able to selectively abort one response without affecting other ongoing movements. It may be that the selective stop task constitutes a dual-task situation, one in which the participant has the added burden of having to keep track of which response is to be aborted and which is to be maintained. By this account, the slowing of the continued response could result from difficulty in assigning the stopping process to the appropriate component of the response. Indeed, a recent study has shown that selective stop interference is minimal or entirely abolished when the stop signal is unambiguously associated with one response or when participants are given extended training [65]. This functional view of the RT cost offers an alternative to accounts that attribute the cost to a structural limitation in which the rapid termination of a movement engages the hyperdirect pathway in a generic manner. More research is clearly required to distinguish between these two hypotheses.

Several lines of evidence are consistent with the idea that selective stopping can arise from a targeted suppression mechanism. For example, inhibition is focal when participants are provided with advance information regarding the potential action that might have to be aborted ('selective stop cue' in Figure 2, lower left panel). Aron and Verbruggen [62] created a variant of the selective stop task in which, on each trial, the go signal is preceded by a cue indicating which of two index finger responses would have to be aborted, should a stop signal appear. Leg muscle MEPs are not suppressed following stop signals in this selective condition (Figure 2C, right panel), a result that stands in contrast to the observations that leg MEPs are suppressed if the stop signal indicates that the response from both hands should be stopped [42,62]. Interestingly, SSRT estimates from the selective stop task are slower compared with those derived from the standard stop signal task. The selectivity of inhibitory influences, as well as the longer SSRT, suggest that selective stopping does not use the hyperdirect cortico-STN pathway, but instead relies on neural circuits associated with more deliberative selection processes, such as the indirect corticostriatal pathway [6,66,67]. Hence, separate mechanisms may be recruited in response to global and selective stop signals, resulting in a trade-off between speed and anatomical selectivity. Humans are more likely to use a global mechanism when speed is of the essence (as in our driving example), whereas they are

more likely to use a selective mechanism when they want to maintain control of particular responses, especially when advanced information indicates which response may need to be stopped.

Proactive Inhibition

As alluded to in the previous paragraph, an important emerging theme in inhibitory control research focuses on how various constraints (e.g., selectivity, speed, etc.) may influence mechanisms underlying reactive stopping. More recently, researchers have also used a range of manipulations to look at cognitive control processes recruited in anticipation of stopping, or what we call 'proactive inhibition'. For example, the probability of a stop signal might be manipulated in a predictive manner to modify the trade-off between the speed of responding and stopping success. In contrast to stimulus-driven reactive stopping, proactive inhibition reflects a top-down control process. To illustrate this point, consider the driving example from before. In the vicinity of a school, our driver may opt to be more cautious and slower to press the accelerator when the traffic light turns green. This type of controlled behavioral slowing can occur in the absence of an overt stimulus distinguishing it from reactive stopping.

Two alternative hypotheses have been proposed to explain patterns of behavioral slowing. The first postulates that slowing reflects a strategic process to delay responding until it becomes clear that a stop signal will not be presented. In this case, there is no need to postulate an active inhibitory process; excitatory processes that drive response execution are simply postponed. Alternatively, proactive control might engage an active inhibitory process that suppresses motor activity when a stop signal is expected [68]. Support for this type of proactive inhibition comes from the observation that, in anticipation of a stop signal in selective stop tasks, MEP amplitudes are suppressed relative to baseline values obtained during the intertrial interval [69,70]. The MEP suppression only concerns effectors that might have to be stopped, leaving the continuing response representations unaffected (Figure 2C, right panel). Hence, in selective stop tasks, proactive inhibition is selectively targeted at specific motor responses, possibly enabling less effortful reactive stopping. Furthermore, when humans anticipate the need to stop, the subsequent reactive inhibition of MEPs in task-irrelevant muscles is attenuated [40], while scalp EEG ERPs and fMRI signals in the basal ganglia, both associated with successful reactive stopping, increase in amplitude [71,72]. Notably, proactive inhibition has only been studied in selective stop tasks but never in standard stop signal tasks. Thus, it remains to be determined whether signatures of proactive inhibition can also be detected when one anticipates a global stop signal requiring the cancellation of the entire response (and not just one component) [73]. Given that reactive inhibition in the latter situation can be implemented via a fast hyperdirect route, there may be no advantage to proactively anticipate a stop signal, since such a strategy can slow down RTs on GO trials.

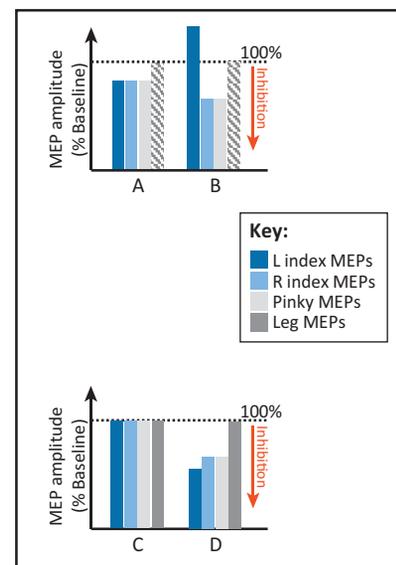
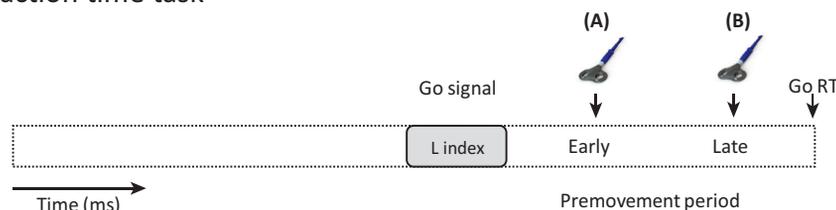
Motor Inhibition Associated with Action Preparation

In the stop signal task, the experimenter introduces an explicit tension between implementing and aborting a planned action. At the behavioral level, there is an obvious need for inhibition, and at the neural level, we can measure the rapid attenuation of excitability in the corticospinal pathway. However, action stopping represents just one situation requiring inhibitory control. Many inappropriate behaviors have also been associated with a lack of inhibitory control in the context of action selection and initiation, (e.g., interrupting a speaker or drinking too much alcohol). Interestingly, several markers of inhibition have been observed during the period preceding a voluntary movement. What function(s) does such inhibition serve as part of action preparation and to what extent does it support behavioral inhibition? These questions have been the focus of considerable work over the past decade.

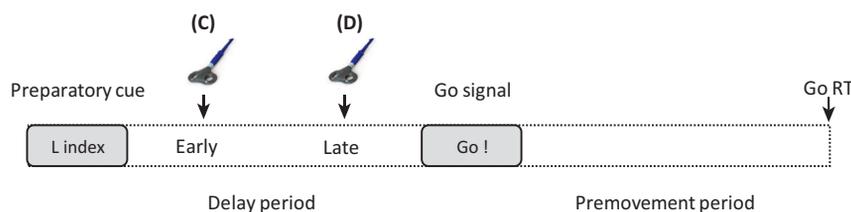
The dynamics of corticospinal excitability during action preparation have been investigated in RT studies where humans are instructed to respond as quickly as possible following a go signal (Figure 3, upper left panel); TMS probes over M1 are applied at several time points between the go signal and the movement onset, with the changes in MEP amplitude (usually expressed with respect to baseline measurements obtained during the intertrial interval) providing a window into the recruitment of the motor system preceding movement onset [2,74]. In the simplest version of this paradigm, the go signal always specifies the same movement within a given block of trials. In this simple RT condition, there is a gradual increase in the amplitude of MEPs recorded from the agonist muscle, starting approximately 100 ms before the onset of the volitional EMG [74,75]. This premovement increase in the amplitude of MEPs is thought to reflect the excitation of the corresponding motor representation in M1 through a joint modulation of facilitatory and inhibitory influences [76].

In more complex versions of the RT task, the go signal requires choosing between a set of options that are predefined within a block of trials (e.g., a left or right index finger response; choice RT task), hence allowing investigation of the physiological correlates of action selection. Here, the MEPs can be compared for conditions in which the muscle is selected or not selected for the forthcoming response and, within the latter, the muscle may be associated with an effector that is part of the response set or that is irrelevant to the task. As expected, MEPs elicited in the selected effector exhibit an increase in amplitude during the premovement period, similar to that observed in simple RT tasks (Figure 3A,B, right panel). However, before the activity begins to ramp up, there is an initial decrease in the amplitude of the MEPs [77,78],

Reaction time task



Instructed-delay reaction time task



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Figure 3. Study of Motor Inhibition during Action Preparation. Reaction time (RT) tasks (upper panel) often require subjects to perform left (L) or right (R) finger responses in a simple or choice setting (L index finger trial in a choice RT task in this example). When transcranial magnetic stimulation (TMS) is applied immediately after the go signal (A), motor evoked potentials (MEPs; expressed as a percentage of baseline) elicited in selected (L index), nonselected (R index), and irrelevant finger (L pinky) muscles are globally suppressed, reflecting widespread inhibition during the EARLY stage of the premovement period. Close to movement onset [LATE (B)], the amplitude of MEPs is increased when the finger muscle is the agonist for the selected response and is attenuated if the muscle is not selected or irrelevant. Broken gray bars are used to represent hypothetical leg MEPs (not investigated to date) based on evidence in instructed-delay RT tasks. In these delay tasks (lower panel), a cued response is prepared but withheld until the go signal. When TMS is applied at the end of the delay period [LATE (D)], MEPs are suppressed regardless of whether the finger muscle is selected, nonselected or task irrelevant, indicating broad preparatory inhibition, although inhibition does not appear to extend to leg muscle representations. Notably, inhibition is often stronger for selected than for nonselected muscles, suggesting some additional focal inhibition targeted at agonist muscles. MEP suppression is not observed when TMS is applied a long time before the go signal, close to the preparatory cue [EARLY (C)].

indicating suppression of the corticospinal pathway associated with the selected movement. A reduction in MEP amplitude is also observed in the nonselected effector and, here, the MEPs display a further drop in amplitude over the course of the premovement period [74,79–81]. These effects are consistent with the hypothesis that action selection involves not only excitation of the selected effector, but also inhibitory processes, initially evident in both selected and nonselected effectors.

Studies of action preparation have also used instructed-delay RT tasks, in which a cue provides advance information about a forthcoming response, but the participant must then wait until the go signal is presented to release his response (Figure 3, lower left panel). This paradigm affords the ability to investigate delay-related processes that are specifically involved in action preparation, both in the context of simple and choice RT tasks, without being confounded by functions related to movement execution. Here too, corticospinal excitability is suppressed when the preparatory cue indicates that the targeted muscle should not be selected for the forthcoming response. Interestingly, inhibition is also observed in the selected hand during the delay period [82,83]. That is, MEPs probed following preparatory cues in a selected effector also become smaller relative to baseline. Moreover, this inhibition is often stronger than that observed when the same muscle is not selected for the forthcoming response [77,84] (but see also [85,86]), especially when probed at the end of the delay period (Figure 3C,D, right panel) [18]. The presence of marked inhibition in the representation of selected effectors close to the time at which they need to be recruited for the forthcoming response has presented a challenge to models of inhibition. In the following sections, we review current hypotheses regarding the role of motor inhibition during action preparation.

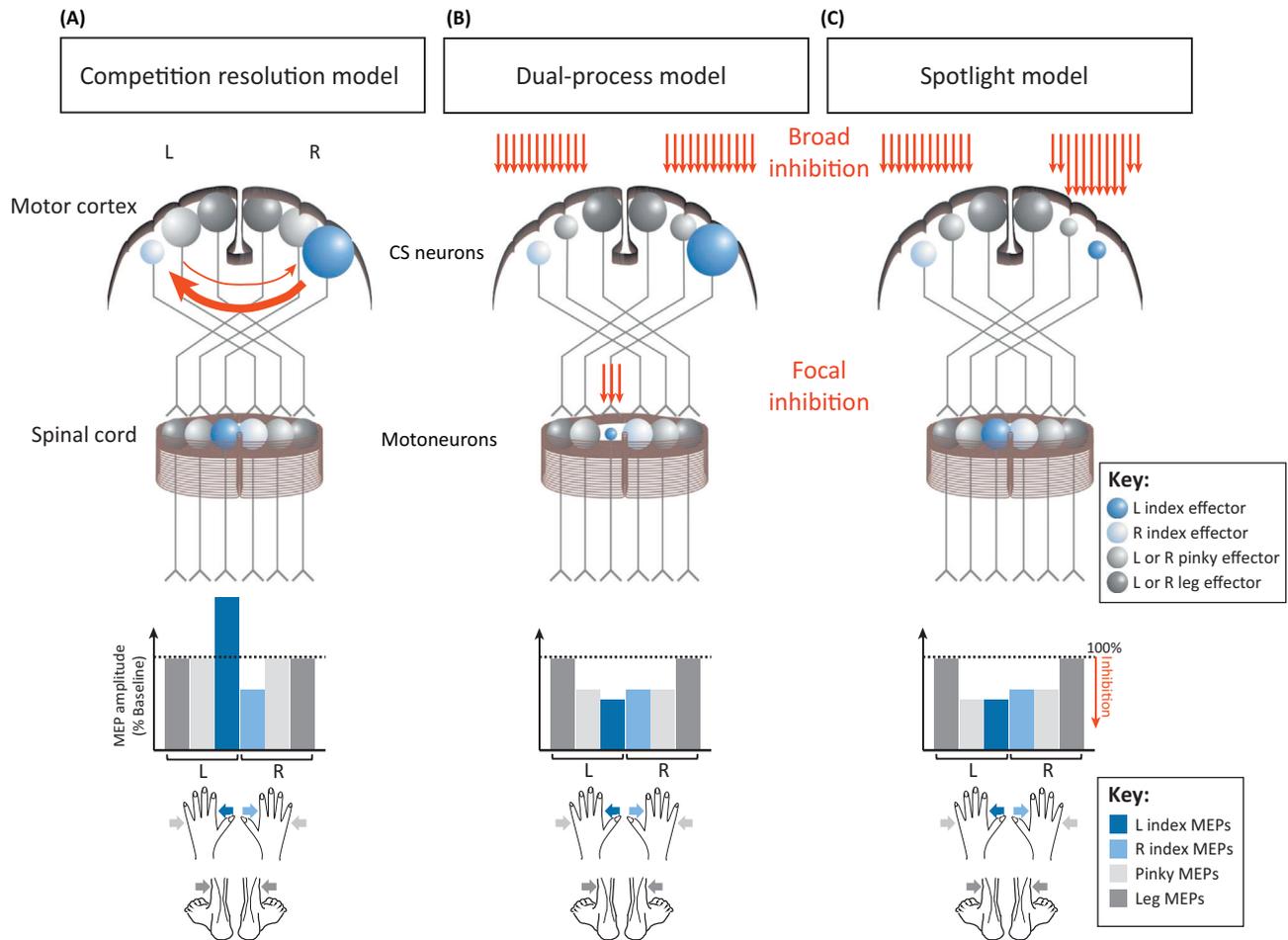
Functional Role of Preparatory Inhibition

The suppression of corticospinal excitability observed before movement initiation has led to several hypotheses regarding the role of motor inhibition during action preparation. One hypothesis has been that preparatory inhibition serves to assist action selection, consistent with a contribution of inhibition to the generation of goal-oriented behaviors [2]. One variant of this idea is that action selection entails a competitive process, whereby selection of the desired response relies on the suppression of nonselected action representations [79,87]. Another variant is that preparatory inhibition assists action selection by producing a global suppression of motor representations to prevent inappropriate action representations from being selected. A second hypothesis has focused on the implementation of the selected response: preparatory inhibition may serve to prevent selected muscles from becoming active prematurely while preparatory activity unfolds across the cortex [17,88]. A third, hybrid hypothesis is that preparatory inhibition serves to modulate the gain of the motor system, increasing the signal:noise ratio [89]. In this case, inhibition may reduce background activity during motor preparation, providing a way to facilitate response implementation [13].

We consider these hypotheses in the following sections, examining three models of preparatory inhibition (Figure 4). We note at the outset that the current evidence does not discriminate between these hypotheses and, indeed, they are not mutually exclusive. We highlight key issues that can guide future experiments (see Outstanding Questions).

Preparatory Inhibition to Assist Action Selection

The hypothesis that preparatory inhibition serves to assist action selection was motivated, in part, by early TMS studies showing consistent MEP suppression in nonselected effectors during choice RT tasks [74,80,90]. This motor inhibition was attributed to a competitive process, whereby nonselected action representations are suppressed, facilitating the selection of the desired response [2,81]. The operation of such an inhibitory process, often called ‘inhibition for competition resolution’, is consistent with decision-making models when



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Figure 4. Models of Preparatory Inhibition. Illustration of the inhibition for competition resolution hypothesis (A), the dual-process model (B), and the spotlight model (C) in the context of a task in which a cue indicates whether the forthcoming response will require a left (L) or right (R) index finger movement (L index finger trial in the current example). Dark- and light-blue circles are used to illustrate the neural representation of the L and R index fingers, respectively, in the motor cortex (upper panel) and in the spinal cord (middle panel). Dark- and light-gray circles are used to display irrelevant leg and pinky muscle representations, respectively. The circle size reflects the activation level of the motor representation. Inhibitory influences are displayed as red arrows. The lower panel shows the amplitude of motor-evoked potentials (MEPs) elicited in the L and R index muscles, as well as in irrelevant pinky and leg muscles. Based on the competition resolution idea (A), activation of the selected (L index) effector produces a selective suppression of the nonselected finger (R index). In the dual-process model (B), a second source of inhibition is directed at the selected effector, probably at the spinal level, resulting in suppressed MEPs in the selected effector despite increasing activation of its cortical representation. Finally, in the spotlight model (C), the inhibitory influences are centered on the selected effector, with inhibition extending to adjacent effectors (e.g., L pinky) and, to a lower degree, to homologous representations in the contralateral hemisphere, perhaps through transcallosal connections. The colored arrows point to the feet and hand muscles from which the corresponding MEPs are recorded. For illustration purposes, the spotlight is shown influencing cortical excitability, although this type of inhibition may occur elsewhere. None of the models predicts inhibition of leg muscles, reflecting the idea that the scope of preparatory inhibition may be narrower during action preparation than during action stopping. Abbreviation: CS, corticospinal.

considered in the context of action selection [91]. That is, competition resolution can help ensure a winner-take-all outcome, where the action that ‘wins’ is executed. While some models posit the competition as an independent race between response alternatives [92], other models posit, at least implicitly, competitive interactions between the alternative response options [93]. That is, each candidate not only accrues supporting evidence, but also inhibits the other options [7,94].

The competition resolution idea associates preparatory inhibition with reciprocal interactions between competing effectors, inducing a progressive inhibition of nonselected action

representations (Figure 4A upper panel) [2,80,81]. One prediction that follows from this hypothesis is that preparatory inhibition should only be observed in competing effectors, leaving the other muscle representations unaffected during action selection. For example, if the choice is between a left or right index finger response, a cue indicating a left response should result in inhibition of the (nonselected) right index finger, but not of other finger, arm, or leg muscles (Figure 4A, lower panel). However, inhibition is reliably observed in task-irrelevant muscle representations, during either a delay period [13,86,95,96] or a premovement period [78]. Thus, preparatory inhibition is not limited to nonselected effectors, but extends to task-irrelevant motor representations.

Moreover, as noted above, inhibition is also observed in the effector that will be used in the forthcoming response, that is, in the effector that will win the competition. For instructed-delay tasks, this effect is most pronounced just before the go signal [18]; for no-delay tasks, this inhibition is evident as a brief transient reduction in MEPs just after the onset of the go signal [90]. These findings, in combination with the consistent picture of inhibition in task-irrelevant muscles, present a major challenge to a model in which preparatory inhibition is assumed to result from reciprocal inhibitory interactions between alternative responses competing for selection. Rather, action preparation appears to entail a broadly tuned inhibition of the motor output system, irrespective of the effector(s) involved in the action that is being prepared [13,78,86,95].

What may be the purpose of broadly tuned inhibition during action preparation? One way to address this question is to consider the constraints on preparatory inhibition. The level of complexity of a prepared response influences the degree of inhibition [95], such that MEP amplitudes are more strongly suppressed when participants prepare a response requiring coordination between effectors compared with when the action involves repetitive movements with a single effector. Moreover, in delayed response tasks, the amount of MEP suppression depends on the anatomical and/or functional relationship between the competing effectors [17]. The suppression of MEPs (as evaluated in nonselected effectors) is more pronounced when the response set includes two hand movements (e.g., right versus left index finger) compared with when the set includes hand and foot responses (e.g., right index versus left ankle).

The strength of preparatory inhibition also increases with the risk of selecting an inappropriate response. This may arise because of incongruent sensory information [97,98] or because a nonselected response is prepotent [99]. More generally, mechanisms generating broad motor inhibition may serve to regulate the trade-off between speed and accuracy [100]: when the emphasis is on accuracy, inhibition might be used to raise the selection threshold. Converging lines of evidence implicate the STN in a threshold-setting process [11,12,101]. In a manner similar to how this structure can shut down the motor system to abort a planned movement, it could also modulate the threshold required to select and initiate a movement (e.g., low threshold to favor speed over accuracy) [102–104]. While these predictions have not been tested with TMS probes of corticospinal excitability, there is evidence that low-frequency oscillatory activity associated with the STN is modulated as a function of whether task instructions emphasize speed or accuracy [105].

Taken together, these findings suggest that inhibition assists action selection, even if the mechanism is not through reciprocal interactions between competing movement representations, but rather, as a result of broad inhibitory signals. These broad signals would provide a way to modulate response selection processes to fit the task context; for example, greater inhibition would be required when the response is complex to ensure adequate preparation or to avoid making prepotent responses.

Multiple Mechanisms of Preparatory Inhibition

Studies using a delayed response task to examine preparatory inhibition have often observed that MEP suppression is stronger in the selected effector compared with nonselected effectors. This result is difficult to reconcile with models relating preparatory inhibition exclusively to action selection. Accordingly, it has led to the hypothesis that the representation of selected effectors is targeted by a separate inhibitory mechanism (Figure 4B). That is, action preparation may engage two inhibitory processes, one producing broad suppression of the motor system to assist action selection, and a second suppressing neural activity of the selected effector [14,88,106]. The latter, often called ‘inhibition for impulse control’, would provide a mechanism to allow preparatory processes to unfold without the engagement of the peripheral motor system [107] (see also [108]). That is, excitatory processes could operate in cortical regions to prepare selected effectors for a forthcoming movement, with inhibition recruited to prevent the release of actual movements until the appropriate time has been reached to initiate the response.

This dual-process hypothesis is motivated, in part, by the observation that MEPs elicited from the agonist of the selected effector are attenuated even though the cortical representation of the movement is showing an increase in activity. This increase is, of course, the classic effect observed in neurophysiological studies with nonhuman primates. Indeed, activation during response preparation allows the forthcoming response to be decoded from the activity of many cortical and subcortical areas of the motor pathway during delay periods [109–111]. Correspondingly, paired-pulse TMS protocols reveal local increases in cortical excitability in human M1: intracortical inhibition is attenuated and intracortical facilitation is enhanced during preparatory periods, even though the overall excitability state of the corticospinal pathway associated with that response is suppressed [84,112,113]. Thus, the MEP suppression observed in selected effectors occurs at a time when the activity is increasing in the involved motor cortex.

This dissociation could come about because of nonlinear transformations in patterns of motor cortex activity; for example, it has been proposed that motor preparation and motor execution are represented along linked, orthogonal dimensions, a solution that could prevent premature movement [114–117]. Alternatively, the corticospinal suppression observed with TMS may originate in cortical regions that bypass M1 or arise from neural loci downstream from M1 [118]. Consistent with this hypothesis, the H-reflex response, a probe of spinal cord excitability [88], is diminished when elicited in the agonist muscle during the delay period, with the effect strongest right around the expected time of the go signal onset [83,119] (but see [18]). Importantly, this suppression of the H-reflex is observed for selected but not for nonselected effectors (see also [80] for premovement recordings of H-reflexes), consistent with the view that representations of the selected effector are targeted by a specific inhibitory form.

Further evidence in favor of a dual-process model comes from a study in which short trains of repetitive TMS pulses (10 Hz, five pulses) over dorsal premotor cortex (PMd) or lateral prefrontal cortex (LPF) were combined with single-pulse TMS over M1 to determine how these perturbations affect preparatory inhibition during the instructed-delay of a choice RT task [14]. rTMS over LPF attenuated inhibition in both the selected and nonselected effectors, suggesting a role for this area in a process associated with broad inhibition of the motor system. This inhibition could come about via transcortical fibers projecting from LPF to M1. Alternatively, this process may involve the basal ganglia and, in particular, the indirect pathway looping through the STN [11,52,61,105,120].

In contrast to the LPF results, transient disruption of PMd produced a more focal effect, releasing inhibition in only the selected effector. It was recently proposed that inhibitory processes in PMd are recruited in parallel with increasing preparatory activity [121]. That is,

PMd may not only help to specify the selected movement [122,123], but may also generate inhibitory signals targeted at structures downstream of M1, to prevent premature movements [124]. For example, PMd may modulate spinal cord excitability through corticospinal projections originating in PMd and targeting spinal interneurons [125,126]. A similar function could be achieved via PMd modulation of subcortical regions, such as the basal ganglia [127] or via brainstem cells projecting onto interneurons located in the intermediate zone of the spinal cord [128] that are involved in the control of distal hand muscles [107,129].

As noted previously, inhibition is also observed in standard (no-delay) RT tasks, where the cue not only specifies the movement, but also serves as the go signal. MEPs are suppressed shortly after the go signal (Figure 3A) and this effect is evident for both selected and nonselected effectors [77,78]. Given uncertainty immediately after the onset of the go signal, such a drop in corticospinal excitability may be due to the fact that all response options accrue some excitation and, at the same time, trigger linked inhibitory processes to avoid premature responding at this initial preparatory stage. Alternatively, this effect could be due to a mechanism producing broad inhibition of the motor system, similar to that observed during instructed delays. Consistent with this hypothesis, task-irrelevant motor representations are also suppressed immediately after the go signal [78]. Hence, both task-relevant and task-irrelevant effectors exhibit attenuation in corticospinal excitability during the premovement period. Whether this inhibition is fully generic or also includes a focal component is not known.

In summary, within the framework of a dual-process model, motor inhibition is important, not only to assist action selection, but also to prevent premature movement [84,88]. The latter initiation regulation process would be particularly important in delayed response tasks in which the implementation of a specified response must be withheld until a go signal. More generally, a downstream braking process would offer a mechanism that prevents premature movement during motor preparation.

Preparatory Inhibition to Modulate the Gain of the Motor System

Recent work has shown that preparatory inhibition is also observed in the absence of a choice. That is, in simple RT tasks, MEPs are suppressed in both the specified effector and task-irrelevant effectors [13]. These results have led to an alternative perspective in which preparatory inhibition is hypothesized to increase the signal:noise ratio within the motor system. By inhibiting the motor system, excitatory inputs will better stand out against a quiescent background. In essence, preparatory inhibition may modulate the gain of the system during action preparation. A primitive gain-modulation mechanism has already been well characterized in the leech motor system [130]. A similar mechanism may be conserved in mammals (see Outstanding Questions).

As mentioned above, MEP suppression is usually stronger in the selected effector compared with nonselected effectors. This result was one of the findings that motivated the dual-process model, with the selected effector targeted for focal inhibition to prevent premature responding. However, the gain modulation hypothesis suggests an alternative account of this phenomenon, given the assumption that preparatory inhibition is directed at (or recruited by) the representation of the selected muscle. Greenhouse et al. [13] offer a spotlight metaphor for gain control (Figure 4C), building on the idea that a spotlight can be described in terms of its position and extent. Centering the spotlight on the representation of the selected response would enhance the sensitivity of excitatory inputs for this action (Figure 4C); thus, inhibition is greatest for the selected effector.

Inhibition of nonselected, or even task-irrelevant effectors, reflects the extent of the spotlight, arising from the spillover of targeted inhibition onto neighboring motor representations. Notably,

leg muscle representations are not inhibited during preparation of finger responses and vice versa [96]. Hence, there appears to be some degree of restriction in the extent of the spotlight, with inhibition only concerning representations that are related either anatomically or functionally. Moreover, the extent of the spotlight may be modulated by task demands. For example, in the context of a choice, the aperture of the inhibitory spotlight might be narrow to produce a sharp gradient given the risk of incorrect choices. By contrast, the spotlight could be wider in simple RT tasks.

While the idea that inhibition might be used to facilitate gain is not novel, the operation of a tuned mechanism within the motor system raises several interesting questions. For example, it is unclear how the tuning may be affected by factors such as the relationship, either anatomical or functional, between selected and other effectors. In addition, the gain modulation spotlight model does not account for the local increase in cortical excitability or the suppression of H-reflexes associated with a selected response. Nonetheless, the spotlight model underscores the important point that one must be cautious in inferring a mapping between physiology and function: inhibition of a physiological measurement (i.e., MEP suppression) need not correspond to inhibition in terms of function. The spotlight idea shifts the emphasis away from inhibition as a way to suppress unwanted or nonselected movements, to one in which inhibition promotes rapid action preparation and implementation.

Shared Motor Inhibition for Action Preparation and Action Stopping

Intriguingly, both action preparation and action stopping appear to recruit processes that can produce inhibition that is either focal or broad, depending on task demands. In the context of action stopping, the influence of these two inhibitory forms appears to depend on whether the emphasis is on speed or selectivity of stopping, respectively. During action preparation, the contribution of these inhibitory processes may also vary according to the complexity of the task and to whether a response must be withheld across a delay period. These similarities raise the following questions: are overlapping mechanisms responsible for motor inhibition in action preparation and action stopping? What evidence do we have (or not have) that common mechanisms may be responsible for motor inhibition in these two contexts?

Although appealing, some reports in the literature are not completely consistent with the idea of a common mechanism. First, reactive stopping appears to have a broader influence on motor activity compared with action preparation. For instance, reactive stopping of finger responses inhibits not only irrelevant finger, but also leg muscle representations. By contrast, preparing a finger response induces inhibition of irrelevant finger representations but not of leg muscles [96]. Second, reactive stopping has been associated with increased intracortical inhibition [43,131], whereas intracortical inhibition is released for selected effectors during action preparation [84,112]. Third, the inferior prefrontal cortex, often implicated in action stopping, is not typically active during action preparation, suggesting that it is not involved in preparatory inhibition.

There are also important differences in the conceptualization of motor inhibition in these two contexts. Namely, whereas inhibition during stopping is thought to serve the sole purpose of suppressing the motor system output, current theories of action preparation shift the emphasis away from inhibition as a way to suppress unwanted movements (i.e., competition resolution idea) to one in which inhibition promotes rapid action selection and implementation (i.e., gain modulation idea). Nevertheless, overlapping inhibitory mechanisms may be engaged, and future investigations will be helpful in disentangling the processes underlying inhibition during action stopping and action preparation.

Concluding Remarks

Prominent signatures of inhibition are observed from probes of corticospinal excitability during human motor behavior. In some conditions, these inhibitory effects are focal, limited to task-relevant motor representations. However, in many conditions, the inhibitory effects are broad, evident in task-irrelevant muscles. The broadest effect is found when an ongoing action must be rapidly aborted; in this context, inhibition appears to be observed across the motor system. The widespread nature of this form of motor inhibition has been associated with the STN, a part of the basal ganglia thought to operate in a nonspecific manner. To date, the role of the STN in motor inhibition has been largely examined in the context of action stopping; its contribution to corticospinal inhibition during action preparation has not been explored, representing an interesting question for future studies (see Outstanding Questions). Indirect evidence suggests that the STN generates motor inhibition to set the threshold for action selection: the deeper the inhibition, the higher the threshold [11,61]. Whereas motor inhibition during action stopping can be easily related to behavioral control, the behavioral significance of preparatory inhibition remains unclear and may reflect the interaction of multiple mechanisms. Several hypotheses have been proposed, including a potential role in competition resolution, initiation regulation, and gain modulation. Future work is required, to not only evaluate these hypotheses, but also explore the relationship between preparatory, proactive, and reactive motor inhibition in terms of functional hypotheses and neural mechanisms.

Acknowledgments

J.D. was supported by grants from the 'Fonds Spéciaux de Recherche' (FSR) of the Université catholique de Louvain, the Belgian National Funds for Scientific Research (FRS-FNRS: MIS F.4512.14) and the 'Fondation Médicale Reine Elisabeth' (FMRE). R.B.I. was supported by grants from the National Institute of Health (NS097480, NS074917, NS092079). We are thankful to Julien Grandjean and Emmanuelle Wilhelm for their valuable comments on an earlier version of the manuscript.

Supplemental Information

Supplemental information associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tins.2017.02.006>.

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Outstanding Questions

The functional significance of preparatory inhibition remains a subject of debate. In addition, the source of corticospinal inhibition needs to be precisely identified, together with the level at which the inhibition is manifest.

Functions of Preparatory Inhibition

Current models of preparatory inhibition focus on functions related to competitive interactions, response initiation, and gain modulation. Critical experiments that pit the models against one another are needed, both to evaluate these models and inspire new hypotheses.

Is there a relationship between the magnitude of MEP suppression and behavioral measures?

Research aimed at investigating the impact of different task demands on motor inhibition should focus on methods that can selectively track inhibitory influences; for example, paired-pulse TMS techniques have proven useful for quantifying the strength of intracortical and transcortical inhibitory pathways. Alternatively, further work could focus on MEPs evoked in task-irrelevant muscles.

How are inhibitory effects associated with the regulation of response initiation related to proactive inhibition?

In addition to somatotopy, the motor cortex has also been mapped in terms of ethologically meaningful actions. Various inhibitory mechanisms may operate either across multiple scales (body map, action maps, upper limb posture, and hand spatial location) or uniquely at a particular level, leading to a variety of functional outcomes.

How are disorders associated with impaired inhibitory control in behavior related to an alteration of inhibitory mechanisms underlying action preparation and action stopping?

Neural Substrates of Preparatory Inhibition

What is/are the source(s) and/or target(s) of preparatory inhibition (cortical, spinal, or corticobasal ganglia loops)?

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In addition to looking at interactions between frontal areas and corticospinal neurons in M1, paired-pulse TMS techniques can be used to investigate the role of interhemispheric interactions in preparatory inhibition. Interactions should be studied in conditions where the probed muscles are selected or nonselected (homologous versus nonhomologous to the selected response) or even task irrelevant.

Surround inhibition has received little attention in regards to preparatory inhibition, although it may suppress neighboring response representations during action selection. To test this hypothesis, it will be important to explore the patterns of inhibition for selected and nonselected muscles as a function of cortical distance (i.e., distance within the cortical homunculus).

Future studies could compare preparatory inhibition according to whether patients with Parkinson's disease are OFF or ON medication (dopamine replacement therapy) or they could examine the impact of STN deep-brain stimulation on motor inhibitory influences during action preparation.

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