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REVIEW

Inhibition for gain modulation in the motor system

Ian Greenhouse[1]

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Abstract
Signatures of inhibition within the cortico-spinal pathway are frequently observed during action preparation in humans. Popular theoretical and computational models highlight a critical role for inhibition as the suppressor of motor system output, e.g., to withhold undesired action tendencies or to stop ongoing movements. However, inhibition frequently serves a modulatory role in non-motor systems. For example, in vision and somatosensory systems, inhibition can adjust the relationships between input and output, a computation referred to as gain modulation. Inhibition may modulate gain within the motor system as well. Changes in cortico-spinal inhibition observed during human behavior can reflect adjustments in motor system gain and may be sensitive to latent behavioral states. This review summarizes roles for inhibition in gain modulation, drawing principally on evidence from non-motor systems, and examines the hypothesis that homologous functions operate in the animal and human motor systems to facilitate action preparation.

Keywords Inhibition · GABA · Gain Modulation · Motor Control · Action Preparation

Introduction

In a healthy person, the transition from thinking of an action to initiating that action is seemingly effortless and reliable. This essential aspect of voluntary behavior depends on a delicate balance of excitatory and inhibitory mechanisms throughout circuits in the brain and spinal cord. Diseases and trauma disrupting this balance impair action initiation (a primary symptom of movement disorders including Parkinson's disease, dystonia, and stroke) and interfere with activities of daily living. Widely accepted neural circuit models attribute impaired action initiation to excessive inhibition of motor output pathways (Mink 1996; Nambu 2005): a proposition influential to the fields of motor, cognitive, and clinical neuroscience (Alexander and Crutcher 1990; Frank et al. 2007; Benjamin et al. 2010; Wessel and Aron 2017; Fife et al. 2017; Soteropoulos 2018). While inhibition is recognized as crucial to behavioral control in humans, the specific neural computations that depend on physiological inhibition are not clearly delineated.

An important distinction must be drawn between physiological inhibition and behavioral inhibition. This distinction is particularly important when considering the neural mechanisms that control actions. Recent evidence motivates a model in which inhibition sculpts cortico-spinal (CS) output rather than simply suppressing it (Greenhouse et al. 2015b; Duque et al. 2017). This revised framework relies on inhibition for gain modulation, a canonical neural computation, which has been well characterized in human sensory and animal motor systems (Hillyard et al. 1998; Salinas and Thier 2000; Serences and Yantis 2006).

Gain modulation has often been associated with a potent and widespread influence of inhibitory gamma-aminobutyric acid (GABA)-ergic interneurons acting on populations of principle neurons (Salinas and Thier 2000; Chance et al. 2002; Baca et al. 2008; Liu et al. 2011; Katzner et al. 2011; Carandini and Heeger 2011; Sadeh et al. 2017; Wilson et al. 2018). Despite compelling evidence (Bollu et al. 2018; Sohn and Hallett 2004a; Baca et al. 2008; Beck et al. 2008; Beck and Hallett 2011; Vestergaard and Berg 2015; Khademi et al. 2018; Stroud et al. 2018), a few studies have directly examined the putative roles of gain modulation in human action control. This is due in part to the significant challenges of measuring motor system gain in humans.

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✉ Ian Greenhouse
img@uoregon.edu

[1] Department of Human Physiology, University of Oregon, Eugene, OR, USA

Multimodal approaches that combine brain stimulation with electrophysiology have overcome many of these challenges and can provide temporally precise measurements of motor system gain during human behavior.

In this review, I define gain modulation and how it is measured. I summarize evidence that indicates a critical role for inhibition in gain modulation in non-motor systems. I examine physiological evidence for parallel functions within the motor system and how various theoretical and computational models converge on a role for inhibition in motor system gain modulation. Finally, I review recent evidence from humans that suggests motor system inhibition may modulate gain during action preparation.

What is gain modulation?

Gain modulation refers to a change in the input–output (I/O) relationship of a neural system (Fig. 1). For example, at rest, increasing the intensity of a stimulus along a particular dimension (e.g., intensity of electrical stimulation, contrast of a visual grating, volume of a sound, etc.) can lead to greater system output, provided the system is sensitive to the stimulus dimension that was manipulated. When there is a change in the state of the system (e.g., a change in behavior, chemical environment, temperature, etc.), the I/O relationship may be adjusted, such that the output increases non-linearly in relation to the increasing input stimulus intensity. This multiplicative change in the I/O relationship is a defining feature of gain modulation. The following sections will address how physiological inhibition, mediated by GABA, is a key modulator of neural system gain, but first it is useful to summarize how gain is measured.

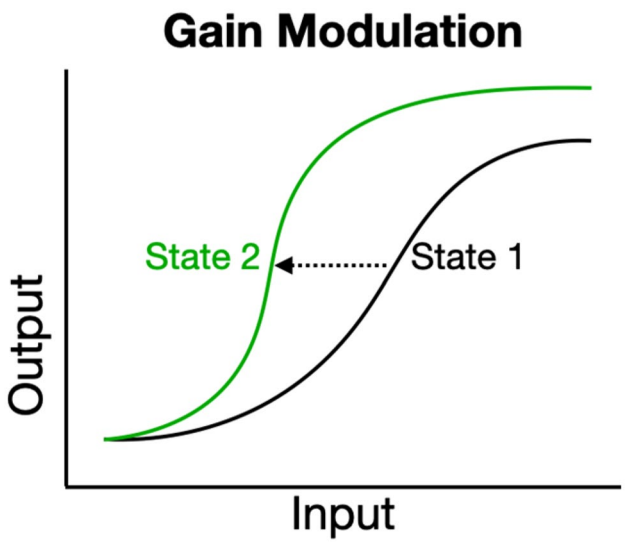

Fig. 1 Gain determines the input/output (I/O) function of a cell or population of cells. The black trace represents the I/O function at rest (State 1), with increasing input corresponding to increasing output. The green trace represents the hypothesized gain increase associated with a change in behavioral state (State 2) as may occur under the influence of widespread inhibition. The multiplicative influence of gain results in a non-linear change in the slope of the I/O function

A variety of different protocols have been applied to evaluate neural gain changes in animals and humans. The type of output depends on the properties of the neural system being measured and the modality of the measurements themselves. Output is commonly in the form of neural firing rates, but can also be the magnitude of electromyographic (EMG) events, force production strength, psychometric functions derived from perceptual discrimination and detection tasks, electroencephalographic (EEG) oscillatory power, and blood oxygen level dependent (BOLD) signal strength measured with functional Magnetic Resonance Imaging (fMRI), among others. These types of measurements are all believed to reflect processes associated with the transmission of information within neural circuits. However, it is important to bear in mind that changes in gain as detected by these different measurements arise from distinct underlying physiological mechanisms and may therefore represent different processes.

Roles for inhibition in gain modulation of non-motor systems

At the level of individual neurons or pools of neurons, GABAergic inhibition modulates gain in different ways. GABAergic inhibition targeted at a particular neuron, or part of a neuron, can decrease the cell's responsiveness to input (Pouille et al. 2013; Tremblay et al. 2016), but inhibition spread across a pool of neurons can increase signal-to-noise throughout the pool. This is because small changes in activity associated with a particular neural representation stand in sharper contrast to a quieter background. Thus, inhibition can improve the signal-to-noise ratio across a population of neurons to facilitate signal propagation and increase system gain. The emergence of this property at the population level depends on the principle of divisive normalization by which each individual cell's activity is divided by the summed activity of a pool of neurons (Fig. 2; Pouille et al. 2009; Carandini and Heeger 2011).

Important work in animal primary visual (V1; (Katzner et al. 2011; Lee et al. 2012; Haider et al. 2013) and other sensory cortices (Murayama et al. 2009; Pouille et al. 2009, 2013) in combination with computational modeling suggests that GABAergic inhibition serves important roles in gain modulation. For example, iontophoresis of gabazine, a selective $GABA_A$ antagonist, in cat V1 resulted in enhanced selectivity for stimulus orientation and direction by suppressing unwanted activity below firing threshold. This finding was captured by a cellular model in which inhibition matched excitation for orientation sensitivity (Katzner

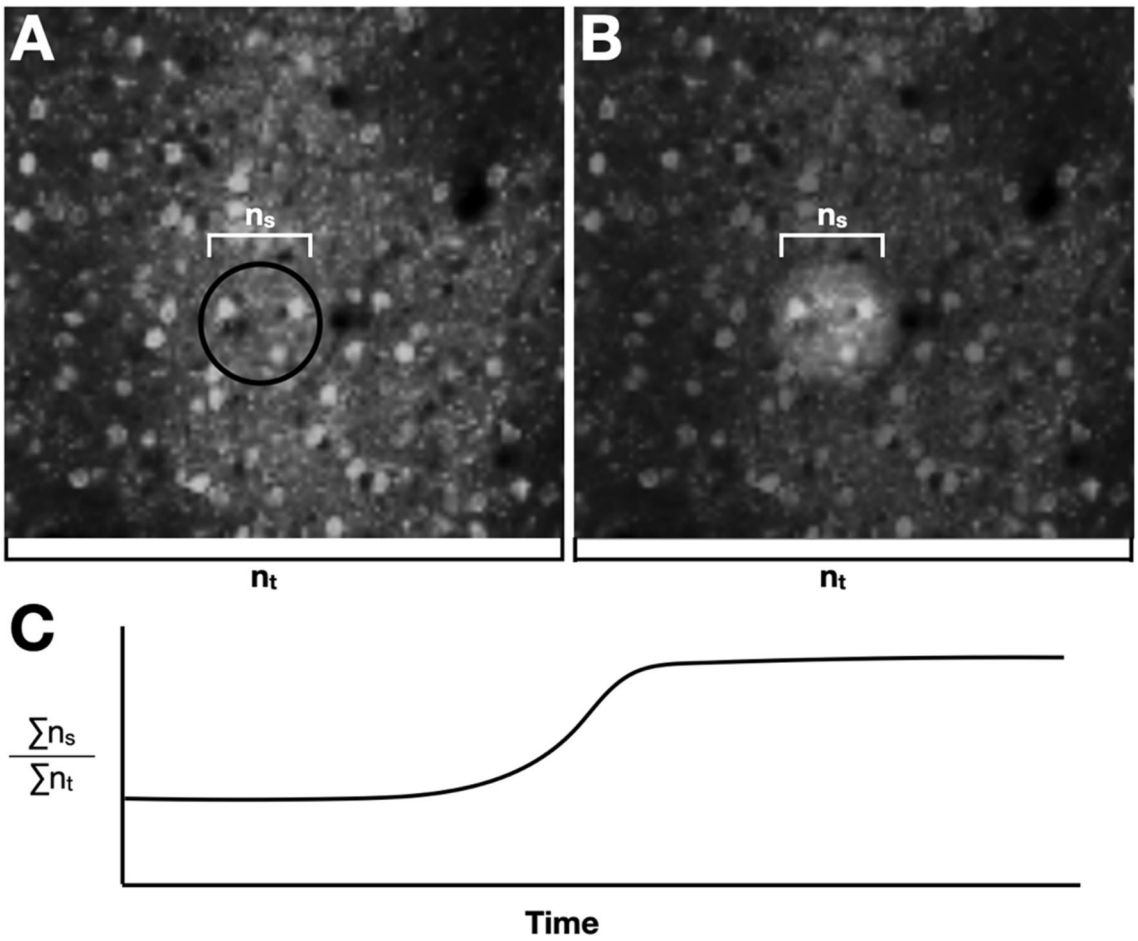

Fig. 2 **A** Example activity across a pool of neurons at rest (State 1, the same as in Fig. 1), as reflected in calcium imaging of M1. A motor representation (circled region) will be selected for action. **B** Activation of the selected representation in the context of widespread inhibition (State 2, the same as in Fig. 1) is depicted as relative differences in intensity. **C** The sum of activity within the selected representation (n_s) is divided by the activity throughout the total pool (n_t) via divisive normalization, corresponding to increased gain of the selected representation

et al. 2011). Thus, neurons remain responsive to the same stimuli (i.e., input sensitivity is constant), and $GABA_A$ergic inhibition modulates the output firing rates. By constraining suprathreshold activity to only those cells that are most responsive, $GABA_A$ inhibition increases overall V1 selectivity. This result was elaborated on by additional optogenetics work, which established that activation of parvalbumin-positive inhibitory interneurons in mouse V1 sharpened neuronal feature selectivity and improved perceptual discrimination. This work further ruled out the possible role of excitatory neurons, as well as other classes of inhibitory interneurons, in determining V1 orientation selectivity and perceptual discrimination (Lee et al. 2012). Collectively, this important work established a specific role for GABAergic inhibition in adjusting gain in V1. Interestingly, broad inhibition greatly outweighs excitation in the awake mouse V1 (Haider et al. 2013), suggesting that inhibition for gain modulation is a dominant feature of V1 computation.

Inhibition for gain modulation appears to operate in a similar manner outside V1. Many of the same properties are observed in the sensorimotor and primary motor (M1) cortex. In rats presented with air-puff stimulation to a hind limb, the slope of the gain of cortical output neurons is determined by a subset of specialized inhibitory interneurons. Specifically, injection of gabazine resulted in a large multiplicative increase in the dendritic population response measured with calcium fluorescence, and di-synaptically evoked dendritic inhibition via a microcircuit involving the recruitment of specialized inhibitory Martinotti cells abolished these calcium spikes (Murayama et al. 2009). Moreover, properties like these are observed subcortically, as well. Feedforward inhibition acting in a uniform manner sets a global threshold for recruitment of pyramidal cell efferents in both hippocampus and primary somatosensory (S1) cortex and helps a network adjust to a range of input stimulus strengths (Pouille et al. 2009). The widespread inhibition is proportional to the

stimulus strength, such that the response output is normalized. Like the observations in V1 made by Katzner et al., only pyramidal cells with excitatory conductance that overcame the modulatory influence of inhibition reached spike threshold. These mechanisms may depend on inhibition for gain modulation to rapidly enhance the output of a particular representation in a non-linear manner when under volitional control, e.g., under the demands of attention.

Additional work in hippocampal and somatosensory cortical slice preparations examined the influence of the location of $GABA_A$ inhibitory synapses activated with muscimol, a $GABA_A$ agonist, on gain. Activation of synapses at the pyramidal cell dendrites resulted in a rightward shift in the input–output curve, whereas synapses at the soma resulted in decreased slope (Pouille et al. 2013). Conductance was held constant in these experiments. This work indicates the location of inhibitory synapses likely plays an important role in determining the type of gain adjustments at the level of individual pyramidal cells. How the synapse-level architecture scales up to population-level computations remains uncertain.

Together, this work suggests that inhibition serves an important role in setting the gain of system output at multiple levels in non-motor systems. Moreover, a consensus emerges across studies to support the idea that increased widespread inhibition can improve the 'precision' of neural representations by suppressing undesired activity and only permitting desired activity to reach suprathreshold levels. This type of contrast enhancement may facilitate appropriate behavior. The question remains whether these properties generalize to the motor system.

Roles for inhibition in gain modulation of the motor system

While the hypothesis that inhibition suppresses motor output has prevailed in the field, alternative hypotheses have existed for decades. The "motor contrast enhancement" hypothesis (Stefanis and Jasper 1964; Georgopoulos and Stefanis 2007) was based on evidence for dynamic recurrent collateral surround inhibition within M1 that suppresses representations neighboring a selected action representation. Despite laudable efforts to characterize surround inhibition in the animal (Schieber and Poliakov 1998; Schneider et al. 2002) and human motor cortex (Hallett 2003; Sohn and Hallett 2004a; Beck et al. 2008; Shin et al. 2009; Beck and Hallett 2011; Poston et al. 2012; Kassavetis et al. 2014; Bächinger et al. 2019), its functional significance remains a topic of debate. Abnormal surround inhibition in Parkinson's disease (Shin et al. 2007; Leon-Sarmiento et al. 2013) and dystonia (Sohn and Hallett 2004b; Beck et al. 2008; Hallett 2011) is linked to disrupted GABAergic neurotransmission (Marjańska et al. 2013; Gallea et al. 2018), suggesting that GABA mediates surround inhibition in M1. However, surround inhibition has not been examined in relation to motor system gain modulation.

Structural differences between non-motor and motor cortex are well documented (Shipp 2005). Nevertheless, GABAergic mechanisms likely support gain modulation within M1 in a manner similar to sensory systems, and important features may generalize across systems. For example, inhibitory gain adjustments are particularly potent in large pyramidal cells (Murayama et al. 2009), suggesting that gain changes may be especially strong in CS projection neurons.

Inhibition has been shown to modulate gain in the motor system of simple nervous systems, i.e., without a neocortex. GABAergic projections from the leech central ganglia to the periphery mediate gain with a widespread influence (Baca et al. 2008). Removing inhibition caused leeches to exhibit weaker local bending responses to aversive stimuli, and increasing motor output positively correlated with the level of inhibition. This is one example case in which widespread inhibition corresponds to increased motor output.

Recent evidence suggests that similar properties are recapitulated in human M1, with overall M1 disinhibition contributing to greater motor slowing and coactivation of antagonist muscles (Bächinger et al. 2019). Scalp electroencephalography (EEG) oscillations in the beta-band, a hypothesized marker of cortical GABAergic inhibition, correlate with input gain changes in the CS pathway, measured with transcranial magnetic stimulation (TMS) elicited motor-evoked potentials (MEPs) (van Elswijk et al. 2010; Khademi et al. 2018). Furthermore, greater intrinsic availability of total GABA in M1, measured with magnetic resonance spectroscopy, correlates with resting CS gain determined with MEPs (Stagg et al. 2011; Greenhouse et al. 2017). Notably, investigations of the relationships between GABA availability and adjustments in motor system gain during the performance of behavioral tasks in humans are lacking in the literature.

Other evidence points to additional roles for inhibition in gain modulation relevant to motor output. Work in animal models showed that inhibition modulates sensory feedback gain in the spinal cord to promote smooth movement. Specialized presynaptic inhibitory cells modulate gain at the level of the synapse between proprioceptor afferents and spinal motor neurons (Stein 1995; Azim and Seki 2019). Other recent work has identified a quintessential role for inhibition in adjusting visuomotor gain within the frontal eye fields during preparation of smooth eye movements (Darlington and Lisberger 2020). However, this work suggests that the frontal eye fields may rely on inhibition for different computations than those observed in M1.

The collective evidence suggests inhibition subserves a variety of computations that influence gain at multiple levels within the motor system throughout the preparation, execution, and termination of movement in animals and humans. Future experiments can examine input/output relationships within the motor system during different behavioral and physiological states. For example, pharmacological, behavioral, and stimulation methods may be used to alter the inhibitory tone within the motor system, while gain is assessed. In addition, assuming the capacity for inhibition depends in part on the local availability of GABA, studies can assess relationships between regional GABA content and patterns of gain.

Computational modeling of inhibition for gain modulation within the motor system

Computational modeling lends further support to the idea GABAergic inhibition modulates gain within individual neurons and neural populations (Salinas and Thier 2000; Ayaz and Chance 2009; Carvalho and Buonomano 2009; Vogels and Abbott 2009; Stroud et al. 2018). This work suggests gain modulation across large populations of M1 neurons during movement preparation and execution accounts for multiple features of motor behavior (Vogels and Abbott 2009; Stroud et al. 2018). The earlier work on this topic focused on the detailed balance between excitatory input and local inhibition for gating transmission of multiple signals via gain adjustments. The more recent work shows how a range of input–output gains in a recurrent neural-network model of M1 can independently control movement shapes and speeds. Inhibitory interneurons with diffuse projections to M1 are a key element of this model, reminiscent of experimental findings from V1.

Relevance to action preparation

Research in humans and animals demonstrates that excitability within the CS pathway, from M1 to muscles in the body, changes during action preparation. Classic electrophysiological studies in non-human primates revealed anticipatory activity in M1 neurons during action preparation (Tanji and Evarts 1976). Accordingly, a long-held assumption was that action preparation involves *increased* CS pathway excitability. Surprisingly, the majority of subsequent studies in humans have observed *decreased* excitability within the CS pathway during the preparation of a planned action—a phenomenon referred to as 'preparatory inhibition' (Hasbroucq et al. 1997, 1999a, b; Touge et al. 1998; Davranche et al. 2007; Sinclair and Hammond 2008, 2009; Duque and Ivry 2009; Duque et al. 2010, 2012, 2014; Labruna et al. 2014, 2019; Greenhouse et al. 2015a, b; Klein et al. 2016; Lebon et al. 2016, 2019; Quoilin et al. 2019; Ibáñez et al. 2020). This reduction in MEP amplitudes could reflect different mechanisms, not only local inhibition within M1 but also decreased excitatory drive to M1 or long-range inhibitory projections acting on M1. Regardless of the source, this pattern of decreased excitability, i.e., below resting levels, extends to task-irrelevant muscles, implicating a modulatory mechanism with widespread effects on the motor system (Greenhouse et al. 2015b; Hannah et al. 2018; Labruna et al. 2019). However, other studies reported conflicting results, with either no change in CS excitability or selectively increased excitability in muscles involved in a prepared action (Chen et al. 1998; Touge et al. 1998; Leocani et al. 2000; van Elswijk et al. 2007; Davranche et al. 2007; Mars et al. 2007; Kennefick et al. 2014; Quoilin et al. 2016; Hannah et al. 2018; Chye et al. 2018; Cirillo et al. 2021). Controversy over the underlying neural mechanisms motivated the development of two competing models.

The first model described preparatory inhibition as a combination of independent processes: (i) an impulse control process for preventing a planned action from premature execution, and (ii) a competition resolution process for suppressing unselected response options in favor of a selected option (Duque et al. 2010, 2017). According to this dual-process model, physiological inhibition suppresses behavioral output (Duque et al. 2012). While this model accounted for early available evidence, it failed to explain some subsequent findings. Specifically, inhibition was found to extend to task-irrelevant muscles, even in the absence of competing response alternatives (Greenhouse et al. 2015b; Duque et al. 2017). This suggests preparatory inhibition involves a process other than response competition. Further evidence showed inhibition persisted when there was no task requirement to delay responses (Greenhouse et al. 2015b), and a greater magnitude of inhibition correlated with faster responses (Hannah et al. 2018). These findings suggest that inhibition can facilitate rather than suppress motor output.

The second model, referred to as the "spotlight" model, was based on the idea that motor system inhibition supports specific computations involved in action preparation rather than suppression of output. According to this model, widespread modulation increases the signal-to-noise ratio within motor output pathways and facilitates action selection as well as the state transition from action preparation to execution. According to this model, a selected action representation is enhanced relative to surrounding background activity in the presence of widespread inhibition. When an independent signal to execute the planned action reaches the motor output pathway, the relative difference in activity between the selected and surrounding motor representations determines the motor output gain. This model draws on examples from non-motor systems and the earlier proposed contrast enhancement hypothesis of Stefanis et al.

The widespread inhibition that is a defining feature of the spotlight model is supported by the observed reduction in MEP amplitudes in task-irrelevant muscles (Greenhouse et al. 2015a, b; Hannah et al., 2018; Labruna et al., 2019). Additionally, the magnitude of MEP suppression has been observed to correlate with reaction time, such that greater suppression corresponded to faster responses (Hannah et al. 2018). This finding suggests that the magnitude of the reduction in CS pathway excitability during preparation facilitates action execution and is in line with the interpretation that inhibition increases motor output gain. Other evidence showed that CS pathway excitability was reduced to a similar extent whether prepared responses were executed in synchrony with external cues or executed freely, i.e., in the absence of exogenous signals (Ibáñez et al. 2020). This finding suggests that reductions in CS pathway excitability are an essential step in the preparation of both stimulus-driven and endogenous goal-directed actions, consistent with the idea that gain modulation is necessary for the execution of a variety of different action types.

However, additional evidence motivates further refinement of the spotlight model. Specifically, Duque and Ivry (2009) used a paired-pulse TMS approach and observed a release of short interval intracortical inhibition during action preparation, which can be interpreted to reflect a decreased influence of GABAa-ergic mechanisms acting within M1. Similarly, a recent study by Gomez et al. (2021) observed decreased cortical silent periods in task-irrelevant muscles during action preparation, providing further indication GABAergic intracortical inhibitory mechanisms decrease their influence on the CS pathway during response preparation. Both pieces of evidence suggest that the source of CS pathway modulation is outside M1 or within pools of M1 inhibitory cells that are not reflected in TMS-elicited measurements. Furthermore, Hannah et al. (2018) observed a dissociation between anterior-to-posterior vs. posterior-to-anterior TMS current directions. MEPs elicited by TMS with an anterior-to-posterior current direction were consistently reduced in amplitude during action preparation, whereas those elicited with a posterior-to-anterior current direction were not, suggesting that MEP reductions may result from decreased excitatory drive via specific inputs to M1 rather than intracortical inhibition within M1. They offered the interpretation that modulation of CS pathway excitability during action preparation reflects a shift in the excitation-inhibition balance believed to occur within a dynamical system framework, in the absence of overt motor output (i.e., output null state). This interpretation is compatible with the spotlight model, which is agnostic about the source of CS pathway modulation, and gain modulation is a candidate process by which the motor system transitions from rest to action. The possible influence of TMS current direction on measurements of motor system gain merits further attention.

Future studies testing these models will help to unify principles of inhibitory computations across systems and also determine those computations which may be unique to motor or non-motor systems. An important step will be to examine patterns of motor system gain changes during the preparation and initiation of various types of actions and under different behavioral contexts and constraints.

Conclusion

Roles for gain in human action control and their links to physiological inhibition merit further investigation. Future studies can explore dynamic changes in gain during human motor behavior. Additional research on the relationship between inhibition and gain modulation in the human motor system could revise our conceptual framework of healthy and disordered behavioral control, and lead to the identification of new therapeutic targets for the treatment of motor disorders.

Declarations

Conflict of interest The author has no competing or financial interests to disclose.

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