Goal-directed action preparation in humans entails a mixture of corticospinal neural computations

Corey G. Wadsley[1,2], Thuan Nguyen[3], Chris Horton[1], Ian Greenhouse[1,2]

[1]Action Control Lab, Department of Human Physiology, University of Oregon, Eugene, Oregon, USA
[2]Institute of Neuroscience, University of Oregon, Eugene, Oregon, USA
[3]School of Public Health, Portland State University-Oregon Health and Science University, Portland, Oregon, USA

Corresponding author: Ian Greenhouse (img@uoregon.edu)

Keywords: Human, Motor cortex, Action preparation, Gain modulation, Noninvasive brain stimulation

Abstract: The seemingly effortless ability of humans to transition from thinking about actions to initiating them relies on sculpting corticospinal output from primary motor cortex. This study tested whether canonical additive and multiplicative neural computations, well-described in sensory systems, generalize to the corticospinal pathway during human action preparation. We used non-invasive brain stimulation to measure corticospinal input-output across varying action preparation contexts during instructed-delay finger response tasks. Goal-directed action preparation was marked by increased multiplicative gain of corticospinal projections to task-relevant muscles and additive suppression of corticospinal projections to non-selected and task-irrelevant muscles. Individuals who modulated corticospinal gain to a greater extent were faster to initiate prepared responses. Our findings provide physiological evidence of combined additive suppression and gain modulation in the human motor system. We propose these computations support action preparation by enhancing the contrast between selected motor representations and surrounding background activity to facilitate response selection and execution.

Significance statement: Neural computations determine what information is transmitted through brain circuits. We investigated whether the motor system uses computations similar to those observed in sensory systems by noninvasively stimulating the corticospinal pathway in humans during movement preparation. We discovered that corticospinal projections to behaviorally relevant muscles exhibit nonlinear gain computations, while projections to behaviorally irrelevant muscles exhibit linear suppression. Notably, individuals with stronger signatures of these computations had faster motor responses. Our findings suggest that certain computational principles generalize to the human motor system and serve to enhance the contrast between relevant and background neural activity.

Introduction

Humans are experts at using their fingers for goal-directed actions to effectively interact with their environment[1]. This behavioral repertoire is supported by a specially evolved neural architecture comprising excitatory and inhibitory mechanisms that sculpt corticospinal (CS) pathway output during goal-directed action preparation[2–4]. While the neural architecture of motor behavior is well characterized[5,6], the precise neural computations that unfold throughout the transition from action preparation to execution are not[7]. Candidate computations have been proposed but are based on neuronal circuit modeling and experimental evidence from investigations of non-motor neural systems and behaviors[8]. Thus, it is unclear whether computational principles from non-motor circuits generalize to the human motor system and account for the top-down modulation of CS output during action preparation.

Influential models of goal-directed action preparation postulate that inhibition of the CS pathway acts as a functional gate, with the removal of inhibition allowing selective excitatory signals to pass through to the musculature and produce intended actions[9,10]. Yet, physiological recordings from non-human primates have provided mixed evidence for gating mechanisms within the CS pathway[11–13]. Indeed, (dis)inhibition supports a variety of computations other than gating in non-motor neural circuits[14–16]. Multifaceted computations are also likely required in the motor system since movements are not static but instead defined by various kinetic and kinematic features that characterize a given action. Therefore, alternative interpretations to the functional gating account should be considered to better explain how preparatory activity determines CS pathway excitability to shape ensuing actions.

The selection and timing of goal-directed actions may be determined by neural computations similar to non-motor circuits. Such computations, responsible for sculpting descending signals, are expected to manifest in distinct patterns of CS input-output during goal-directed action preparation. One candidate computation is gain modulation, defined in studies of sensory processing as a multiplicative (non-linear) change in a system‘s input-output relationship and a proposed feature of canonical normalization processes within the brain[17–19]. Computational models indicate gain modulation is important in determining primary motor cortex (M1) output[20,21], the predominant source of descending signals of the

human CS tract[22]. Additive modulation, defined by a linear shift across an input-output spectrum[23], is an alternative candidate computation that may account for CS input-output adjustments during action preparation. Computational models of additive modulation indicate effective changes in an input-output threshold[24], whereby widespread suppression can stabilize a neuronal population by reducing the preponderance of spontaneous firing[25]. During action preparation, additive modulation may function as the 'quiet before the storm' to prepare the CS pathway for impending descending commands.

A third alternative is that multiplicative and additive computations are concurrent and complementary. Within a divisive normalization framework[26], the activity of a motor representation selected for action is divided by the summed activity of alternative non-selected and bystander motor representations, producing enhanced signal-to-noise[8,27]. A combination of multiplicative and additive computations could serve to separate figure from ground in a manner resembling neural sensory processing and would be consistent with a general neurocomputational principle throughout the human nervous system akin to exponentiation, linear filtering, and divisive normalization[26]. In this study, we tested the presence of multiplicative and additive computations in human CS input-output during the behavioral state change from rest to action preparation of goal-directed finger movements (Figure 1a). We hypothesized that goal-directed action preparation involves a concurrent gain increase and additive suppression to enhance the contrast between selected and background motor representations along the CS pathway.

Results

Thirty-nine neurologically healthy adult participants performed instructed-delay two-choice reaction time tasks to assess physiological changes in CS input-output during goal-directed action preparation (Figure 1b). To probe CS input-output dynamics, transcranial magnetic stimulation (TMS) was applied over right M1 to activate the first dorsal interosseous (FDI) muscle of the left index finger during rest (baseline during the intertrial interval) and when the muscle was selected (i.e., the agonist for prepared action), nonselected, or task-irrelevant (Figure 1c). Nonselected refers to the context in which the left index finger was a choice alternative in the task but was not cued to respond on a given trial, while

task-irrelevant refers to the context in which the left index finger was never a choice alternative in the task. We applied TMS at five intensities, with motor-evoked potential (MEP) amplitude recorded with electromyography (EMG) as our index of CS output[28]. Context-dependent modulation of CS input-output was assessed with a population-based nonlinear mixed effects model using a modified three-parameter Boltzmann function to capture the sigmoidal CS input-output relationship observed with TMS[29]. Here, the Midpoint and Slope parameters indicate additive and multiplicative computations, respectively (Figure 1d; Methods).

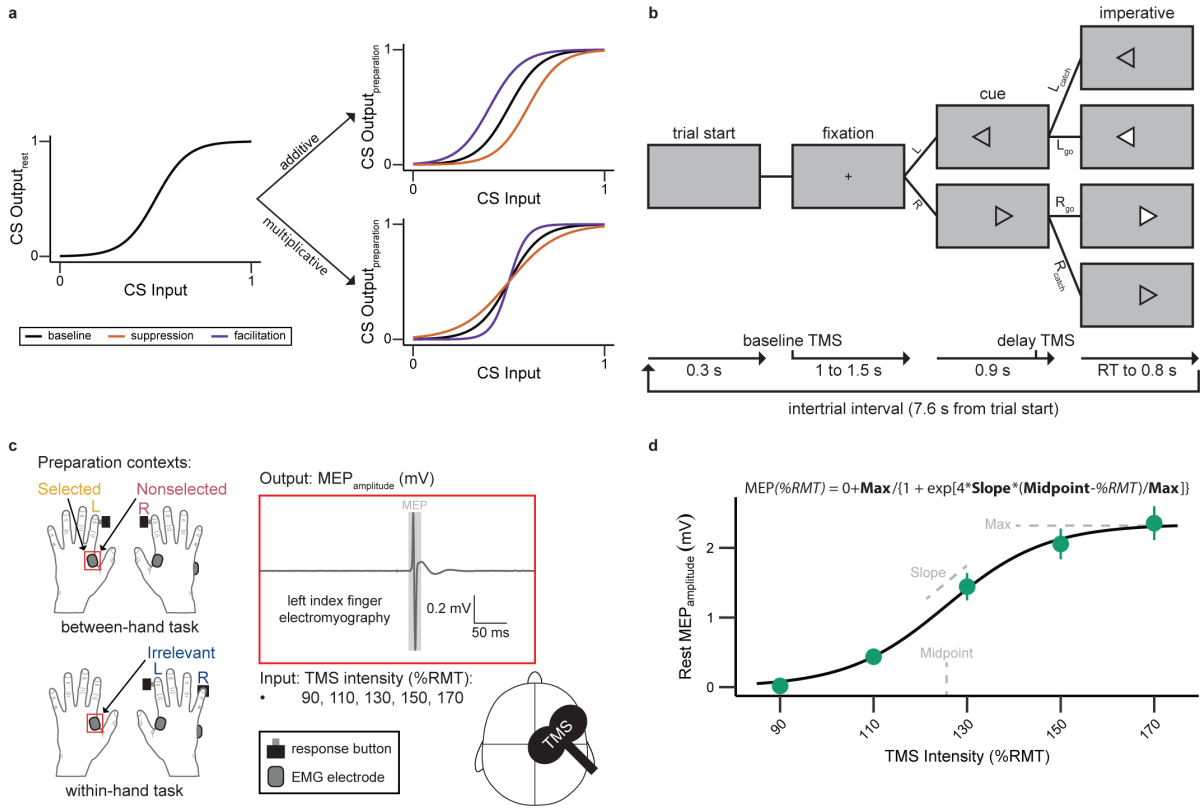


Figure 1: Assessment of human CS input-output during goal-directed action preparation. **a**, Corticospinal (CS) input-output can exhibit additive and/or multiplicative modulation from baseline rest to a preparatory state. **b**, Goal-directed action preparation was assessed with an instructed-delay two-choice reaction time task requiring left (L) or right (R) responses. Most trials were go trials during which the imperative stimulus appeared until a reaction time (RT) was recorded or 0.8 s elapsed. A subset of catch trials (~8%) was included to prevent participants from predicting imperative stimulus onset. **c**, The experiment was split into between-hand and within-hand tasks, enabling the assessment of CS output from the left index finger with single-pulse transcranial magnetic stimulation (TMS) when the targeted motor representation was at baseline and when it was selected, nonselected, or irrelevant for action preparation. Here, input was TMS intensity relative to a participant's resting motor threshold (%RMT), and output was the amplitude of ensuing motor evoked potentials (MEPs). **d**, CS input-output curves derived from pre-task resting state MEP data and fit with a population-based nonlinear mixed effects model using a three-parameter Boltzmann function. Green dots and error bars indicate mean MEP amplitude ± SEM at each TMS intensity. Dashed grey lines illustrate parameter estimates.

CS gain increases during response preparation for task-relevant representations

CS input-output parameters changed during goal-directed action preparation in a context-dependent manner (Figure 2a) and were not affected by participant sex or task order (Figure S1). The Slope of CS input-output differed significantly across Context ($F_{3,730}$ = 4.26, P = 0.005). Specifically, context-dependent multiplicative modulation of CS input-output was explained by an increase of Slope when the stimulated motor representation was selected or nonselected for forthcoming action (i.e., task-relevant) compared to baseline or when it was task-irrelevant (Figure 2b). Such nonlinear increases in sensitivity to excitatory inputs are associated with response potentiation across sensory systems[30]. Multiplicative gain modulation may be important for maximizing signal-to-noise and, computationally, can extend the dynamic range of neuronal operations[24,31]. Of note is that increased Slope was observed in both the selected and nonselected preparation contexts, indicating a general role of gain modulation in potentiating task-relevant motor representations rather than promoting effector-specific action selection. Max of CS input-output also differed significantly across Context ($F_{3,730}$ = 24.04, P < 0.001); however, it was greater during selected than nonselected and irrelevant contexts, but not baseline (Figure 2c). Therefore, gain modulation may be pertinent for establishing the pool of candidate actions.

Additive suppression of CS input-output in nonselected and task-irrelevant preparatory contexts

The Midpoint of CS input-output differed significantly across Context ($F_{3,730}$ = 11.48, P < 0.001). Specifically, context-dependent modulation of CS input-output was explained by an additive rightward shift of the Midpoint when the stimulated motor representation was task-irrelevant or nonselected for the forthcoming action compared to when it was selected (Figure 2d). The additive increase of the Midpoint during nonselected and irrelevant contexts was also greater than baseline, consistent with inhibition of CS input-output relative to intertrial rest[5]. This nonspecific and apparently uniform suppression of irrelevant and nonselected motor representations may reflect widespread noise reduction within the CS pathway[32]. Importantly, muscle activity preceding TMS was not different across contexts or from baseline (Figure S2), indicating that differences in alpha motoneuron depolarization did not explain the modulation of CS input-output[33]. These findings extend previous studies of preparatory inhibition and are consistent with a

mechanism for enhancing the contrast of selected motor representations through the suppression of background activity.

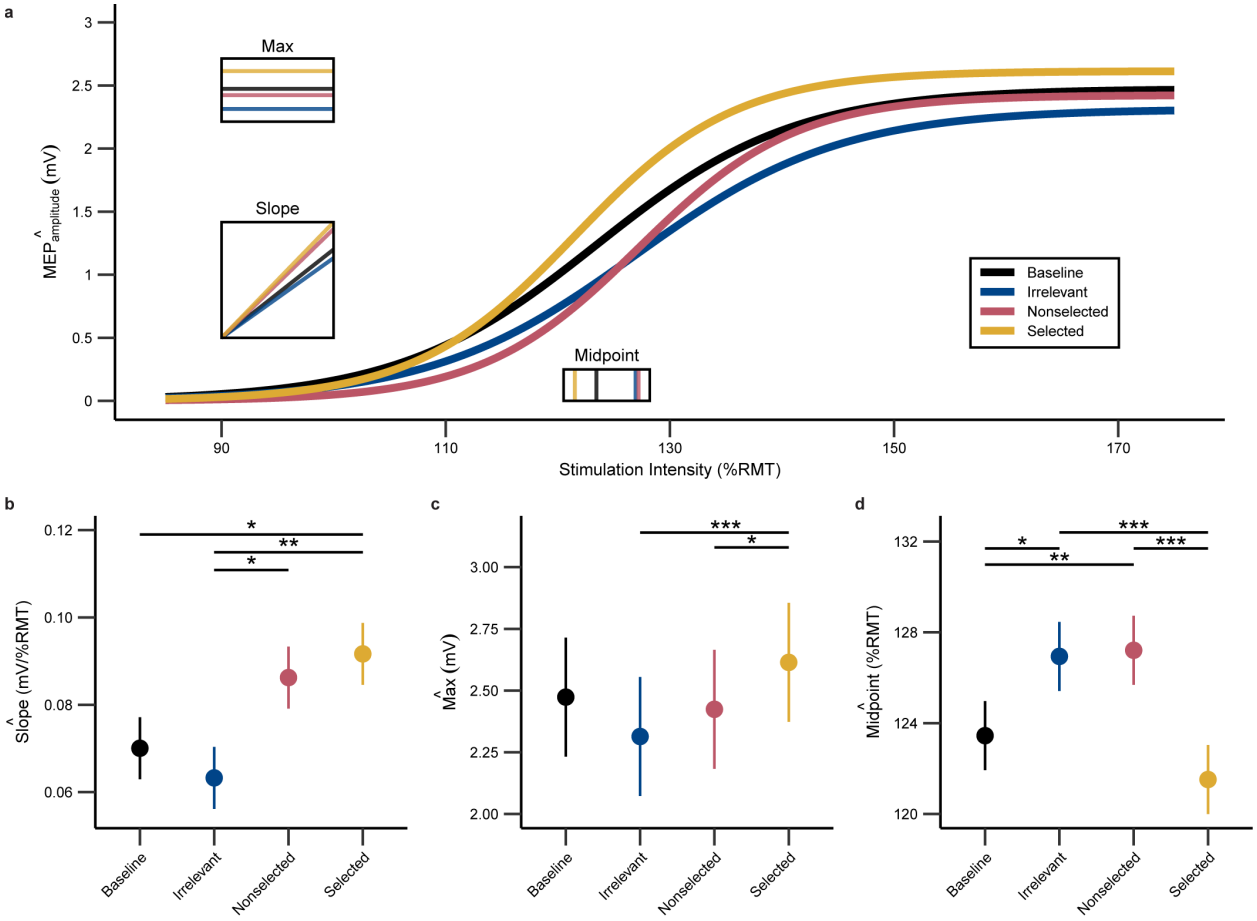


Figure 2: Modulation of CS input-output across goal-directed action preparation contexts. **a**, CS input-output curves across action preparation contexts. Insets indicate the estimated Max, Slope, and Midpoint parameters. **b**, Estimated Slope was greater in the selected context compared to baseline ($F_{1,730}$ = 5.42, P = 0.040) and the irrelevant context ($F_{1,730}$ = 9.76, P = 0.011). Estimated Slope in the nonselected context was also greater than the irrelevant context ($F_{1,730}$ = 5.87, P = 0.040) but not baseline ($F_{1,730}$ = 2.79, P = 0.143). There were no significant differences between baseline and irrelevant ($F_{1,730}$ = 0.95, P = 0.397) as well as nonselected and selected contexts ($F_{1,730}$ = 0.23, P = 0.628). **c**, Estimated Max was greater in the selected context compared to irrelevant ($F_{1,730}$ = 14.62, P = 0.001) and nonselected ($F_{1,730}$ = 6.44, P = 0.034) contexts, which did not differ from each other ($F_{1,730}$ = 1.89, P = 0.204). There were no differences between baseline and other contexts (all P > 0.050). **d**, Estimated Midpoint was greater in the irrelevant context than baseline ($F_{1,730}$ = 7.00, P = 0.012) and the selected context ($F_{1,730}$ = 18.54, P < 0.001). Estimated Midpoint in the nonselected context was also greater than baseline ($F_{1,730}$ = 9.65, P = 0.004) and the selected context ($F_{1,730}$ = 25.32, P < 0.001). There was no significant difference between nonselected and irrelevant ($F_{1,730}$ = 0.05, P = 0.828) and between baseline and selected contexts ($F_{1,730}$ = 2.50, P = 0.137). Data ranges represent mean ± SEM in panels b – d.

An interesting observation from the current study was the lack of MEP suppression in the selected context (Figure 3a). Previous TMS studies have observed *preparatory suppression* (i.e., reduced MEP amplitude below baseline during action preparation) across selected, nonselected, and task-irrelevant contexts, albeit variably[2]. Our finding of enhanced CS gain in task-relevant contexts may appear in conflict with inhibitory accounts[34]. However, previous studies often used a TMS intensity of ≤

120 %RMT and, thus, only captured CS output at the lower end of the input spectrum. By using a range of TMS intensities, we could model the entire CS input-output function, providing a more complete picture of the underlying processes. Mathematically, both additive and multiplicative changes in a sigmoidal input-output function would have complex effects on whether context-dependent modulation is captured as suppression or enhancement when input intensity is below or above the Midpoint (Figure 3b). We speculate that previous evidence of preparatory suppression of task-relevant motor representations may result from TMS intensities below the CS input-output Midpoint. Importantly, TMS may not mimic endogenous input to the CS pathway when transitioning from action preparation to execution, which remains open for further investigation.

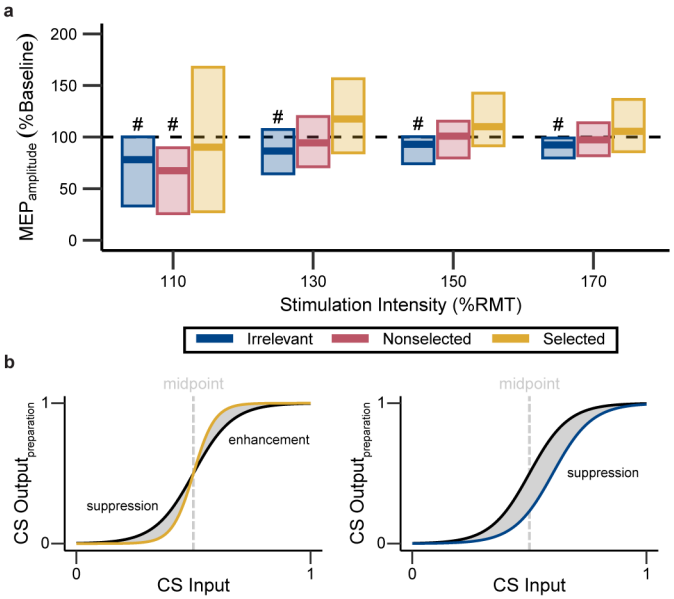


Figure 3: Preparatory suppression during goal-directed action preparation. **a**, Preparatory suppression, expressed as a reduced MEP amplitude relative to baseline, was observed during the irrelevant context across all stimulation intensities (110: $W = 615$, $P = 0.004$; 130: $W = 573$, $P = 0.029$; 150: $W = 608$, $P = 0.005$; 170: $W = 616$, $P = 0.004$), only at the 110 %RMT stimulation intensity during the nonselected context (110: $W = 644$, $P = 0.001$; 130: $W = 501$, $P = 0.372$; 150: $W = 411$, $P = 1.000$; 170: $W = 446$, $P = 1.000$), and at no stimulation intensity during the selected context (110: $W = 393$, $P = 1.000$; 130: $W = 238$, $P = 0.100$; 150: $W = 271$, $P = 0.296$; 170: $W = 280$, $P = 0.382$). Crossbar boxes indicate median hilows and the dashed horizontal line indicates baseline MEP amplitude. Statistical results were obtained from paired Wilcoxon-signed rank tests of mean MEP amplitude against baseline. **b**, Conceptual overview of how CS input-output modulation can reflect preparatory suppression or enhancement depending on CS input and modulation. Here, assuming fixed alternative parameters, a multiplicative increase would be captured as preparatory suppression or enhancement at input intensities below or above the midpoint, respectively. In contrast, an additive increase (i.e., rightward shift) would be captured as preparatory suppression irrespective of the input intensity relative to the midpoint.

Gain modulation of CS input-output across preparatory contexts is associated with reaction time

Participants responded accurately and quickly during the behavioral tasks. There were no significant differences in accuracy across the response options during either go (Go: $X^2_3 = 5.08$, $P = 0.166$) or catch ($X_2^3 = 3.93$, $P = 0.269$) trials, with a high average trial success indicating that participants performed the tasks correctly (Figure 4a). Reaction time (RT), calculated based on EMG burst onset, was measured during task trials without TMS to avoid the direct influence of stimulation on motor output[35]. RT differed across response options ($F_{1,114} = 10.18$, $P = 0.002$), with faster responses when the prepared

action involved a within-hand choice between the fingers of the dominant hand compared to a between-hand choice. However, RTs remained fast across all response alternatives (Figure 4b). Importantly, RTs were correlated between the two tasks (R = 0.38, P = 0.001), indicating individuals differed reliably in their RTs.

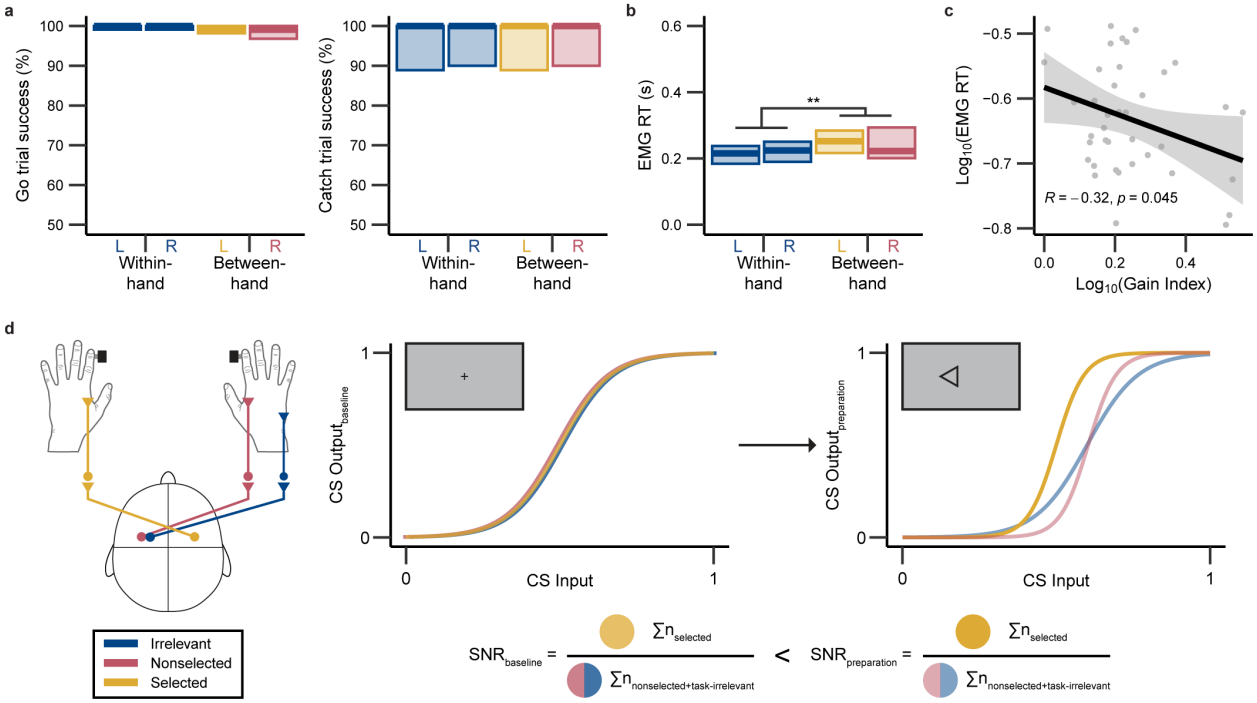


Figure 4: Behavioral performance and relationship to CS input-output gain modulation. **a**, Accuracy during go (left) catch (right) trials for which there was no significant effect of Response type on either measure (see Methods for calculation). **b**, A two-way linear mixed effects model indicated a significant fixed factor of Task on EMG RT, with faster responses in the within-hand compared to the between-hand task. There was no fixed effect of Side ($F_{1,114}$ = 0.17, P = 0.684) or a Task × Side interaction ($F_{1,114}$ = 2.88, P = 0.092). **c**, There was a significant negative Pearson correlation between Gain Index and EMG RT from non-TMS trials whereby participants with greater gain in task-relevant than task-irrelevant action preparation contexts were faster responders. Crossbar boxes indicate median hilows in all panels. **d**, CS input-output during action preparation depends upon task contexts. Schematized CS input-output plots represent the multiplicative increase in the selected and nonselected contexts and the additive increase in nonselected and task-irrelevant contexts. Speculatively, complementary additive and multiplicative changes can enhance the signal-to-noise ratio (SNR) between selected and bystander motor representations through divisive normalization to improve the fidelity of descending CS commands during action preparation.

Such interindividual differences in task performance may depend on the ability to modulate CS input-output during response preparation. We *post priori* calculated a gain modulation index to capture interindividual differences in CS input-output Slopes to evaluate whether the observed context-dependent gain adjustments correlated with task behavior. Briefly, the gain modulation index reflects differences in the Slope of CS input-output between task-relevant (i.e., selected and nonselected) and task-irrelevant contexts normalized to baseline (see Methods for detailed description). We compared this gain modulation index against RT and observed that participants with a larger gain modulation index had

204 faster RTs (Figure 4c). That is, participants who increased CS gain to task-relevant muscles,
205 comparatively to task-irrelevant muscles, were faster to initiate responses.

206 Recurrent neural network models of non-human primate motor cortex suggest that gain
207 modulation determines features of motor output, such as speed[20]. Our data provide corroborative
208 physiological evidence for these models by suggesting that gain modulation along the human CS
209 pathway during a preparatory state facilitates the execution of subsequent actions. Based on our data, we
210 propose that increased gain of task-relevant motor representations occurs against a backdrop of
211 suppressed nonselected and irrelevant motor representations to enhance the contrast between selected
212 and bystander motor representations[32]. We theorize this extension to existing models further promotes
213 the initiation of prepared responses by increasing signal-to-noise within the CS pathway via divisive
214 normalization (Figure 4d).

215 **Discussion**

216 Overall, the present study provides physiological evidence of multiplicative and additive neural
217 computations within the human CS pathway during goal-directed action preparation. Specifically, we
218 showed that the gain of behaviorally relevant motor representations (selected and non-selected)
219 increases against a background of additive suppression of nonselected and task-irrelevant motor
220 representations during goal-directed action preparation. Furthermore, the magnitude of gain modulation
221 was associated with behavioral output, such that stronger modulators were faster responders. These
222 findings have several implications for understanding state-dependent computations within the human CS
223 pathway during motor control.

224 First, the findings indicate canonical computations well-described in sensory cortices[23,24,36]
225 generalize to the human motor system. Previous work has established feature-based attention modulates
226 gain within visual cortices[37], and normalization in the human visual system further supports attentional
227 processes by theoretically separating figures from the ground[38]. Similar gain adjustments have been
228 observed in the auditory cortex to increase spectrotemporal contrast[39]. Computational models of
229 auditory[16] and visual[40] sensory systems further indicate specific roles of gain for normalization and may

230 mirror the contrast enhancement mechanism we propose operates within the CS pathway during action
231 preparation. Such state-dependent gain adjustments for contrast enhancement could facilitate the
232 transmission of descending signals along the CS pathway, similar to models of basal ganglia output for
233 action selection[41]. Importantly, while sensory and motor systems differ in their representational content
234 and anatomy, they share critical functional similarities for guiding behavior[42]. Therefore, contrast
235 enhancement via simultaneously increased gain of behaviorally relevant and suppression of background
236 neural representations may be a canonical motif for sculpting cortical circuit output.

237 The current findings also align with computational models of the motor cortex that indicate a
238 specific role of gain modulation in moderating movement features such as speed[20]. Such models are
239 typically based on electrophysiological recordings from a neuronal subpopulation in a target region. Here,
240 by controlling the input intensity and tailoring it to each participant, we demonstrate that signatures of
241 canonical neural computations are observable along the entire CS pathway. Our data can also inform
242 computational models of motor cortex by providing useful information about the dynamic range of
243 physiological outputs along with behavioral relationships in a human model. Translation of the context-
244 dependent approach to other model systems can help evaluate whether CS input-output adjustments
245 during an output-null (preparatory) motor state hasten the transition to an output-potent (execution) motor
246 state[7,43].

247 Simultaneous gain adjustments and the suppression of background activity along the CS pathway
248 may rely on cooperative subcortical-cortical mechanisms. For example, thalamic projections to the
249 prefrontal cortex selectively influence signal (figure) and noise (ground) to guide cued behavior in the
250 context of uncertainty via two distinct intracortical mechanisms[44]. Similar motifs may exist in thalamic
251 projections to M1 to modulate CS output[45]. According to this framework, both increased gain of selected
252 motor representations and suppressed background activity would arise from a modulatory influence of
253 intracortical inhibitory circuits[25]. Alternatively, inhibition of background activity may reflect the engagement
254 of CS projections to spinal inhibitory neurons to suppress muscles that, if activated, would interfere with
255 the execution of the prepared action[46]. Future experiments will be able to determine the neural
256 mechanisms by leveraging multimodal approaches to better characterize the multifaceted neuronal

257 response to noninvasive brain stimulation and by studying clinical populations known to have CS input-
258 output irregularities, such as Parkinson's disease[47].

259 In conclusion, we provided physiological evidence that goal-directed action preparation of finger
260 responses entails a mixture of input-output computations within the human motor system. These
261 computations are context-dependent, characterized by gain increases in task-relevant motor
262 representations against a backdrop of suppression in bystander motor representations, potentially
263 facilitating action initiation through contrast enhancement. The recapitulation of canonical neural
264 computations across motor and non-motor neuronal circuits suggests that these processes may
265 generalize throughout the human nervous system.

266 **Materials and Methods**

267 *Participants*

268 Forty-five young, neurologically healthy adults volunteered to participate. The study was
269 approved by the institutional review board of the University of Oregon and performed with each
270 participant's understanding and written consent. All participants self-reported as right-handed and were
271 screened for contraindications to TMS before data collection. Five participants were excluded from data
272 collection due to a high resting motor threshold (≥ 60% maximum stimulator output), making the TMS
273 input-output protocol unfeasible. An additional participant was excluded after data collection due to
274 noncompliance with task instructions. The remaining 39 participants completed the entire study and were
275 available for statistical analyses (20 females, 19 males; mean age 20.3 yrs., range 18 to 30 yrs.).

276 *Task protocol*

277 Goal-directed action preparation was assessed with an instructed-delay two-choice reaction time
278 task. Participants were seated comfortably in front of a computer monitor (59 Hz refresh rate, ~60 cm
279 viewing distance) with their hands palm-down and shoulder-width apart on a table surface. The task was
280 designed using Psychtoolbox-3 integrated with MATLAB (R2019b; The MathWorks) and a custom
281 response board (Makey Makey v.1.2; Joylabz) for accurate timing. Stimuli were synchronized with task

282 equipment through an analog-to-digital data-acquisition module (PCI-6620; National Instruments) and
283 verified during later offline analyses using photodiode recordings. The default task display consisted of a
284 blank grey background at trial onset. A fixation cue (centered white rectangle, 20 x 20 pixels) appeared
285 0.3 s after trial onset. A warning cue appeared 1 to 1.5 s after trial onset (randomly drawn from a uniform
286 distribution) and indicated the forthcoming response (hollow leftward or rightward pointed triangle, 140 x
287 150 pixels). An imperative stimulus (triangle filling white) appeared 0.9 s after the warning cue and lasted
288 until a button press was recorded or 0.8 s elapsed. Each trial was followed by an intertrial interval (blank
289 grey background) after the imperative stimulus and lasted until 7.6 s had elapsed from the trial onset.

290 The task was split into between-hand and within-hand choice variations with a counterbalanced
291 order across participants. Left and right imperative stimuli required button presses from the left and right
292 index fingers during the between-hand choice task and button presses from the right index and pinky
293 fingers during the within-hand task. The above design enabled assessment of CS output corresponding to
294 the left *first dorsal interosseous* (FDI) muscle representation at baseline (fixation period onset of between-
295 hand and within-hand tasks) and when it was task-irrelevant (within-hand), task-relevant but nonselected
296 (between-hand$_{right}$), as well as task-relevant and selected (between-hand$_{left}$). Participants were instructed
297 to relax during the fixation period, to prepare but not execute the forthcoming response during the cue
298 period, and to execute the cued response as fast as possible when the imperative stimulus was
299 presented. A subset of no-go catch trials (i.e., no imperative stimulus; 8% of trials) was included to
300 discourage participants from responding prematurely in anticipation of the imperative stimulus. There
301 were 238 trials evenly distributed across left and right imperative stimuli and split across 4 blocks,
302 alternating between 59 and 60 trials for each choice variation. The entire experiment lasted 2.5 hours on
303 average.

304 *Electromyography*

305 Surface electromyography (EMG) was collected from the left and right FDI and the right *abductor*
306 *digiti minimi* (ADM) using bipolar Ag-AgCl surface electrodes (Delsys Incorporated). These hand muscles
307 corresponded to the primary agonist muscles for between-hand$_{left}$ (left FDI), between-hand$_{right}$ and within-

308 $hand_{left}$ (right FDI), and within-$hand_{right}$ (right ADM) choice alternatives. An additional EMG electrode was
309 positioned over the C3 vertebra of the neck to record TMS artifacts, and a shared ground electrode was
310 positioned on the left ulnar styloid process. EMG activity was amplified (×1000), bandpass filtered (20 –
311 450 Hz), and sampled at 5000 Hz with a Bagnoli-8 amplifier (Delsys Incorporated) connected to a BNC-
312 2090A terminal block (National Instruments). EMG data were recorded on each trial for 4 s from onset
313 using the MATLAB-based VETA toolbox[48] and stored for later offline analyses.

314 *Transcranial Magnetic Stimulation*

315 Single-pulse TMS was delivered using a 70 mm figure-of-eight coil connected to a MagStim 200[2]
316 stimulator (MagStim Ltd.). The coil was oriented to induce a posterior-to-anterior flowing current in the
317 underlying cortical tissue. The optimal coil position ('motor hotspot') over right M1 for eliciting a motor
318 evoked potential (MEP) in the left FDI was then assessed and marked on the scalp. The resting motor
319 threshold (RMT) of left FDI was defined as the minimum stimulator output required to elicit an MEP
320 amplitude of at least 0.05 mV at rest using a maximum-likelihood parameter estimation by sequential
321 testing strategy[49]. TMS was delivered across a range of stimulation intensities relative to a participant's
322 RMT (90%, 110%, 130%, 150%, and 170%; 14 stimuli per intensity) to derive CS input-output curves.
323 The TMS input-output protocol was performed at baseline (start of fixation period) and during action
324 preparation (100 ms before the imperative stimulus) in the between-hand and within-hand tasks.

325 *Dependent measures*

326 Data were preprocessed using the VETA toolbox in two stages. In the first stage, EMG bursts,
327 MEPs, and TMS artifacts were marked with the automated detection *findEMG.m* function. In the second
328 stage, data was manually reviewed using the *visualizeEMG.m* function to ensure the accuracy of EMG
329 measures. Here, EMG data contaminated by artifacts were rejected and EMG burst onset timings were
330 adjusted when required. Dependent measures were then extracted with custom scripts in MATLAB.
331 Behavioral measures were analyzed from non-TMS trials to avoid the influence of TMS on response
332 times. Go success was calculated as the percentage of go trials where a correct response was made
333 within 0.8 s from imperative stimulus onset. Catch trial success was calculated as the percentage of no-

go trials where the cued response was withheld correctly. Trials with behavioral RTs less than 100 ms or EMG RTs less than 50 ms were then marked as premature responses and excluded from subsequent analyses (*M* = 2.2 % of all trials). There was a strong positive correlation between behavioral and EMG RT ($r = 0.68$, $P < 0.001$), as such, we report only EMG-based RTs for subsequent analyses since it is free from electromechanical delays.

Dependent measures from stimulated trials during the between-hand and within-hand choice tasks included pre-trigger root mean square EMG and MEP amplitudes. Trials with TMS were excluded when pre-trigger root mean square EMG activity exceeded 30 μV in a -30 to -5 ms pre-TMS window or when outlier MEP amplitudes were identified, defined as values more than three scaled MAD from the median (*M* = 11.4 % of stimulated trials). The mean pre-TMS root mean square EMG activity of the left FDI was calculated from the remaining trials for each preparation context, collapsed across stimulation intensities. CS output of the left FDI was calculated as the mean MEP peak-to-peak amplitude for each preparation context and stimulation intensity separately.

Statistical analyses

Statistical analyses were performed using R software (Version 4.3.0). The normality of data and model-averaged residual plots were visually inspected where appropriate. Logarithmic transformations were used in the case of non-normally distributed data. The alpha level was set to 0.05 for statistical significance. P-values for pairwise post-hoc comparisons were adjusted for multiple comparisons using the Benjamini-Hochberg method to control the false discovery rate at 5%. In-text data are presented as nontransformed mean ± standard deviation unless otherwise specified.

Go and catch trial success were both analyzed using an omnibus Friedman test with the factor of Response (within-hand$_{left}$, within-hand$_{right}$, between-hand$_{left}$, between-hand$_{right}$) to verify task performance was high and consistent across response alternatives. EMG RT was analyzed using a linear mixed-effects model with fixed effects of Task (within-hand, between-hand) and Side (left, right) and random effect of participant specificity to verify participants were responding fast and to determine any differences between tasks and response alternatives.

We employ a population-based nonlinear mixed-effects model to determine the influence of action preparation context on the CS input-output relationship. A modified three-parameter Boltzmann sigmoid function[50] was used to model the nonlinear input-output relationship between TMS intensity and MEP amplitude:

$$MEP(\%RMT) = 0 + Max/\{1 + exp[4 * Slope * (Midpoint - \%RMT)/Max]\}$$

where MEP(%RMT) is the predicted peak-to-peak amplitude at a given TMS intensity, calculated as a function of Max (upper plateau), Midpoint (inflection point), and Slope (maximum rate of change) input-output parameter estimates. The lower plateau of CS input-output was constrained to 0 mV for greater biological plausibility (i.e., MEP amplitude cannot be negative and should always be 0 mV at a 0% TMS intensity) and provided a better fit of the data compared to an unconstrained model (constrained AIC: 1307.5, unconstrained AIC: 1317.0).

Initial parameter estimates for the nonlinear mixed-effects models were derived from pre-task resting state data to ensure independence between model optimization and statistical analyses. Specifically, initial estimates were set to mean MEP amplitude at 170% RMT for Max, median stimulation intensity for Midpoint (i.e., 130% RMT), and the linear gradient between 110% and 130% RMT for Slope based on visual inspection of averaged MEP amplitude data. We then applied nonlinear least squares modeling (*nls* function in R) with these initial parameter estimates to obtain corresponding optimal parameter estimates of 2.34 mV for Max, 125.6 %RMT for Midpoint, and 0.055 mV/%RMT for Slope with an iterative numerical integration procedure. These estimates were subsequently applied to a model of in-task TMS data (*nlme* function in R). Max, Midpoint, and Slope parameters were estimated from this random intercept model to account for participant variability. The model was then updated with the fixed effect of Context (baseline, irrelevant, nonselected, selected) to examine the influence of action preparation context on CS input-output. Updated models with the fixed effect of Task Order (within-hand first, between-hand first) or Sex (male, female) were also included to determine any effects of task order or participant sex on CS input-output parameters.

A linear mixed-effects model with a fixed effect of Context (baseline, irrelevant, nonselected, selected) was used to confirm modulation of CS input-output was not attributable to shifts in pre-TMS root mean square EMG activity.

We estimated a Gain Index for each participant to determine brain-behavior correlations between CS input-output modulation and task performance. Direct parameter estimations could not be used from the population-based model since variance is shared across participants and, thus, interindividual differences between contexts are not meaningful. As such, we estimated the Gain Index by 1) extracting the estimated Midpoint for each context and participant separately, 2) determining the two neighboring input TMS intensities (e.g., 110% and 130% RMT if the estimated Midpoint was within these bounds), 3) estimating the linear gradient (slope) between the mean MEP amplitudes from their individual data corresponding to the selected input TMS intensities, and 4) calculating the estimated difference between task-relevant contexts (average of selected and nonselected contexts) and task-irrelevant contexts, normalized to baseline, i.e. $(slope_{relevant} - slope_{irrelevant})/slope_{baseline}$. The association between mean EMG RT, collapsed across all response types, and the Gain Index was then tested using Pearson's correlation.

Data availability statement

The data and reproducible code supporting this study's findings will be made publicly available in OSF upon publication, reference number osf.io/837ms.

Acknowledgments: The authors thank Kate Bakken, Mitch Fisher, Charlie Lewkowitz, Hayami Nishio, Michelle Ortman, and Tania Sarabia for their help with data collection and preprocessing. The authors also thank Luca Mazzucato and Richard Ivry for their helpful feedback on this manuscript. This research was supported by NIH grant NINDS R01NS123115.

Author contributions: Conceptualization, C.G.W and I.G.; Methodology, C.G.W, T.N., and I.G.; Formal Analysis, C.G.W. and T.N.; Investigation, C.G.W. and C.H.; Writing – Original Draft, C.G.W. and I.G.; Writing – Reviewing & Editing, C.G.W, T.N., C.H., and I.G.; Visualization, C.G.W.; Supervision, I.G.; Funding acquisition, I.G.

Declaration of interests: The authors declare no competing interests.

411 **References**

412 1. Xu, J., Mawase, F. & Schieber, M. H. Evolution, biomechanics, and neurobiology converge to
413 explain selective finger motor control. *Physiol Rev* **104**, 983–1020 (2024).

414 2. Bundt, C. & Huster, R. J. Corticospinal excitability reductions during action preparation and action
415 stopping in humans: Different sides of the same inhibitory coin? *Neuropsychologia* **195**, 108799
416 (2024).

417 3. Duque, J., Greenhouse, I., Labruna, L. & Ivry, R. B. Physiological Markers of Motor Inhibition
418 during Human Behavior. *Trends Neurosci* **40**, 219–236 (2017).

419 4. Prut, Y. & Fetz, E. E. Primate spinal interneurons show pre-movement instructed delay activity.
420 *Nature* **401**, 590–594 (1999).

421 5. Derosiere, G. & Duque, J. Tuning the Corticospinal System: How Distributed Brain Circuits Shape
422 Human Actions. *The Neuroscientist* **26**, 359–379 (2020).

423 6. Wang, X. *et al.* Deconstruction of Corticospinal Circuits for Goal-Directed Motor Skills. *Cell* **171**,
424 440-455.e14 (2017).

425 7. Churchland, M. M. & Shenoy, K. V. Preparatory activity and the expansive null-space. *Nat Rev*
426 *Neurosci* **25**, 213–236 (2024).

427 8. Greenhouse, I. Inhibition for gain modulation in the motor system. *Exp Brain Res* **240**, 1295–1302
428 (2022).

429 9. Zagha, E., Ge, X. & McCormick, D. A. Competing Neural Ensembles in Motor Cortex Gate Goal-
430 Directed Motor Output. *Neuron* **88**, 565–577 (2015).

431 10. Soteropoulos, D. S. Corticospinal gating during action preparation and movement in the primate
432 motor cortex. *J Neurophysiol* **119**, 1538–1555 (2018).

433 11. Merchant, H., Naselaris, T. & Georgopoulos, A. P. Dynamic Sculpting of Directional Tuning in the
434 Primate Motor Cortex during Three-Dimensional Reaching. *The Journal of Neuroscience* **28**,
435 9164–9172 (2008).

436 12. Kaufman, M. T., Churchland, M. M. & Shenoy, K. V. The roles of monkey M1 neuron classes in
437 movement preparation and execution. *J Neurophysiol* **110**, 817–825 (2013).

438 13. Kaufman, M. T. *et al.* Roles of Monkey Premotor Neuron Classes in Movement Preparation and
439 Execution. *J Neurophysiol* **104**, 799–810 (2010).

440 14. Lee, S.-H. *et al.* Activation of specific interneurons improves V1 feature selectivity and visual
441 perception. *Nature* **488**, 379–383 (2012).

442 15. Katzner, S., Busse, L. & Carandini, M. $GABA_A$ Inhibition Controls Response Gain in Visual
443 Cortex. *The Journal of Neuroscience* **31**, 5931–5941 (2011).

444 16. Mischler, G., Keshishian, M., Bickel, S., Mehta, A. D. & Mesgarani, N. Deep neural networks
445 effectively model neural adaptation to changing background noise and suggest nonlinear noise
446 filtering methods in auditory cortex. *Neuroimage* **266**, 119819 (2023).

447 17. Pi, H.-J. *et al.* Cortical interneurons that specialize in disinhibitory control. *Nature* **503**, 521–524
448 (2013).

449 18. Salinas, E. & Thier, P. Gain Modulation. *Neuron* **27**, 15–21 (2000).

450 19. Hillyard, S. A., Vogel, E. K. & Luck, S. J. Sensory gain control (amplification) as a mechanism of
451 selective attention: electrophysiological and neuroimaging evidence. *Philos Trans R Soc Lond B*
452 *Biol Sci* **353**, 1257–1270 (1998).

453 20. Stroud, J. P., Porter, M. A., Hennequin, G. & Vogels, T. P. Motor primitives in space and time via
454 targeted gain modulation in cortical networks. *Nat Neurosci* **21**, 1774–1783 (2018).

455 21. Pouget, A. & Snyder, L. H. Computational approaches to sensorimotor transformations. *Nat*
456 *Neurosci* **3**, 1192–1198 (2000).

457 22. Welniarz, Q., Dusart, I. & Roze, E. The corticospinal tract: Evolution, development, and human
458 disorders. *Dev Neurobiol* **77**, 810–829 (2017).

459 23. Silver, R. A. Neuronal arithmetic. *Nat Rev Neurosci* **11**, 474–489 (2010).

460 24. Mitchell, S. J. & Silver, R. A. Shunting Inhibition Modulates Neuronal Gain during Synaptic
461 Excitation. *Neuron* **38**, 433–445 (2003).

462 25. Ferguson, K. A. & Cardin, J. A. Mechanisms underlying gain modulation in the cortex. *Nat Rev*
463 *Neurosci* **21**, 80–92 (2020).

464 26. Carandini, M. & Heeger, D. J. Normalization as a canonical neural computation. *Nat Rev Neurosci*
465 **13**, 51–62 (2012).

466 27. Georgopoulos, A. P. & Stefanis, C. N. Local shaping of function in the motor cortex: Motor
467 contrast, directional tuning. *Brain Res Rev* **55**, 383–389 (2007).

468 28. Bestmann, S. & Duque, J. Transcranial Magnetic Stimulation. *The Neuroscientist* **22**, 392–405
469 (2016).

470 29. Kukke, S. N., Paine, R. W., Chao, C.-C., de Campos, A. C. & Hallett, M. Efficient and Reliable
471 Characterization of the Corticospinal System Using Transcranial Magnetic Stimulation. *Journal of*
472 *Clinical Neurophysiology* **31**, 246–252 (2014).

473 30. Wood, K. C., Blackwell, J. M. & Geffen, M. N. Cortical inhibitory interneurons control sensory
474 processing. *Curr Opin Neurobiol* **46**, 200–207 (2017).

475 31. Shine, J. M., Aburn, M. J., Breakspear, M. & Poldrack, R. A. The modulation of neural gain
476 facilitates a transition between functional segregation and integration in the brain. *Elife* **7**, (2018).

477 32. Greenhouse, I., Sias, A., Labruna, L. & Ivry, R. B. Nonspecific Inhibition of the Motor System
478 during Response Preparation. *Journal of Neuroscience* **35**, 10675–10684 (2015).

479 33. Devanne, H., Lavoie, B. A. & Capaday, C. Input-output properties and gain changes in the human
480 corticospinal pathway. *Exp Brain Res* **114**, 329–338 (1997).

481 34. Ibáñez, J., Hannah, R., Rocchi, L. & Rothwell, J. C. Premovement Suppression of Corticospinal
482 Excitability may be a Necessary Part of Movement Preparation. *Cerebral Cortex* **30**, 2910–2923
483 (2020).

484 35. Foltys, H. *et al.* Motor control in simple bimanual movements: a transcranial magnetic stimulation
485 and reaction time study. *Clinical Neurophysiology* **112**, 265–274 (2001).

486 36. Salinas, E. & Sejnowski, T. J. Book Review: Gain Modulation in the Central Nervous System:
487 Where Behavior, Neurophysiology, and Computation Meet. *The Neuroscientist* **7**, 430–440 (2001).

488 37. Treue, S. & Trujillo, J. C. M. Feature-based attention influences motion processing gain in
489 macaque visual cortex. *Nature* **399**, 575–579 (1999).

490 38. Bloem, I. M. & Ling, S. Normalization governs attentional modulation within human visual cortex.
491 *Nat Commun* **10**, 5660 (2019).

492 39. Rabinowitz, N. C., Willmore, B. D. B., Schnupp, J. W. H. & King, A. J. Contrast Gain Control in
493 Auditory Cortex. *Neuron* **70**, 1178–1191 (2011).

494 40. Polack, P.-O., Friedman, J. & Golshani, P. Cellular mechanisms of brain state–dependent gain
495 modulation in visual cortex. *Nat Neurosci* **16**, 1331–1339 (2013).

496 41. Nambu, A., Tokuno, H. & Takada, M. Functional significance of the cortico–subthalamo–pallidal
497 'hyperdirect' pathway. *Neurosci Res* **43**, 111–117 (2002).

498 42. Hatsopoulos, N. G. & Suminski, A. J. Sensing with the Motor Cortex. *Neuron* **72**, 477–487 (2011).

499 43. Hannah, R., Cavanagh, S. E., Tremblay, S., Simeoni, S. & Rothwell, J. C. Selective Suppression
500 of Local Interneuron Circuits in Human Motor Cortex Contributes to Movement Preparation. *The*
501 *Journal of Neuroscience* **38**, 1264–1276 (2018).

502 44. Mukherjee, A., Lam, N. H., Wimmer, R. D. & Halassa, M. M. Thalamic circuits for independent
503 control of prefrontal signal and noise. *Nature* **600**, 100–104 (2021).

504 45. Halassa, M. M. & Sherman, S. M. Thalamocortical Circuit Motifs: A General Framework. *Neuron*
505 **103**, 762–770 (2019).

506 46. Griffin, D. M. & Strick, P. L. The motor cortex uses active suppression to sculpt movement. *Sci*
507 *Adv* **6**, (2020).

508 47. Bologna, M. *et al.* Neurophysiological correlates of bradykinesia in Parkinson's disease. *Brain* **141**,
509 2432–2444 (2018).

510 48. Jackson, N. & Greenhouse, I. VETA: An Open-Source Matlab-Based Toolbox for the Collection
511 and Analysis of Electromyography Combined With Transcranial Magnetic Stimulation. *Front*
512 *Neurosci* **13**, (2019).

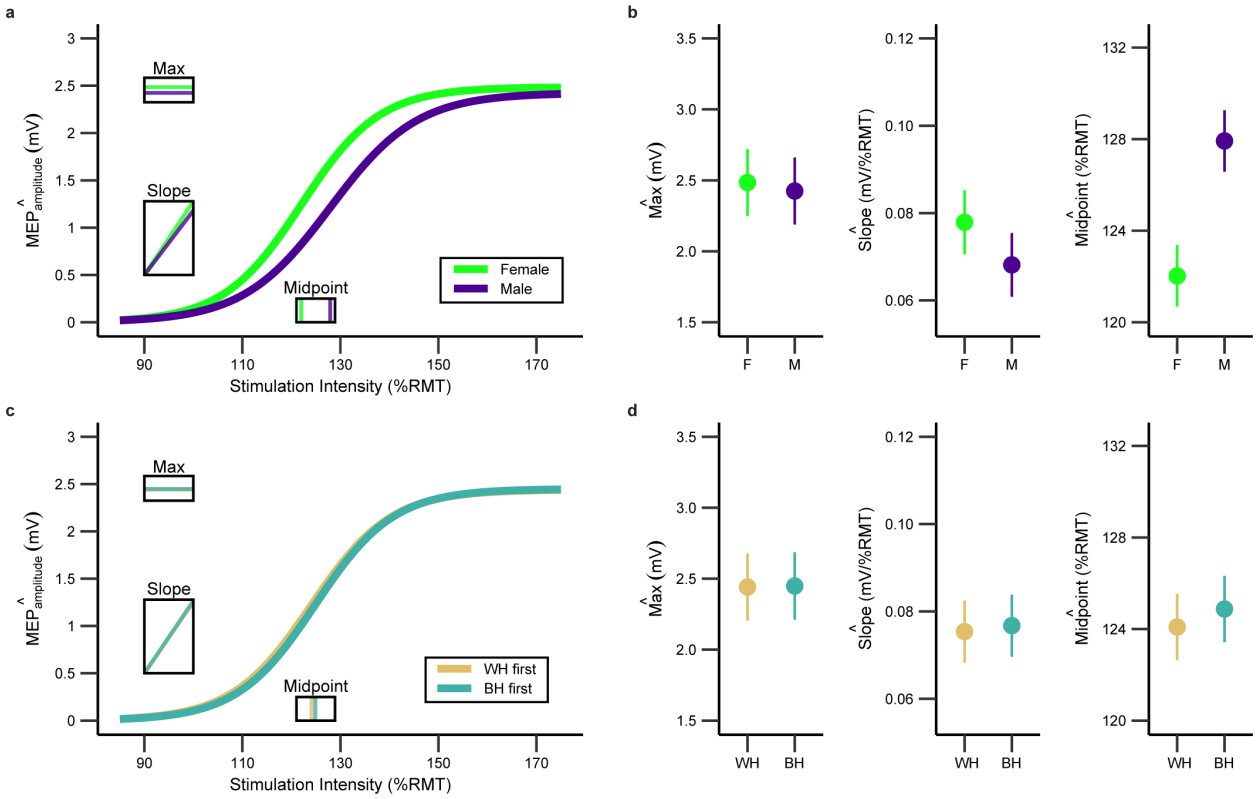
513 49. Silbert, B. I., Patterson, H. I., Pevcic, D. D., Windnagel, K. A. & Thickbroom, G. W. A comparison
514 of relative-frequency and threshold-hunting methods to determine stimulus intensity in transcranial
515 magnetic stimulation. *Clinical Neurophysiology* **124**, 708–712 (2013).

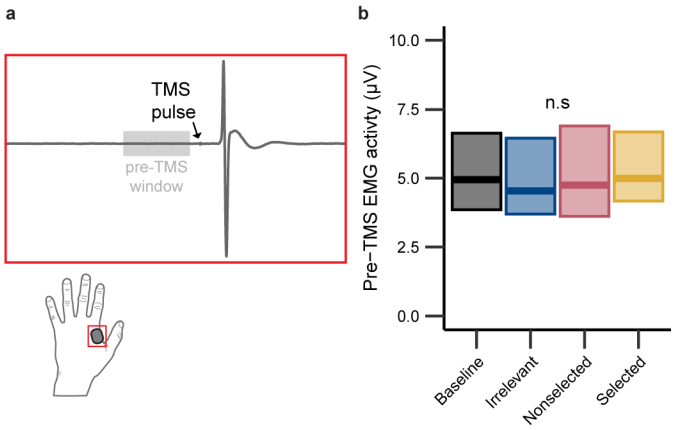
516 50. Heusser, K. *et al.* Baroreflex Curve Fitting Using a WYSIWYG Boltzmann Sigmoidal Equation.
517 *Front Neurosci* **15**, (2021).

518

519

Supplementary information



Supplementary Figure 1: Modulation of CS input-output across participant sex and task order. **a**, CS input-out curves derived from the Sex model, which did not provide a better fit of the data than the null model (Sex AIC: 1319.1, Null AIC: 1312.9). **b**, There were no significant effects of Sex on estimated Max ($F_{1,736}$ = 0.61, P = 0.434), Slope ($F_{1,736}$ = 0.27, P = 0.605), or Midpoint ($F_{1,736}$ = 2.85, P = 0.092) CS input-output parameters. **c**, CS input-output curves derived from the Order model did not fit the data better than the null model (Order AIC: 1320.1). **d**, There were no significant effects of Order (WH: within-hand; BH: between-hand) on estimated Max ($F_{1,736}$ = 0.04, P = 0.844), Slope ($F_{1,736}$ < 0.01, P = 0.944), or Midpoint ($F_{1,736}$ = 0.02, P = 0.876) CS input-output parameters. Insets indicate estimated population means for the Max, Slope, and Midpoint parameters, and data ranges represent mean ± SEM.

Supplementary Figure 2: Pre-TMS muscle activity during goal-directed action preparation. **a**, Pre-TMS muscle activity was calculated as the root mean square of electromyographic activity in a -30 to -5 ms pre-TMS pulse window. **b**, There was no significant effect of Context on pre-TMS muscle activity ($F_{3,144}$ = 0.58, P = 0.629), which was below 10 μV in all contexts and indicated that participants' muscles rested during action preparation.