Inhibition during response preparation is sensitive to response complexity

Ian Greenhouse, Dylan Saks, Timothy Hoang and Richard B. Ivry

J Neurophysiol 113:2792-2800, 2015. First published 25 February 2015; doi:10.1152/jn.00999.2014

Journal of Neurophysiology publishes original articles on the function of the nervous system. It is published 12 times a year (monthly) by the American Physiological Society, 9650 Rockville Pike, Bethesda MD 20814-3991. ISSN: 0022-3077, ESSN: 1522-1598. Visit our website at http://www.the-aps.org/.

J Neurophysiol 113: 2792–2800, 2015.
First published February 25, 2015; doi:10.1152/jn.00999.2014.

Inhibition during response preparation is sensitive to response complexity

Ian Greenhouse, Dylan Saks, Timothy Hoang, and Richard B. Ivry
Department of Psychology, University of California, Berkeley, California

Submitted 11 December 2014; accepted in final form 24 February 2015

Greenhouse I, Saks D, Hoang T, Ivry RB. Inhibition during response preparation is sensitive to response complexity. *J Neurophysiol* 113: 2792–2800, 2015. First published February 25, 2015; doi:10.1152/jn.00999.2014.—Motor system excitability is transiently suppressed during the preparation of movement. This preparatory inhibition is hypothesized to facilitate response selection and initiation. Given that demands on selection and initiation processes increase with movement complexity, we hypothesized that complexity would influence preparatory inhibition. To test this hypothesis, we probed corticospinal excitability during a delayed-response task in which participants were cued to prepare right- or left-hand movements of varying complexity. Single-pulse transcranial magnetic stimulation was applied over right primary motor cortex to elicit motor evoked potentials (MEPs) from the first dorsal interosseous (FDI) of the left hand. MEP suppression was greater during the preparation of responses involving coordination of the FDI and adductor digiti minimi relative to easier responses involving only the FDI, independent of which hand was cued to respond. In contrast, this increased inhibition was absent when the complex responses required sequential movements of the two muscles. Moreover, complexity did not influence the level of inhibition when the response hand was fixed for the trial block, regardless of whether the complex responses were performed simultaneously or sequentially. These results suggest that preparatory inhibition contributes to response selection, possibly by suppressing extraneous movements when responses involve the simultaneous coordination of multiple effectors.

response preparation; inhibition; TMS; response complexity; motor control

RESPONSE PREPARATION ENTAILS the transient inhibition of the motor system. Signatures of this inhibition have been observed in studies that use transcranial magnetic stimulation (TMS) to elicit motor evoked potentials (MEPs) during the preparatory period of delayed-response tasks (Duque and Ivry 2009; Duque et al. 2010, 2012, 2014; Hasbroucq et al. 1997, 1999a, 1999b; Labruna et al. 2014; Sinclair and Hammond 2008, 2009; van den Hurk et al. 2007). MEP amplitudes are consistently reduced during this preparatory period relative to resting baseline measurements. This effect has been attributed to two distinct mechanisms (Duque et al. 2010, 2012). The first mechanism is hypothesized to facilitate the selection of appropriate responses by suppressing the representations of undesired responses, a process that has been referred to as "competition resolution." The second mechanism is hypothesized to reflect the suppression of the selected response to prevent premature movement initiation, a process that has been referred to as "impulse control." In the present work, we set out to test whether the complexity of a response influences the level of inhibition associated with one or both of these mechanisms.

Address for reprint requests and other correspondence: I. Greenhouse, Dept. of Psychology, Univ. of California, Berkeley, 3210 Tolman Hall, Berkeley, CA 94720-1650 (e-mail: igreenhouse@berkeley.edu).

Neuroimaging studies have consistently shown that activation across many areas of the cortex, including sensorimotor cortex, increases as a function of movement complexity (Rao et al. 1993; Shibasaki et al. 1993; Verstynen et al. 2005; Wexler et al. 1997). Moreover, the influence of complexity is not restricted to contralateral motor cortex, but is also pronounced in ipsilateral motor cortex (Hackley and Miller 1995; Shibasaki et al. 1993; Verstynen and Ivry 2011; Verstynen et al. 2005). The greater recruitment of ipsilateral motor cortex associated with complex responses may reflect a spillover from the opposite hemisphere when preparatory processes are taxed. In support of this hypothesis, when people plan a complex sequence of unilateral movements (Verstynen and Ivry 2011) or a coordinated movement of the upper and lower limbs (van den Berg et al. 2011), MEPs are larger in homologous muscles of the resting hand. This spillover may arise from interhemispheric connections between homologous muscles (Kanouchi et al. 1997; Kobayashi et al. 2003) or the engagement of bihemispheric planning processes (Cramer et al. 1999; Hanakawa et al. 2005; Shibasaki et al. 1993; Verstynen et al. 2005). Moreover, as the complexity of movement execution increases, greater inhibition may be required to uncouple the two hands (Meyer-Lindenberg et al. 2002), with failures of this form of inhibition underlying the manifestation of mirror movements (Verstynen and Ivry 2011).

Given the pronounced effects of movement complexity on cortical dynamics, both within and between hemispheres, we set out to examine the relevance of complexity on inhibitory mechanisms that operate during movement preparation. Participants were required, in separate blocks, to prepare either an easy, single-effector response or a more complex response requiring coordinated gestures of two effectors. We used TMS to probe motor excitability during the preparation of each type of response and compared trials in which the targeted muscle was either involved or not involved in the planned response. We hypothesized that competition resolution would be sensitive to response complexity, with greater inhibition observed in the nonselected effector when the task required a more complex movement. This prediction was based on the assumption that more inhibition would be required to offset the bilateral recruitment of the motor pathways for complex movements. In contrast, we did not expect impulse control to be sensitive to response complexity and thus predicted that inhibition of the selected effector would be similar for easy and complex responses. This prediction was based on the assumption that constraints on movement initiation would be comparable.

The convention in previous studies has been to use an intermanual choice reaction time (RT) task (Duque et al. 2010, 2012; Labruna et al. 2014). We opted to focus on intermanual competition in the current study, providing an opportunity to replicate past work as part of our extension into the study of

response complexity. However, in addition to our basic choice RT tasks in which the required movements varied across trials within a block, we also included simple RT blocks in which the same movement was repeated on every trial. If inhibition of the nonselected effector reflects the operation of a process involved in resolving response competition, we would expect to see diminished inhibition in the simple RT condition, independent of response complexity.

METHODS

Participants. Twenty-four healthy young adults participated in the study, 12 in *experiment 1* (age 22.4 ± 3.0 yr, 3 female, 2 left handed) and a different group of 12 participants in *experiment 2* (age 21.4 ± 1.9 yr, 1 female, all right handed). Participants provided informed consent before the start of the study under a protocol approved by the IRB of the University of California, Berkeley.

Task. We used a delayed-response task similar to that employed in previous studies (Duque et al. 2010, 2012; Labruna et al. 2014; see Fig. 1*A*). Participants were seated comfortably in front of a computer monitor with their hands palm down on a pillow in their lap. Each trial began with the presentation of a fixation stimulus for 100 ms, followed by a blank screen for 600 ms. An informative cue in the form of a bracket opening to the left or right was then presented, indicating that the forthcoming response should be performed with the left or right hand, respectively. The cue remained visible for 900 ms, and participants were instructed to prepare the cued response during this preparatory period. At the end of this period, an imperative stimulus was added to the display. On 81% of the trials, this stimulus was an "O" and signaled to the participant to produce the prepared response. On the remaining 19% of trials, the imperative was an "X"; for these trials, the participant was instructed to withhold their planned response. These "catch" trials were included to limit anticipatory responses. The display was blanked 300 ms after the onset of the imperative stimulus and initiated a variable intertrial interval (3,000-3,500 ms, uniform distribution).

In each experiment participants completed 8 blocks of 42 trials each. Four of the blocks required making a choice between the two hands. During these choice RT blocks, the cue indicated on a trial-to-trial basis whether to prepare a right- or left-hand response. Each hand was cued on 21 trials per bock in a random order. The other four blocks did not involve a choice, with the response hand fixed for the entire block (simple RT: 2 blocks left hand, 2 blocks right hand). During these blocks, the cue indicated the preparation of the same response on every trial. The blocks were further divided by whether responses were easy or complex. Easy responses in both experiments consisted of a lateral movement of the specified index finger toward the midline. In *experiment 1*, complex responses required that the same lateral movement of the index finger be performed simultaneously with a downward movement of the pinky finger on the same hand (Fig. 1*B*), a coordinated gesture that participants found demanding. In *experiment 2*, the complex responses required that these two gestures be performed sequentially rather than simultaneously. That is, the participant first produced the lateral movement with the index finger and then produced the downward movement with the pinky finger. As such, the initial gesture is essentially identical in the easy and complex conditions in *experiment 2*. In summary, each participant completed two complex choice blocks, two complex simple blocks (one with each hand), two easy choice blocks, and two easy simple blocks (one with each hand).

The order of conditions was randomized across participants with the two choice blocks within each level (easy or complex) adminis-

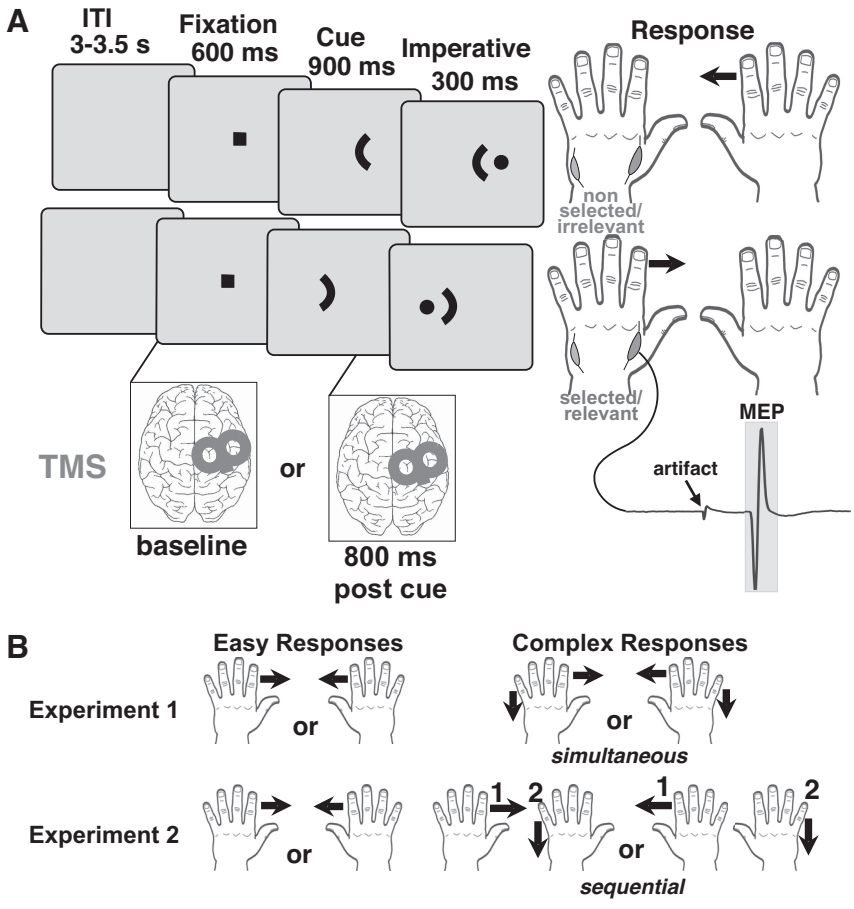

Fig. 1. *A*: delayed-response task. A fully informative cue (bracket) indicated which hand to prepare for a forthcoming speeded response. The delay period ended with the presentation of an imperative signal ("O") on go trials. The circle was replaced by an "X" on no-go catch trials. Transcranial magnetic stimulation (TMS) was delivered at fixation (baseline) or 100 ms before the imperative (delay). Motor evoked potentials (MEPs) were always recorded from the first dorsal interosseous (FDI) muscle in the left hand. *B*: in both experiments, easy responses involved lateral flexion of the left or right index finger. In *experiment 1*, complex responses involved lateral flexion of the index finger with simultaneously coordinated abduction of the pinky finger of the same hand. In *experiment 2*, complex responses involved the lateral flexion of the index finger followed sequentially by the abduction of the pinky of the same hand.

tered consecutively. Before each block, participants were instructed how to execute the desired responses and completed 10 trials of practice without any TMS. Participants were instructed to keep their hands at rest when not responding.

Transcranial magnetic stimulation. TMS was administered using a Magstim 200-2 stimulator (Magstim, Whitland, UK) with a 7-cm-diameter figure-of-eight coil. Stimulation was targeted at the right primary motor cortex (M1) to elicit MEPs from the left first dorsal interosseous (FDI) muscle, the agonist for the lateral index finger movement. Electromyographic (EMG) activity was also recorded from the right FDI and both abductor digiti minimi (ADM) muscles.

To target the M1 representation of the left FDI, TMS intensity was first set to 30% of maximum stimulator output, and the isocenter of the coil was positioned ~5 cm lateral and 2 cm anterior to the vertex, with the coil orientation ~45° off of the midline. A single TMS pulse was administered every 3 s, with stimulation intensity gradually increased and the coil repositioned, until reliable MEPs were observed. A marker was used to record the optimal stimulation position on participants' scalps. The resting motor threshold (RMT) was then determined by adjusting the TMS intensity until MEPs with peak-to-peak amplitude >50 μV were observed on 5 of 10 trials at the optimal target location. TMS intensity during the experimental tasks was fixed at 115% of the RMT. RMT was 44 ± 7% maximum stimulator output in *experiment 1* and 45 ± 7% maximum stimulator output in *experiment 2*.

In both experiments, TMS was either administered at fixation onset (baseline: 4 per block, or 32 trials total) or 800 ms after the cue onset (delay period: 24 per block, or 192 trials total). Each block also included 14 trials without TMS. These trials were included to measure EMG onset times in the absence of TMS. In *experiment 2*, we also obtained 40 MEP measurements at rest, 20 before the first experimental block and 20 after the last experimental block (interpulse interval 3,300 to 3,900 ms, uniform distribution). These pre- and posttask baseline measurements were included to assess changes in resting motor excitability during the experimental session.

Data analysis. The EMG data were analyzed offline with Matlab, using automated routines and visual inspection for the detection of artifacts. RT was defined as the interval from the onset of the imperative stimulus to the onset of the EMG burst in the responding FDI. EMG burst onset was defined as the first data point following the imperative onset in which the signal exceeded 0.1 mV and was 3 standard deviations (SD) greater than the mean of the rectified signal for the entire trial epoch. The same criteria were used for detecting responses following imperative and catch stimuli. Trials in which EMG activity was detected before the onset of the imperative (go or catch) were excluded from the analysis. For the majority of participants, zero or one trial in total was excluded due to premature or erroneous responses, and the maximum number of trials removed for any single participant was 10. On average, fewer than 1% of trials were excluded per condition in each experiment. Individual participants' mean RTs were used for statistical analyses in repeated-measures ANOVA with the factors TMS (delay vs. absent), response type (easy vs. complex), condition (choice vs. simple), and hand (left vs. right). EMG burst peak-to-peak amplitude was also calculated, and these data, limited to trials without TMS, were submitted to an ANOVA with the factors response type (easy vs. complex), condition (choice vs. simple), and hand (left vs. right).

To measure corticospinal excitability, we calculated the peak-to-peak amplitude of the MEPs elicited by the TMS pulses. MEP amplitudes were calculated on a trial-by-trial basis prior to averaging. For statistical analyses, mean MEP amplitudes during the delay period were converted to percentage scores, relative to mean baseline MEP amplitudes. Paired-samples one-tailed *t*-tests were used to compare MEP amplitudes in all conditions against baseline. We also compared the easy selected and easy nonselected conditions with a *t*-test, because this contrast provides a replication of the main conditions included in previous studies (Duque et al. 2010, 2012; Labruna et al. 2014). For each experiment, the MEP data were analyzed in a repeated-measures ANOVA with the factors response type (easy vs. complex), condition (choice vs. simple), and relevance (selected vs. nonselected/irrelevant). We grouped the irrelevant hand in the simple condition with the nonselected hand in the choice condition because in both cases the contralateral homologous muscles were used for the response. These conditions provide a test of changes in corticospinal excitability emerging in the ipsilateral motor cortex. Note that levels of the relevance factor in the MEP analysis and levels of the hand factor in the RT analysis refer to the same task conditions. We chose these different terminologies for the sake of clarity.

We also performed an exploratory analysis on the MEP and RT data between the two experiments. The easy responses in the two experiments were identical. Therefore, a mixed ANOVA restricted to these conditions was used to assess between-group differences and/or effects of task context given that the complex responses differed between the two experiments. This ANOVA included the between-subject factor experiment (E1 vs. E2) and within-subject factors condition (choice vs. simple) and relevance (selected vs. nonselected/irrelevant). To compare the two types of complex responses, we calculated an MEP difference score (complex − easy) for each pair of response conditions (i.e., complex choice − easy choice and complex simple − easy simple for selected and nonselected/irrelevant responses). These difference scores were submitted to the same mixed ANOVA as employed in the between-experiment analysis of the easy conditions.

RESULTS

Experiment 1. The EMG-based RT data for FDI responses are presented in Fig. 2*A*. A repeated-measures ANOVA showed a main effect of TMS [$F(1,11) = 30.6$, $P < 0.001$]. Consistent with previous results (Duque et al. 2012; Labruna et al. 2014), RTs were faster on TMS trials compared with no-TMS trials. There was a trend-level effect of hand [$F(1,11) = 3.8$, $P = 0.08$], with faster RTs for right-hand responses. There were no other significant main effects or interactions. Note that an effect of response type was not expected because of the relatively long preparatory interval and training on the complex responses. On complex simultaneous response trials, ADM EMG onset was 16 ± 18 ms later than FDI onset, indicating that the ADM movement initiated at approximately the same time as the FDI movement. FDI EMG activity above baseline was detected on 24 ± 14% of catch trials, although the EMG bursts were often attenuated on these trials compared with the go trials. EMG burst amplitude on trials without TMS was smaller for complex responses, relative to easy responses [$F(1,11) = 19.6$, $P < 0.001$; Table 1].

The MEP data for *experiment 1* are depicted in Fig. 3*A*. Peak-to-peak raw MEP amplitudes were 1.1 ± 0.6 mV (range 0.4 to 2.3 mV) for the baseline condition in *experiment 1*. Relative to baseline, MEPs were attenuated during the preparatory delay period. This inhibition was significant in all conditions (all $P < 0.05$) except on trials in the easy choice blocks, in which the response was made with the right index finger (nonselected condition); even here, the effect was marginally significant [$t(11) = -1.6$, $P = 0.07$, 1-tailed]. The pattern for the easy choice blocks was similar to that observed in prior studies (Duque et al. 2010, 2012; Labruna et al. 2014). Inhibition was greater when the left FDI was selected for the forthcoming response compared with when it was not selected [$t(11) = 2.8$, $P < 0.01$, 1-tailed].

MEP amplitudes were more suppressed during the preparation of complex responses compared with the preparation of

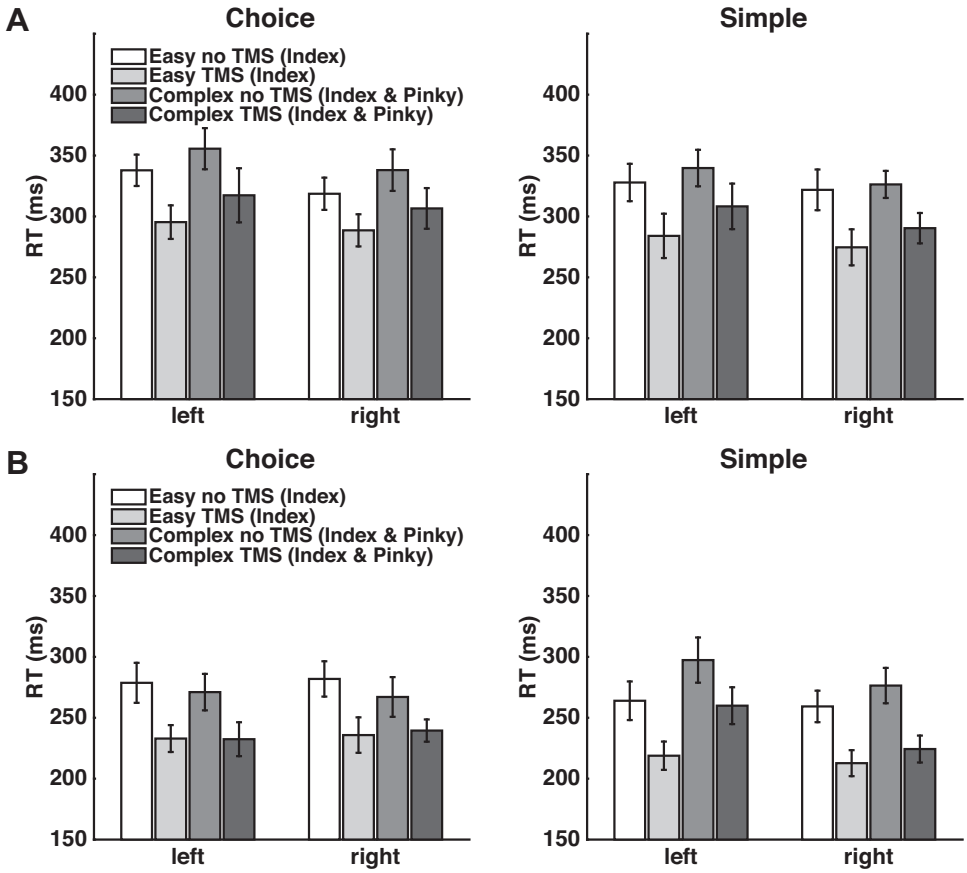

Fig. 2. Reaction times (RT; ms) based on electromyographic (EMG) records for *experiment 1* (*A*) and *experiment 2* (*B*) were faster for TMS trials compared with no-TMS trials.

easy responses [$F(1,11) = 7.4$, $P < 0.05$; Fig. 3*A*]. This effect was amplified when the left hand was the nonselected/irrelevant hand compared with when the left hand was selected for the forthcoming response, resulting in a significant two-way interaction between response type and relevance [$F(1,11) = 6.5$, $P < 0.05$]. The increased inhibition observed when participants prepared a complex response tended to be greater in the choice condition, although the two-way interaction of response type and condition was only marginally significant [$F(1,11) = 4.6$, $P = 0.06$]. There was also a reliable two-way interaction of condition and relevance [$F(1,11) = 8.4$, $P < 0.05$]. As noted above, MEP amplitudes were significantly smaller in the selected compared with the nonselected hand in the choice condition. In contrast, in the simple condition, MEPs were slightly larger when the finger was relevant (selected) than when it was irrelevant for the forthcoming response. There were no other significant main effects or interactions.

In summary, MEPs were consistently attenuated just before the onset of an imperative signal, an observation consistent with previous studies. This preparatory inhibition was larger when participants prepared a complex response compared with an easy response, especially when MEPs were measured from the nonselected or irrelevant hand. This latter effect is consistent with the hypothesis that the demands for inhibition are greater when preparing complex responses, possibly related to the recruitment of ipsilateral M1. Contrary to our predictions, this complexity effect was also observed when the muscle was selected for the forthcoming response. This result suggests that the competition resolution mechanism may influence the level of excitability for the entire set of possible responses, i.e., both selected and nonselected response representations, or that there

Table 1. *EMG peak-to-peak amplitude for correct responses*

	Experiment 1				*Experiment 2*			
	LFDI	RFDI	LADM	RADM	LFDI	RFDI	LADM	RADM
Choice easy no TMS	2.6 (1.4)	2.7 (1.3)			2.7 (1.4)	2.5 (1.2)		
Choice easy TMS	2.5 (1.5)	2.8 (1.5)			2.6 (1.4)	2.6 (1.4)		
Simple easy no TMS	2.3 (1.1)	2.7 (1.4)			2.7 (1.3)	2.5 (1.2)		
Simple easy TMS	2.4 (1.2)	2.6 (1.4)			2.5 (1.3)	2.6 (1.2)		
Choice hard no TMS	1.7 (0.9)	2.2 (1.5)	2.0 (1.2)	1.4 (0.9)	2.6 (1.5)	2.2 (1.0)	1.3 (0.6)	1.4 (0.7)
Choice hard TMS	1.7 (1.0)	2.2 (1.6)	2.2 (1.5)	1.7 (1.1)	2.6 (1.6)	2.4 (0.9)	1.2 (0.6)	1.3 (0.7)
Simple hard no TMS	1.6 (1.0)	1.9 (1.1)	1.5 (1.0)	1.5 (0.9)	2.8 (1.7)	2.5 (1.1)	1.3 (0.5)	1.5 (0.7)
Simple hard TMS	1.6 (1.0)	1.9 (1.0)	1.7 (1.1)	1.6 (1.0)	2.8 (1.6)	2.5 (1.0)	1.2 (0.4)	1.5 (0.6)

Values are means (SD) of electromyographic (EMG) activity for correct hand movement responses. LFDI and RFDI, left and right first dorsal interosseous; LADM and RAMD, left and right adductor digiti minimi; TMS, transcranial magnetic stimulation.

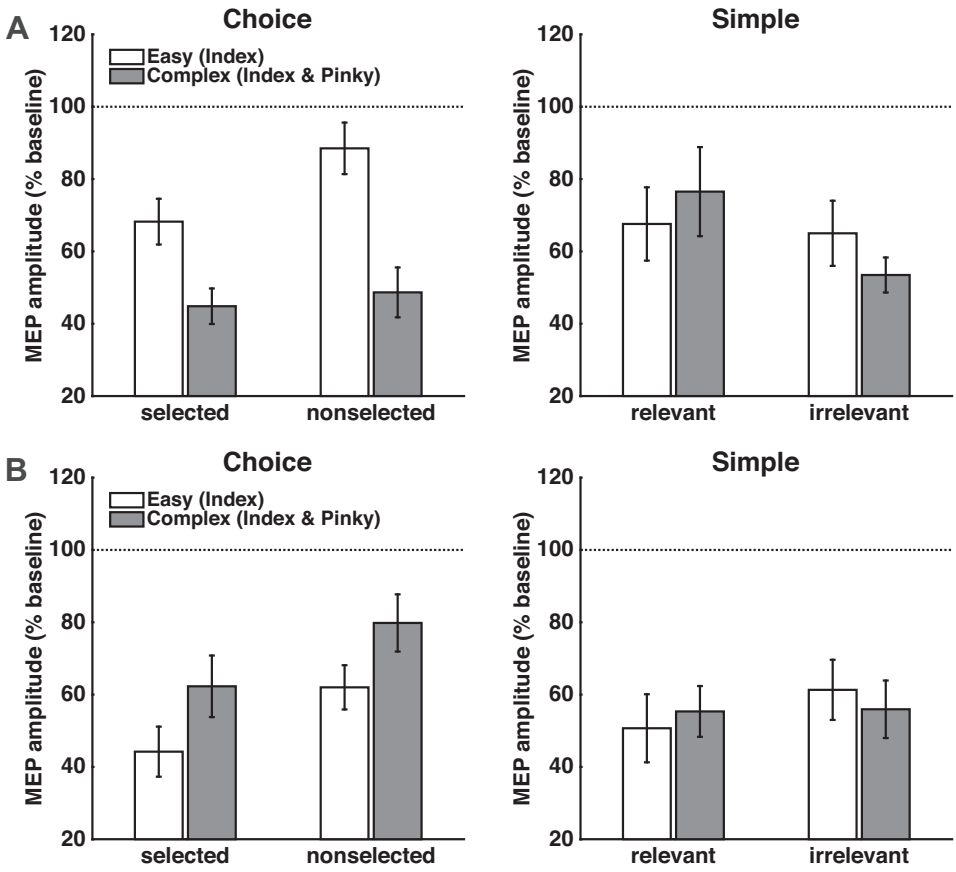

Fig. 3. Ratio of MEPs obtained during the delay period relative to baseline. *A*: *experiment 1* showed increased inhibition for simultaneous complex relative to easy responses. *B*: *experiment 2* showed a trend toward decreased inhibition for sequential complex relative to easy responses.

may be additional inhibition of the selected response when preparing a complex response that is associated with another mechanism, e.g., impulse control.

The effect of response complexity was less clear in the simple than in the choice condition. Although the effect of complexity was not reliable, and nor was the interaction of this factor with task relevance for simple responses, we did observe unexpected suppression of left FDI MEPs regardless of whether this muscle was the agonist for the forthcoming response (left-hand blocks) or irrelevant to the task (right-hand blocks). There are at least two possible explanations for this unexpected result. The underlying inhibitory mechanism may have a broad influence on motor system excitability that extends beyond the set of possible responses. Alternatively, response preparation could always engage ipsilateral M1 representations of only the homologous effectors, even in the absence of a choice between the two hands.

Experiment 2. In *experiment 2*, we repeated the design of *experiment 1* using sequential gestures for the complex responses. Sequential responses enabled us to match the initial gesture in the complex condition to the easy response gesture, a lateral index finger movement. As such, we assessed whether the increased inhibition during complex responses is unique to movements that require inter-effector coordination.

Similar to results of *experiment 1*, EMG-based RTs were faster on TMS trials compared with no-TMS trials [$F(1,11) = 13.2$, $P < 0.001$; Fig. 2*B*]. Right-hand RTs tended to be faster than left-hand RTs [$F(1,11) = 3.7$, $P = 0.08$], and there was a trend-level interaction indicating that this pattern was more pronounced for simple than for choice RTs [$F(1,11) = 4.5$, $P = 0.06$]. In addition, there was a significant condition by response type interaction [$F(1,11) = 5.1$, $P < 0.05$]. RTs were slower for the complex than for the easy responses in the simple condition, but this pattern was slightly reversed in the choice condition. For sequential complex responses, ADM movements were initiated 304 ± 86 ms after FDI movements. FDI EMG activity above baseline was detected on 18 ± 8% of catch trials. Unlike *experiment 1*, EMG burst amplitudes on trials without TMS did not differ between the different response conditions (see Table 1).

Peak-to-peak raw MEP amplitudes were 1.2 ± 1.0 mV (range 0.4 to 3.7 mV) for the baseline condition in *experiment 2*. In agreement with *experiment 1* and previous studies of preparatory inhibition, MEP amplitudes during the delay period were significantly smaller than those measured at baseline in every condition (all $P < 0.05$; Fig. 3*B*), and this inhibition was greater in the easy choice condition when the left finger was selected for the forthcoming response [$t(11) = 4.6$, $P < 0.001$, 1-tailed]. In contrast to *experiment 1*, inhibition did not increase when the complex responses required the sequential execution of two gestures. Indeed, MEP amplitudes tended to be larger in the complex condition relative to the easy condition, although this effect was only marginally reliable [$F(1,11) = 4.5$, $P = 0.06$; Fig. 3*B*]. Overall, MEP amplitudes across all conditions were significantly smaller during preparation of responses involving the selected/relevant hand compared with the nonselected/irrelevant hand [$F(1,11) = 8.6$, $P < 0.05$].

We again observed considerable corticospinal inhibition in the simple condition. This effect was similar in magnitude

regardless of whether the effector was relevant or irrelevant for the forthcoming response.

MEP amplitudes measured during the task baseline did not differ significantly from resting MEP amplitudes measured before [$t(11) = -0.70$, $P > 0.05$, 2-tailed] or after [$t(11) = -0.59$, $P > 0.05$, 2-tailed] the experiment.

Between-experiment exploratory analyses. As can be seen by comparing Fig. 3, *A* and *B*, the pattern of corticospinal inhibition differed dramatically between the two experiments in the choice condition. To assess these effects statistically, we conducted two post hoc exploratory analyses. The first, mixed ANOVA, was restricted to the easy response trials since these were the same in the two experiments. This test yielded a trend toward a main effect of experiment [$F(1, 22) = 3.9$, $P = 0.06$], with MEPs tending to have smaller amplitude in *experiment 2* compared with *experiment 1*. There was also a main effect of relevance [$F(1, 22) = 9.4$, $P < 0.01$], with generally smaller MEP amplitudes in the selected than in the nonselected/irrelevant hand. Notably, there was not a difference in baseline MEP amplitudes between the two experiments [$t(11) = 0.3$, $P = 0.75$].

Participants responded significantly faster in *experiment 2* than in *experiment 1* [$F(1,22) = 11.7$, $P < 0.005$]. Easy choice responses were 53 ms faster in *experiment 2* than in *experiment 1*, and easy simple responses were 63 ms faster in *experiment 2* than in *experiment 1*. Complex responses were 77 ms faster in *experiment 2* than in *experiment 1*, and complex simple responses were 52 ms faster in *experiment 2* than *experiment 1*. Importantly, there were no significant correlations between RT and MEP amplitudes for the easy response conditions in either experiment (all $-0.35 < R < 0.38$ and all $P > 0.23$).

Because the complex responses differed between the two experiments, we compared the effect of complexity on MEP amplitudes across the two experiments by calculating a difference score, defined by subtracting the MEP values for easy responses from the corresponding MEP values for the complex responses (Fig. 4). The condition (simple or choice) by experiment (E1 or E2) interaction for this difference score was significant [$F(1, 22) = 6.8$, $P < 0.05$]. In the choice condition, inhibition increased when participants prepared simultaneous gestures (E1) but decreased when participants prepared sequential gestures (E2); all difference scores were significantly different from zero (all $P \leq 0.05$). In contrast, the pattern for the simple responses was highly similar across the two experiments, with no reliable difference between the complex and easy conditions, with all the difference scores not significantly different from zero (all $P > 0.17$).

We recognize that the difference score comparison could potentially be accounted for by the pattern of MEPs on easy trials only. To rule out this possible explanation, we ran a separate mixed ANOVA mirroring that performed for the easy trial MEPs, this time including data only from complex trials. The condition (simple or choice) by experiment (E1 or E2) interaction was significant [$F(1,22) = 7.7$, $P < 0.05$], reflecting that the level of inhibition on complex trials was reliably different between the two experiments for the choice condition, but not for the simple condition. This pattern indicates that the difference score results cannot be explained only by data from easy trials. The condition by relevance interaction was also significant [$F(1,22) = 7.0$, $P < 0.05$], which indicates there was less MEP suppression associated with the nonselected than with the selected complex responses, but only in the choice condition. A similar pattern was also observed for the easy trials.

On trials without TMS in *experiment 1*, EMG amplitudes were greater when the participants performed an easy response compared with a complex response. It is possible that this difference is related to the effect of complexity on preparatory inhibition. To explore this possibility, we calculated a difference score for the EMG amplitudes (complex − easy) and compared this to the MEP difference score described above, using the data from the choice condition. The EMG difference scores for the left FDI or right FDI did not predict the MEP difference scores in left FDI when this muscle was either selected for the forthcoming response ($R = -0.1$, $P = 0.75$) or not selected ($R = 0.43$, $P = 0.15$), respectively. Moreover, we did not observe a difference in EMG amplitude between the easy and complex responses in *experiment 2*, providing further evidence against the hypothesis that preparatory inhibition is a function of the intensity of the forthcoming response, rather than the complexity of the response.

DISCUSSION

In two experiments we have shown that response complexity influences motor excitability during response preparation and that this effect is most robust in the context of a choice. In *experiment 1*, preparatory inhibition as reflected in reduced MEP amplitudes relative to baseline was greater during the preparation of complex responses relative to easy responses.

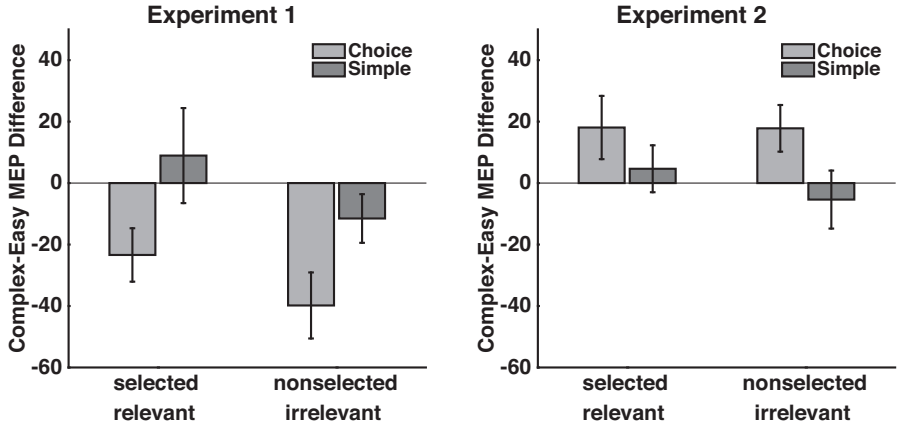

Fig. 4. MEP difference score (complex − easy). *Experiments 1* and *2* reveal an opposing influence of response complexity on motor inhibition for the choice but not the simple responses.

For *experiment 2*, this pattern was reversed. Here, inhibition was greater for easy responses relative to complex responses, although this effect was only marginally reliable. A complex-easy difference score for MEP amplitudes was calculated for both experiments and reinforced the observation that the effect of complexity was most pronounced in the context of a choice. Unrelated to the effect of response complexity, we also observed inhibition in the resting, task-irrelevant, left hand during the preparation of simple responses involving the right hand. We did not predict this pattern of results, and it is unlikely to be explained by a mechanism involved in intermanual choice because simple response trials did not involve a choice.

Models have accounted for preparatory inhibition by referring to mechanisms associated with response competition (Duque et al. 2010, 2012; Swinnen 2002; van den Berg et al. 2011; Verstynen and Ivry 2011) and impulse control (Aron 2011; Dalley et al. 2011; Davranche et al. 2007; Duque et al. 2010, 2012; Frank 2006; Hasbroucq et al. 1999b; Sinclair and Hammond 2009). In the following sections, we review how the current results inform these models and highlight alternative hypotheses concerning how inhibitory processes influence corticospinal excitability during response preparation.

Response complexity. Neuroimaging studies indicate that complex or difficult movements recruit representations in ipsilateral motor cortex (Hackley and Miller 1995; Shibasaki et al. 1993; van den Berg et al. 2011; Verstynen and Ivry 2011; Verstynen et al. 2005). This ipsilateral recruitment may contribute to the expression of mirror movements in contralateral homologous effectors. When a choice pits homologous effectors against each other, the ipsilateral activity may be suppressed to facilitate the correct choice. In line with this interpretation, TMS studies with choice RT tasks have shown that corticomotor excitability is reduced in a nonselected effector as participants prepare and execute responses with a competing effector (Duque et al., 2010, 2012; Hasbroucq et al. 1999b; Labruna et al. 2014; Leocani et al. 2000; van den Hurk et al. 2007; Verleger et al. 2009), an effect that has been interpreted to reflect the operation of a "competition resolution" mechanism (Duque et al. 2010, 2012; Klein et al. 2012; Labruna et al. 2014). On the basis of these separate lines of evidence, we predicted that response complexity would selectively modulate motor excitability during the preparation of responses when there is a competition, i.e., a choice between the two hands. Our results were in line with this prediction (see Fig. 4). Moreover, the pattern of results we observed suggests that the inhibitory influence of a competition resolution mechanism is not restricted to the nonselected response but may also influence the selected response.

Our results are a first step toward establishing that motor system excitability dynamics during response preparation are sensitive to task demands such as response complexity. Competitive interactions between response representations are unlikely to play out within motor cortex alone. A distributed network of brain areas is hypothesized to support the large repertoire of human behaviors involving interlimb coordination (Swinnen 2002). For example, previous evidence implicates a role for lateral prefrontal cortex (LPFC) in response selection, and this brain region may be especially sensitive to the influence of response complexity. Disruption of the LPFC with repetitive TMS during the preparatory period, identical to the easy choice RT conditions used in the present study, was shown to release MEP suppression of both the selected and nonselected response representations (Duque et al. 2012). Interactions between LPFC and medial frontal cortex are believed to play an important role in action monitoring, with the latter assaying the level of conflict and performance outcomes as a way to modulate activity in the LPFC (Botvinick et al. 2001; Gehring and Knight 2000; Ridderinkhof et al. 2004). We propose that recruitment of LPFC is greater during the preparation of complex responses because of the increased likelihood of response selection and execution errors (e.g., selection of the wrong effector or poor configuration of the correct effector in the complex response condition). Future studies should explore a relationship between preparatory inhibition and subsequent action errors, for example, whether the level of inhibition during response preparation predicts errors and whether disruption of this inhibition leads to increased error likelihood.

Our findings that baseline MEP amplitudes did not differ between *experiments 1* and *2*, and that the baseline MEP amplitudes in *experiment 2* did not differ from those measured outside the task, are informative concerning the time course of preparatory inhibition. Specifically, MEPs were not tonically suppressed but were dynamically adjusted during the preparation of responses. This lends further support to the hypothesis that inhibitory mechanisms are engaged in a dynamic manner during response preparation. As in previous studies (Duque et al. 2010, 2012, 2014; Klein et al. 2012; Labruna et al. 2014), this inhibition is pronounced in both selected and nonselected effectors, a finding that is consistent with the idea of a functional role in competition resolution. However, we also observed inhibition in left FDI when that muscle was not relevant to the task. Brain networks involving pathways between the cortex and basal ganglia have been proposed to exert global as well as selective effects on motor system excitability (e.g., Majid et al. 2013). Although the nonselective inhibition here might be a form of global suppression, we note that the left FDI, even when task irrelevant, was also homologous to a task-relevant muscle (i.e., right FDI).

The results of the two experiments reveal important constraints on the modulation of inhibitory processes by response complexity. First, a lateral flexion of the index finger was a component of every response in both experiments, yet the level of inhibition in this effector was modulated as a function of the context in which this response was performed. This observation underscores the point that the degree of motor suppression is contingent on task goals. Second, the increased inhibition associated with preparing complex responses was absent when the complex response was composed of sequential gestures rather than simultaneous gestures; indeed, inhibition tended to be reduced when participants prepared a sequential response compared with a simple response, even though the first component of the sequential response was identical to the simple response. Neuroimaging studies have shown similar changes in activation patterns as movements require more complex configural or sequential gestures (Hackley and Miller 1995; Shibasaki et al. 1993; Verstynen and Ivry 2011; Verstynen et al. 2005). TMS, of course, affords the opportunity to probe the system with greater temporal resolution and suggests that simultaneous and sequential responses have dissociable effects on response preparation mechanisms. Third, there was a trend toward greater corticospinal inhibition in the easy condition in

experiment 2 compared with *experiment 1*, although this condition was identical in the two experiments. Although this pattern could indicate that inhibitory processes are sensitive to the overall context, it may be related to the parallel finding that RT decreased in *experiment 2*.

Functional accounts of preparatory inhibition have emphasized how corticospinal suppression may serve to sharpen processes associated with response selection or preclude premature responses (Duque et al. 2010, 2012, 2014; Klein et al. 2012; Labruna et al. 2014). An alternative hypothesis is that preparatory inhibition, at least of the selected effector, enhances response initiation by increasing the signal to noise ratio after the onset of the imperative. That is, inhibition of the selected effector might not serve to avoid premature responses (as implied by the term, impulse control) but to facilitate response initiation (see Hasbroucq et al. 1997). Although this hypothesis merits further consideration, it does not offer a parsimonious account of the current results. RTs were reduced in all conditions in *experiment 2*, yet the parallel reductions in MEP amplitudes differed across the easy and complex conditions, complicating any relationship between RT and MEP suppression. Moreover, within each experiment we failed to observe a relationship between the level of MEP suppression in the delay period and RT.

It is important to note that the differential complexity effects for the two experiments do not appear to be driven by the MEP change associated with easy responses. Just focusing on the MEPs in the complex conditions revealed an interaction between the two different experiments and the simple vs. choice responses. Moreover, the complex-easy difference scores for the simple responses did not differ between the two experiments.

Inhibition of task-irrelevant muscles. In addition to the effect of response complexity, we observed that MEP amplitudes were reduced below baseline preceding all the simple responses in both experiments. This pattern suggests that some form of inhibition is engaged during the preparation of any response and that this inhibition can be observed regardless of whether the probed effector is task relevant or task irrelevant. This observation would suggest that rather than the view that preparatory inhibition represents reciprocal inhibition between competing candidate responses, inhibitory signals may operate in a broad manner. Such broadly focused suppression might increase the signal to noise within the motor system, a hypothesis noted above (Hasbroucq et al. 1997). This process could facilitate response selection by dampening down noise within the motor system and could be generic or have some broad tuning that extends to motor representations that are functionally or anatomically related to the selected response. The current set of experiments was not specifically designed to explore the spatial extent of this inhibitory signature because MEPs were only measured from muscles that were task relevant or homologous to task-relevant muscles.

Nevertheless, it seems unlikely that this inhibition results from a mechanism involved in response competition because there was no choice in the simple task blocks; participants executed the same response on each trial. Moreover, this inhibitory signature appears to be distinct from that associated with response complexity because the complex-easy MEP difference scores were not reliably different from zero for the simple response blocks. Thus response complexity did not impact the level of inhibition when there was no choice. Most surprising, the level of inhibition in left FDI was the same when participants were preparing to make left- or right-hand responses.

Inhibition observed in the simple RT conditions may reflect the operation of a different inhibitory mechanism than that observed during choice tasks. It is possible that in the absence of a choice, ipsilateral motor cortex is recruited in a similar manner as contralateral motor cortex. Alternatively, the inhibition observed in the simple conditions may reflect the operation of a process that broadly influences the motor system. Studies that compare task-irrelevant inhibition as a function of whether the selected response involves a homologous or nonhomologous contralateral effector will help to determine how broadly the motor system is suppressed.

Conclusion. The current results demonstrate that inhibitory mechanisms recruited during response preparation are sensitive to response complexity, at least when preparation entails a choice between the two hands. In contrast, our complexity manipulation did not influence the level of motor suppression when the same, simple response was executed on every trial. This pattern is consistent with the hypothesis that one aspect of preparatory inhibition is related to a mechanism involved in response selection, perhaps reflecting the operation of a competitive process. The need for inhibitory mechanisms may be especially acute when preparing simultaneous gestures with multiple effectors, given the evidence of increased bilateral recruitment of the motor system during the execution of complex movements. Manipulating the complexity of the required response offers a novel way to assess constraints on inhibitory mechanisms involved in the preparation of voluntary movements.

ACKNOWLEDGMENTS

We thank Timothy Verstynen for conceptual contribution to this work.

GRANTS

This work was supported by National Institute of Neurological Disorders and Stroke Grant NS074917.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

I.G., D.S., T.H., and R.B.I. conception and design of research; I.G., D.S., and T.H. performed experiments; I.G., D.S., and T.H. analyzed data; I.G., D.S., T.H., and R.B.I. interpreted results of experiments; I.G. prepared figures; I.G. drafted manuscript; I.G., D.S., T.H., and R.B.I. edited and revised manuscript; I.G., D.S., T.H., and R.B.I. approved final version of manuscript.

REFERENCES

Aron AR. From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. *Biol Psychiatry* 69: e55–e68, 2011.

Botvinick M, Braver T, Barch D, Carter C. Conflict monitoring and cognitive control. *Psychol Rev* 108: 624–652, 2001.

Cramer SC, Finklestein SP, Schaechter JD, Bush G, Rosen BR. Activation of distinct motor cortex regions during ipsilateral and contralateral finger movements. *J Neurophysiol* 81: 383–387, 1999.

Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. *Neuron* 69: 680–694, 2011.

Davranche K, Tandonnet C, Burle B, Meynier C, Vidal F, Hasbroucq T. The dual nature of time preparation: neural activation and suppression revealed by transcranial magnetic stimulation of the motor cortex. *Eur J Neurosci* 25: 3766–3774, 2007.

Duque J, Ivry RB. Role of corticospinal suppression during motor preparation. *Cereb Cortex* 19: 2013–2024, 2009.

Duque J, Labruna L, Cazares C, Ivry RB. Dissociating the influence of response selection and task anticipation on corticospinal suppression during response preparation. *Neuropsychologia* 65: 287–296, 2014.

Duque J, Labruna L, Verset S, Olivier E, Ivry RB. Dissociating the role of prefrontal and premotor cortices in controlling inhibitory mechanisms during motor preparation. *J Neurosci* 32: 806–816, 2012.

Duque J, Lew D, Mazzocchio R, Olivier E, Ivry RB. Evidence for two concurrent inhibitory mechanisms during response preparation. *J Neurosci* 30: 3793–3802, 2010.

Frank MJ. Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. *Neural Netw* 19: 1120–1136, 2006.

Gehring WJ, Knight RT. Prefrontal-cingulate interactions in action monitoring. *Nat Neurosci* 3: 516–520, 2000.

Hackley SA, Miller J. Response complexity and precue interval effects on the lateralized readiness potential. *Psychophysiology* 32: 230–241, 1995.

Hanakawa T, Parikh S, Bruno MK, Hallett M. Finger and face representations in the ipsilateral precentral motor areas in humans. *J Neurophysiol* 93: 2950–2958, 2005.

Hasbroucq T, Kaneko H, Akamatsu M, Possamaï CA. Preparatory inhibition of cortico-spinal excitability: a transcranial magnetic stimulation study in man. *Brain Res Cogn Brain Res* 5: 185–192, 1997.

Hasbroucq T, Kaneko H, Akamatsu M, Possamaï CA. The time-course of preparatory spinal and cortico-spinal inhibition: an H-reflex and transcranial magnetic stimulation study in man. *Exp Brain Res* 124: 33–41, 1999a.

Hasbroucq T, Osman A, Possamaï CA, Burle B, Carron S, Dépy D, Latour S, Mouret I. Cortico-spinal inhibition reflects time but not event preparation: neural mechanisms of preparation dissociated by transcranial magnetic stimulation. *Acta Psychol (Amst)* 101: 243–266, 1999b.

Kanouchi T, Yokota T, Isa F, Ishii K, Senda M. Role of the ipsilateral motor cortex in mirror movements. *J Neurol Neurosurg Psychiatry* 62: 629–632, 1997.

Klein PA, Olivier E, Duque J. Influence of reward on corticospinal excitability during movement preparation. *J Neurosci* 32: 18124–18136, 2012.

Kobayashi M, Hutchinson S, Schlaug G, Pascual-Leone A. Ipsilateral motor cortex activation on functional magnetic resonance imaging during unilateral hand movements is related to interhemispheric interactions. *Neuroimage* 20: 2259–2270, 2003.

Labruna L, Lebon F, Duque J, Klein PA, Cazares C, Ivry RB. Generic inhibition of the selected movement and constrained inhibition of nonselected movements during response preparation. *J Cogn Neurosci* 26: 269–278, 2014.

Leocani L, Cohen LG, Wassermann EM, Ikoma K, Hallett M. Human corticospinal excitability evaluated with transcranial magnetic stimulation during different reaction time paradigms. *Brain* 123: 1161–1173, 2000.

Majid DSA, Cai W, Corey-Bloom J, Aron AR. Proactive selective response suppression is implemented via the basal ganglia. *J Neurosci* 33: 13259–13269, 2013.

Meyer-Lindenberg A, Ziemann U, Hajak G, Cohen L, Berman KF. Transitions between dynamical states of differing stability in the human brain. *Proc Natl Acad Sci USA* 99: 10948–10953, 2002.

Rao SM, Binder JR, Bandettini PA, Hammeke TA, Yetkin FZ, Jesmanowicz A, Lisk LM, Morris GL, Mueller WM, Estkowski LD. Functional magnetic resonance imaging of complex human movements. *Neurology* 43: 2311–2318, 1993.

Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. *Science* 306: 443–447, 2004.

Shibasaki H, Sadato N, Lyshkow H, Yonekura Y, Honda M, Nagamine T, Suwazono S, Magata Y, Ikeda A, Miyazaki M, Fukuyama H, Asato R, Konishi J. Both primary motor cortex and supplementary motor area play an important role in complex finger movement. *Brain* 116: 1387–1398, 1993.

Sinclair C, Hammond GR. Reduced intracortical inhibition during the foreperiod of a warned reaction time task. *Exp Brain Res* 186: 385–392, 2008.

Sinclair C, Hammond GR. Excitatory and inhibitory processes in primary motor cortex during the foreperiod of a warned reaction time task are unrelated to response expectancy. *Exp Brain Res* 194: 103–113, 2009.

Swinnen SP. Intermanual coordination: from behavioural principles to neural-network interactions. *Nat Rev Neurosci* 3: 348–359, 2002.

van den Berg FE, Swinnen SP, Wenderoth N. Excitability of the motor cortex ipsilateral to the moving body side depends on spatio-temporal task complexity and hemispheric specialization. *PLoS One* 6: e17742, 2011.

van den Hurk P, Mars RB, van Elswijk G, Hegeman J, Pasman JW, Bloem BR, Toni I. Online maintenance of sensory and motor representations: effects on corticospinal excitability. *J Neurophysiol* 97: 1642–1648, 2007.

Verleger R, Kuniecki M, Möller F, Fritzmannova M, Siebner HR. On how the motor cortices resolve an inter-hemispheric response conflict: an event-related EEG potential-guided TMS study of the flankers task. *Eur J Neurosci* 30: 318–326, 2009.

Verstynen T, Diedrichsen J, Albert N, Aparicio P, Ivry RB. Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. *J Neurophysiol* 93: 1209–1222, 2005.

Verstynen T, Ivry RB. Network dynamics mediating ipsilateral motor cortex activity during unimanual actions. *J Cogn Neurosci* 23: 2468–2480, 2011.

Wexler BE, Fulbright RK, Lacadie CM, Skudlarski P, Kelz MB, Constable RT, Gore JC. An fMRI study of the human cortical motor system response to increasing functional demands. *Magn Reson Imaging* 15: 385–396, 1997.