Inhibition during response preparation is sensitive to response complexity

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**Abstract**

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 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 (Hasbroucq et al., 1997; 1999a; 1999b; van den Hurk et al., 2007; Sinclair and Hammond, 2008; Duque and Ivry, 2009; Sinclair and Hammond, 2009; Duque et al., 2010; 2012; 2014; Labruna et al., 2014). 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.’ Here, we set out to test whether the complexity of a response influences the level of inhibition associated with one or both of these mechanisms.

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; Wexler et al., 1997; Verstynen et al., 2005). Moreover, the influence of complexity is not restricted to contralateral motor cortex, but is also pronounced in ipsilateral motor cortex (Shibasaki et al., 1993; Hackley and Miller, 1995; Verstynen et al., 2005; Verstynen and Ivry, 2011). 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 bi-hemispheric planning processes (Shibasaki et al., 1993; Cramer et al., 1999;
Hanakawa et al., 2005; 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 non-selected 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 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 non-selected 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 (22.4 ± 3.0 years of age, 3 female, 2 left handed) and a different group of 12 participants in Experiment 2 (21.4 ± 1.9 years of age, 1 female, all right handed). Participants provided informed consent prior to 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 Figure 1a). Participants were seated comfortably in front
of a computer monitor with their hands palm-down on a pillow in their laps. 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 inter-trial
interval (3000-3500 ms, uniform distribution).

In each experiment participants completed eight 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 cued on 21 trials per block in a random order. The other four blocks did not involve a
choice, with the response hand fixed for the entire block (simple RT: two blocks left hand, two
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
towards 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 (Figure 1b), 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) administered consecutively. Before each block, participants were instructed how to execute the desired responses and completed ten 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 (Magstim, Whitland, Dyfed, UK) stimulator with a 7-cm diameter figure-of-eight coil. Stimulation was targeted at the right primary motor cortex (M1) to elicit motor evoked potentials (MEPs) from the left first dorsal interosseous (FDI) muscle, the agonist for the lateral index finger movement. EMG 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 approximately 5 cm lateral and 2 cm anterior to the vertex, with the coil orientation approximately 45 degrees off of the midline. A single TMS pulse was administered every 3 seconds 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 greater than 50 µV were observed on five out 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: four 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 (inter-pulse interval 3300 to 3900 ms, uniform distribution). These pre- and post-task 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 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 prior to 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 ten. On average, less 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 non-selected conditions with a \( t \)-test since 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. non-selected/irrelevant). We grouped the irrelevant hand in the simple condition with the non-selected hand in the choice condition since 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. non-selected/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 non-selected/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 Figure 2a. 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 to 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 to 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 Figure 3a. 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’s < 0.05) except on trials in the easy choice blocks in which the response was made with the right index finger (non-selected condition); even here, the effect was marginally significant (t(11) = -1.6, p = 0.07, one-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 to when it was not selected (t(11) = 2.8, p < 0.01, one-tailed).

MEP amplitudes were more suppressed during the preparation of complex responses compared to the preparation of easy responses (F(1,11) = 7.4, p < 0.05; Figure 3a). This effect was amplified when the left hand was the non-selected/irrelevant hand compared to when the left hand was selected for the forthcoming response, resulting in a significant two-way interaction between Response Type and Relevancy (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 Relevancy ($F(1,11) = 8.4, p < 0.05$). As noted above, MEP amplitudes were significantly smaller in the selected compared with the non-selected 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 to an easy response, especially when MEPs were measured from the non-selected 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 non-selected response representations, or that there 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. While the effect of complexity was not reliable nor the interaction of this factor with task relevancy 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 Experiment 1, EMG-based RTs were faster on TMS trials compared to no TMS trials ($F(1,11) = 13.2$, $p < 0.001$; Figure 2b). 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 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 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 $304 \pm 86$ ms after FDI movements. FDI EMG activity above baseline was detected on $18 \pm 8\%$ 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’s < 0.05, Figure 3B), 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, one-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; Figure 3b). Overall, MEP amplitudes across all conditions were significantly smaller during preparation of responses involving the selected/relevant hand compared to the non-selected/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 > .05, two-tailed) or after (t(11) = -0.59, p > .05, two-tailed) the experiment.

**Between Experiment Exploratory Analyses**

As can be seen by comparing Figure 3a with Figure 3b, 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 to Experiment 1. There was also a main effect of relevancy ($F(1, 22) = 9.4, p < 0.01$), with generally smaller MEP amplitudes in the selected than in the non-selected/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 Experiment 1 ($F(1,22) = 11.7, p < 0.005$). Easy choice responses were 53 ms faster in Experiment 2 than Experiment 1, and easy simple responses were 63 ms faster in Experiment 2 than Experiment 1. Complex responses were 77 ms faster in Experiment 2 than 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 < $R$'s < 0.38 and $p$'s > 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 (Figure 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 significantly different than zero ($p$'s <= 0.05). In contrast, the pattern for the simple responses was highly similar across the two experiments, with no reliable
difference between the difficult and easy conditions, with all the difference scores not significantly different than zero ($p's > 0.17$).

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 which we 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 non-selected than 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 to 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 showed 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. 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 inter-manual choice because simple response trials did not involve a choice.

Models have accounted for preparatory inhibition by referring to mechanisms associated with response competition (Swinnen, 2002; Duque et al., 2010; van den Berg et al., 2011; Verstynen and Ivry, 2011; Duque et al., 2012) and impulse control (Hasbroucq et al., 1999b; Frank, 2006; Davranche et al., 2007; Sinclair and Hammond, 2009; Duque et al., 2010; Aron, 2011; Dalley et al., 2011; Duque et al., 2012). 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 (Shibasaki et al., 1993; Hackley and Miller, 1995; Verstynen et al., 2005; van den Berg et al., 2011; Verstynen and Ivry, 2011). 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 non-selected effector as participants prepare and execute responses with a competing effector (Hasbroucq et al., 1999b; Leocani et al., 2000; van den Hurk et al., 2007; Verleger et al., 2009; Duque et al., 2010; 2012; Labruna et al., 2014), 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). Based upon 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 Figure 4). Moreover, the pattern of results we observed suggests that the inhibitory influence of a competition resolution mechanism is not restricted to the non-selected 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 inter-limb 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 here, was shown to release MEP suppression of both the selected and non-selected 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 (Gehring and Knight, 2000; Botvinick et al., 2001; Ridderinkhof et al., 2004). We propose that recruitment of LPFC is greater during the preparation of complex responses due to 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 non-selected 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). While the non-selective 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 upon 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 to 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 (Shibasaki et al., 1993; Hackley and Miller, 1995; Verstynen et al., 2005; Verstynen and Ivry, 2011). 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 towards
greater corticospinal inhibition in the easy condition in Experiment 2 compared to Experiment
1, although this condition was identical in the two experiments. While 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). While 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 view preparatory inhibition
as a 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 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 non-homologous 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.
Table 1. Mean (std) EMG peak-to-peak amplitude (mV) for correct responses.

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References


Figure Legends

Figure 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 (circle) 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 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.

Figure 2. Reaction times (ms) based on EMG records for Experiment 1 (A) and Experiment 2 (B) were faster for TMS trials compared to no TMS trials.

Figure 3. The ratio of motor evoked potentials (MEP) obtained during 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.

Figure 4. MEP Difference score (Complex – Easy). Experiments 1 and 2 reveal an opposing influence of response complexity on motor inhibition for the choice (white bars), but not the simple responses (gray bars).
A

Experiment 1

Fixation 600 ms
Cue 900 ms
Imperative 300 ms

Response
non selected/ irrelevant
selected/ relevant

TMS
baseline
800 ms post cue

B

Experiment 1

Easy Responses
Complex Responses

Experiment 2

Easy Responses
Complex Responses

simultaneous
sequential
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Experiment 1

Complex-Easy MEP Difference

Experiment 2

Complex-Easy MEP Difference