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The Fall and Rise of Corticomotor Excitability with Cancellation and Reinitiation of Prepared Action

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Abstract

The sudden cancellation of a motor action, known as response inhibition (RI), is fundamental to human motor behavior. The behavioural selectivity of RI can be studied by cueing cancellation of only a subset of a planned response, which markedly delays the remaining executed components. The present study examined neurophysiological mechanisms that may contribute to these delays. In two experiments, human participants received single and paired-pulse transcranial magnetic stimulation while performing a bimanual anticipatory response task. Participants performed most trials bimanually (Go trials) and were sometimes cued to cancel the response with one hand, while responding with the other (Partial trials). Motor evoked potentials were recorded from left first dorsal interosseous (FDI) as a measure of corticomotor excitability (CME) during Go and Partial trials. CME was temporally modulated during Partial trials in a manner that reflected anticipation, suppression, and subsequent initiation of a reprogrammed response. There was an initial increase in CME, followed by suppression 175 ms after the stop signal, even though the left hand was not cued to stop. A second increase in excitability occurred prior to the (delayed) response. We propose an activation threshold model to account for non-selective RI. To investigate the inhibitory component of our model, we investigated short latency intracortical inhibition (sICI), but results indicated that sICI cannot fully explain the observed temporal modulation of CME. These neurophysiological and behavioural results indicate that the default mode for reactive partial cancellation is suppression of a unitary response followed by response reinitiation with an inevitable time delay.

Introduction

The ability to suddenly cancel an action is perhaps as fundamental to human behavior as action itself. Cancellation or "stopping" engages a right-lateralized cortico-subcortical inhibitory network, with downstream effects on the primary motor cortex (M1) (Aron et al. 2003; Aron and Poldrack 2006; Coxon et al. 2009; Coxon et al. 2012; Garavan et al. 1999; Liddle et al. 2001; Rubia et al. 2003; Stinear et al. 2009; Zandbelt et al. 2013; Zandbelt and Vink 2010). Sometimes a subset of the action must be cancelled while the remaining elements continue. How the motor system prepares for this eventuality relates to the presence or absence of foreknowledge, termed proactive and reactive inhibition, respectively (Aron 2011; Cai et al. 2011). When foreknowledge about stopping is available, the costs associated with partial cancellation are reduced (Aron and Verbruggen 2008; Cai et al. 2011; Claffey et al. 2010). However, the most vital and time-sensitive inhibitory responses in everyday life are most commonly associated with sudden and unexpected events where no warning is available e.g. avoiding a car accident. Without foreknowledge, partial cancellation of movement is difficult and executed components are markedly slowed (Aron and Verbruggen 2008). For example, in a bimanual anticipatory response task, partial cancellation of self-initiated responses leads to marked delays in the responding effector (Coxon et al. 2007; Coxon et al. 2012; MacDonald et al. 2012). It is our contention that delays during reactive partial cancellation reflect neuroanatomical constraints that limit the ability to selectively suppress prepared actions.

Transcranial magnetic stimulation (TMS) is routinely used to non-invasively examine task-dependent effects on M1. Single-pulse TMS of M1 probes excitability of the entire corticomotor pathway i.e. the net effect of facilitatory and inhibitory inputs to all synapses between the coil and muscle. Corticomotor excitability (CME) of involved motor representations

increases during motor preparation, in advance of execution (Chen et al. 1998; Marinovic et al. 2011; Pascual-Leone et al. 1992). When a stop signal is presented during preparation, CME is suppressed 100 – 200 ms after the stop signal (Coxon et al. 2006; Hoshiyama et al. 1997; Yamanaka et al. 2002; Yamanaka and Nozaki 2013). Suppression is observed not only for the task relevant effector, but also task-irrelevant effectors, suggesting that RI is associated with "global" effects on the motor system (Badry et al. 2009; Cai et al. 2012; Coxon et al. 2006; Greenhouse et al. 2012; Majid et al. 2012; Wessel et al. 2013). The majority of the above studies investigated CME during cancellation of simple unimanual responses, with or without a preceding choice decision. Majid et al. (2012) examined partial cancellation of a bimanual response in the context of proactive stopping, but they did not examine CME in the task-relevant effectors. Here we examine how CME is modulated in the task-relevant effectors during partial cancellation of a bimanual response without foreknowledge. Crucially, we are only examining cancellation of task-relevant muscles, which are always prepared to respond at the beginning of a trial.

Our main aim was to investigate temporal modulation of CME preceding and during partial cancellation of movement (*experiment 1*) in a reactive RI task requiring bimanual response preparation. Participants performed a bimanual anticipatory response inhibition (ARI) task requiring execution (Go trials), and occasional complete, or partial cancellation (Partial trials) of responses. We hypothesized that partial cancellation would reveal neuroanatomical constraints on behaviourally selective suppression. This would be evident in CME which would initially increase in both Go and Partial trials, then subsequently decrease after the stop cue in Partial trials, followed by a second increase and a substantially delayed response. We present a computational model encapsulating the empirical data. Based on the model, we tested whether

short latency intracortical inhibition (sICI) during Partial trials could explain the inhibitory component of the model (*experiment 2*). We hypothesized that modulation of sICI during Partial trials would coincide with changes in CME.

General Methods

Participants

Fifteen healthy adults with no neurological impairment participated in *experiment 1* (mean age 25.5 years, range 21 – 37 years, 8 male). Thirteen of the same participants took part in *experiment 2* (mean age 26.1 years, range 24 – 37 years, 6 male). All participants were right handed (laterality quotient: *experiment 1* mean 0.73, *experiment 2* mean 0.78, range 0.36 - 1) as assessed using the Edinburgh Handedness Inventory (Oldfield 1971). The study was approved by the University of Auckland Human Participant Ethics Committee and written informed consent was obtained from each participant.

ARI task

The bimanual ARI task is based on the paradigm by Slater-Hammel (1960), adapted for investigating the behavioural selectivity of RI (Coxon et al. 2007; MacDonald et al. 2012). Participants were seated 1 m in front of a computer display while performing the task. The display consisted of two vertically oriented indicators 2 cm apart, each 18 cm in length and 2 cm in width (Fig1). The left indicator corresponded to the left-hand index finger and the right indicator to the right-hand index finger. The forearms rested on a table, positioned midway between supination and pronation. The task was controlled using custom software written with MATLAB (MathWorks USA, R2011a, version 7.12) and interfaced with two custom-made switches, attached via an A/D USB interface (National Instruments, NI-DAQmx 9.7). The

medial aspect of each index finger was used to depress the switches (index finger adduction). Each trial commenced after a variable delay when both switches were depressed. Following the delay, both indicators moved upward from the bottom at equal rates, reaching the target after 800 ms.

The majority of trials (66% in *experiment 1*, 70% in *experiment 2*) involved index finger abduction to release both switches in time to stop both indicators at the target (Go trials, GG). Visual feedback was displayed at the completion of each trial, indicating whether the indicator(s) had been stopped sufficiently close to the target (within 30 ms), to emphasize that trials were to be performed as accurately as possible. Occasionally one or both indicators stopped automatically before reaching the target, cueing the participant to inhibit responding with the corresponding digit(s) (Stop trials). There were three types of trials requiring RI: Stop Both (SS), when both indicators stopped automatically, and Partial trials which included Stop Left - Go Right (SG) and Go Left - Stop Right (GS), when only the left or right indicator stopped, respectively. SS trials were included as catch trials so that GS trials could not be anticipated (*experiment 1*), and to investigate neurophysiological mechanisms during complete cancellation of the bimanual response for comparison with partial cancellation (*experiment 2*). The pairing of letters (e.g. GS) represents the spatial mapping of index fingers; the letter on the left denotes the action of the left index finger, the letter on the right denotes the right index finger.

A color-coded feedback display indicated whether inhibition of one or both responses was successful. The indicator was set to stop automatically 250 ms prior to the target on Partial trials and 200 ms prior to the target on Stop Both trials, both producing about 50% probability of success as determined using the staircase design in previous research (MacDonald et al. 2012). Predetermined stop times allowed comparison of motor evoked potentials (MEPs) between

subjects at the same absolute stimulation times during the trial. All participants completed preliminary practice blocks consisting of only Go trials in both experiments (40 – 80 trials). Practice blocks were used for participant familiarization and setting TMS intensities.

Recording procedure

MEPs were recorded from left first dorsal interosseus (FDI), since the non-dominant hand is more strongly affected than the dominant hand by the processes required to successfully cancel a subset of a motor action (MacDonald et al. 2012). Surface electromyography (EMG) was recorded from left FDI using a belly-tendon montage. The ground electrode was placed on the posterior surface of the hand. EMG signals were amplified (CED 1902, Cambridge, United Kingdom), bandpass filtered (20 - 1000 Hz) and sampled at 2 kHz (CED 1401, Cambridge, United Kingdom). The EMG collection system was triggered when the indicators started to rise in the behavioral task, and EMG was recorded for 1 second. Data were saved for offline analysis using Signal (CED, Cambridge, United Kingdom) and custom software (MATLAB, MathWorks USA, R2011a, version 7.12).

TMS

TMS was applied to right M1 using a figure-of-eight D70^2 coil and Magstim200 unit (Magstim, Dyfed, United Kingdom), or through a Bistim unit (Magstim) connected to two Magstim200 units (*experiment 2*). The optimal coil position was found (and marked on the scalp) that elicited MEPs of the largest amplitude in the left FDI using a slightly suprathreshold stimulus intensity. The coil was positioned tangentially to the head with the handle directed posteriorly at a 45 degree angle to the midline of the head, inducing a current directed posterior to anterior in the underlying cortical tissue.

Experiment 1 Methods

Protocol

The task consisted of 12 blocks each comprising 36 trials. There were 432 trials in total of which 288 (66%) were Go trials and 144 (33%) were Stop trials pseudo-randomized across the 12 blocks. The high proportion of Go trials ensured that this was the default response. The main trials of interest were GG and GS trials. SS and SG conditions made up 30 catch trials of no interest that did not include stimulation. Catch trials were included to ensure that participants could not anticipate a GS response, and guarded against the task being performed in a choice reaction manner (between GG and GS).

Task motor threshold (TMT) was determined while the participant pressed the left switch as they would in the task. TMT was defined as the minimum stimulus intensity required to evoke FDI MEPs of at least 50 μV amplitude in 4 out of 8 stimuli. Test stimulus (TS) intensity was initially set at participant's TMT and increased by 1 – 2% of maximum stimulator output (MSO) if necessary to obtain a MEP amplitude of 0.1 – 0.2 mV during practice blocks, without affecting behavioral performance. Timing of TMS is reported relative to the anticipated response target (0 ms). For Go trials, single-pulse TMS was delivered at 7 time points from 250 to 100 ms before the target in 25 ms intervals i.e. -250, -225, -200, -175, -150, -125 and -100 ms, to obtain 12 stimuli at each time (Fig 2A). There were 204 Go trials with no TMS interspersed throughout the blocks. Of the Stop trials, the 114 GS trials were of most interest. In order to compare GS with Go trials, the 7 time points for single-pulse TMS were offset on GS trials by 100 ms, delivered at -150, -125, -100, -75, -50, -25 and 0 ms (12 stimuli per stimulation time, Fig 2A), as responses are delayed by about 100 ms on Partial trials (Coxon et al. 2007; Coxon et al. 2012; MacDonald

et al. 2012). Stimulation times were pseudo-randomized. Practice blocks consisted of only Go trials and stimulation occurred at -200 ms relative to target, before the onset of FDI muscle activity. The TS intensity remained constant for the remaining data collection.

Dependent measures

Lift times (LTs) were determined for successful Go and Partial trials. Average LTs were calculated after removing outliers (± 3 SD) (1.0 ± 0.1% and 0.2 ± 0.2%, respectively). LT from successful Partial trials corresponds to the responding digit. All LTs are reported in milliseconds relative to the target.

Percentage of successful trials and stop signal reaction time (SSRT) were determined for only GS trials. SSRTs were calculated using the integration method (Logan and Cowan 1984; Verbruggen et al. 2013), so that SSRT was estimated by subtracting the fixed stop time from the finishing time of the stop process. The Go LTs were rank ordered and the *n*th LT selected, where *n* was obtained by multiplying the number of Go LTs by the probability of responding to a stop signal.

Mean MEP amplitude and mean pre-trigger root mean squared (rms) EMG was determined for each subject and stimulation time, for GG and GS trials. The difference in MEP amplitudes between GG and GS trials was of primary interest. MEP amplitudes from 110 to 170 ms prior to group average LT for GG and GS trials were also plotted separately to compare the rate of rise in CME leading to the lift response. Peak rate of onset for the main EMG burst was used as an index of motor output gain as described previously (Coxon et al. 2007; MacDonald et al. 2012). Peak rate of EMG onset was determined for GG and GS trials, calculated using a dual-pass 20-Hz Butterworth filter prior to differentiation.

Statistical analysis

Dependent measures were subjected to repeated measures (RM) analysis of variance (ANOVA) with post hoc and planned comparisons when necessary. LT was examined in a 2 Digit (Left, Right) x 2 Trial Type (Go, Partial) RM ANOVA, and the predetermined indicator stop times were checked by comparing the percentage of successful Stop trials against 50% using one-sample *t* tests. The criterion for statistical significance was $\alpha = 0.05$. Greenhouse-Geisser *P* values are reported for non-spherical data. All results are shown as group means ± standard error.

A 2 Trial Type (GG, GS) x 7 Stimulation Time RM ANOVA tested for differences in MEP amplitude and pre-trigger rmsEMG between GG and GS trials. Differences in peak rate of EMG onset between GG and GS trials was tested with a one-way RM ANOVA with Trial Type (GG,GS) as the factor. A paired-sample *t* test compared rate of increase in CME prior to the lift response between GG and GS trials. Rate was calculated using the linear gradient of change in MEP amplitude from 110 – 170 ms prior to average LT for both trial types.

Experiment 1 Results

Behavioral Data: Lift times and SSRT

For Go trials, LTs occurred on average 14 ± 2 ms after the target, indicating successful timed response performance as reported previously (Coxon et al. 2007; MacDonald et al. 2012). All LTs are shown in Table 1. There was a main effect of Trial Type ($F_{1,14} = 421.3$, $P < 0.001$) with LTs delayed to an average of 98 ± 4 ms after the target on Partial trials. There was a main effect of Digit ($F_{1,14} = 4.6$, $P = 0.049$) with left LT faster than right LT when collapsed across

Trial Type (51 ± 3 ms vs. 61 ± 4 ms, relative to the target). There was no Trial Type x Digit interaction ($F_{1,14}$ = 0.8, P = 0.393).

The success rate during GS trials of 48.3 ± 5.5% was as expected, and not different from 50% (t_{14} = -0.3, P = 0.759). SSRT for GS trials was 260 ± 5 ms.

Neurophysiological Data: MEP amplitude and pre-trigger rmsEMG

TMT was 35 ± 2% MSO and TS intensity was 37 ± 2% MSO (106% TMT). For the ANOVA of MEP amplitude on successful GG and GS trials there was a Trial Type x Stimulation Time interaction ($F_{6,84}$ = 3.5, P = 0.039, Fig 3A), a main effect of Stimulation Time ($F_{6,84}$ = 11.9, P < 0.001) and no main effect of Trial Type ($F_{1,14}$ = 1.8, P = 0.197). For Go trials, MEP amplitude increased from -250 ms relative to target (0.10 ± 0.01 mV) to -175 ms (0.16 ± 0.02 mV, t_{14} = 3.1, P = 0.007) and remained facilitated (all P < 0.013). Comparing GG and successful GS trials, average MEP amplitude did not differ at -150 ms (t_{14} = 0.9, P = 0.363), but trended towards larger MEPs on GG trials at -125 ms and -100 ms (both t_{14} = 2.1, P = 0.052). For successful GS trials, MEP amplitude increased from -150 ms (0.15 ± 0.03 mV) to -100 ms (0.40 ± 0.09 mV; t_{14} = 2.5, P = 0.025). This increase in MEP amplitude was not sustained, with MEP amplitude reducing from -100 ms to -75 ms before the target (0.18 ± 0.02 mV; t_{14} = 2.3, P = 0.039) *even though the left digit was not cued to stop*. MEP amplitude increased again from -75 ms to -25 ms before the target (0.44 ± 0.07 mV; t_{14} = 3.9, P = 0.002) and remained facilitated at 0 ms (0.40 ± 0.05 mV; t_{14} = 4.5, P < 0.001).

On unsuccessful GS trials, the temporal pattern of MEP amplitude modulation mirrored that on successful trials (Fig 3D). MEP amplitude decreased between -100 to -75 ms (1.03 ± 0.63 mV to 0.47 ± 0.33 mV; t_{14} = 3.6, P = 0.003). Importantly, between these two time points, MEP

amplitude decreased to a lower absolute level on successful than unsuccessful trials (t_{13} = 3.0, P = 0.010). This indicates that MEP suppression occurred during unsuccessful GS trials, likely reflecting that a reactive stopping mechanism was recruited, but was insufficient to suppress the bimanual response.

There was a trend for MEP amplitude to increase more rapidly prior to the lift response on GG trials compared to GS trials (t_{12} = 1.8, P = 0.090, Fig 3C).

Mean pre-trigger rmsEMG level was 10 ± 1 μV indicating that the FDI remained at rest throughout testing. There were no effects or interactions for pre-trigger rmsEMG (all P > 0.09).

EMG Data: Peak rate of EMG onset

There was a main effect of Trial Type ($F_{1,14}$ = 17.5, P = 0.001). Peak rate of EMG onset was higher on GS trials (6.8 ± 1.2 mV/s) than Go trials (5.6 ± 1.1 mV/s), indicative of a higher gain during GS trials.

Modeling

An activation threshold model (ATM, Fig 4) is proposed to account for variation in lift time, CME and EMG (gain) between Partial and Go trials. The ATM is predicated on modulation of CME which is the net balance of facilitatory and inhibitory processes that compete upstream of the final common motor pathway. The activation threshold is initially set by a tonic inhibitory input to maintain a resting state (Fig 4A & B). Responses only occur when facilitation surpasses inhibition i.e., the activation threshold. Facilitation is modeled as a ramp function with slope k_{facGo} and time constant τ_{facGo} to reflect sensorimotor processing.

$$\text{Facilitation} = \frac{1}{k_{facGo}}\left[time - \tau_{facGo}\left(1 - e^{-time/\tau_{facGo}}\right)\right]$$

On Partial trials, inhibition increases in response to a step input (I, Fig 4C & D) during processing of the stop signal with amplitude A_{inh}, slope k_{inh} and time constant τ_{inh} to reflect stop signal processing.

$$I = Inhibition + A_{inh}/k_{inh}\left(1 - e^{-time/\tau_{inh}}\right)$$

On Partial trials, an additional facilitatory drive (F, Fig 4C) reflects the initiation of the new, reprogrammed (single component) response at a higher gain. This is modeled as a ramp function of slope $k_{facGoNew}$ and time constant $\tau_{facGoNew}$ and is additive to the pre-existing Go trial facilitation.

$$F = Facilitation + \frac{1}{k_{facGoNew}}\left[time - \tau_{facGoNew}\left(1 - e^{-time/\tau_{facGoNew}}\right)\right]$$

To capture the empirical data, model parameters were identified to reflect the following: a 50% decrease in CME slope on GS trials compared to Go trials (Fig 3C); the higher gain of the reinitiated response on Partial trials as evident from EMG (Fig 4); and the average left LT delay of 82 ms on GS trials (Table1). Arbitrarily setting an amplitude of inhibition increase A = 1.555, values of gain (k) and time delay (τ) parameters could be found to capture the empirical results described above. With $k_{facGo} = 0.2$; $\tau_{facGo} = \tau_{inh} = 0.8$; $k_{inh} = 1.2$; $k_{facGoNew} = 0.091$ and $\tau_{facGoNew} = 2.4$; the ATM captures behavioral and neurophysiological effects of Partial (GS) trials (Fig 4).

Experiment 1 Discussion

The rise, fall, and rise again of CME during Partial (GS) trials is a novel finding in support of our hypothesis of a non-selective neural RI mechanism. Suppression occurred on GS trials

even though the left hand was not cued to stop. This modulation of CME reflects anticipation, suppression and subsequent initiation of a reprogrammed response. The novel neurophysiological findings are in line with previous behavioural data, which also demonstrate non-selective RI (Coxon et al. 2007; Coxon et al. 2012; MacDonald et al. 2012). Overall, these results support the idea that neuroanatomical constraints prevent purely selective inhibition, at least when foreknowledge about cancellation is unavailable (Cai et al., 2011). The default process appears to be suppression of a unitary response and initiation of a reprogrammed response with an inevitable time delay. Selective inhibition therefore may only be possible in the context of proactive inhibition.

Anticipation of action modulates excitability of involved motor representations prior to execution (Chen et al. 1998; Duque et al. 2010; Marinovic et al. 2013; Marinovic et al. 2011; Pascual-Leone et al. 1992). FDI MEP amplitude was facilitated above baseline from 175 ms prior to target on Go trials (Fig 3A). This confirms that CME reliably increases in a temporally appropriate manner during internally generated movements intrinsic to the ARI task (Coxon et al. 2006). Similarly, MEP amplitude increased 150–100 ms prior to target on GS trials as the default response was initiated. Pre-trigger rmsEMG remained at resting levels, confirming MEP amplitude facilitation reflects modulation upstream of the alpha motoneuron pool, and is presumably cortical in origin.

Unimanual RI studies show MEP amplitude attenuation 100–200 ms after stop signal presentation (Coxon et al. 2006; Hoshiyama et al. 1997; Hoshiyama et al. 1996; Yamanaka and Nozaki 2013). The present study extends these findings to a bimanual task requiring partial response cancellation. As predicted, the initial rise in CME on GS trials was followed by a significant decrease in excitability 175 ms after the stop signal (Fig 3A). Left FDI MEP

amplitude decreased despite the left hand not being cued to stop. From this key finding, we contend that inhibition cannot be purely "selective" for this task. Pre-planned multi-component responses are integrated into a single unitary response through "conceptual binding" (Wenderoth et al. 2009). Suppression of this unitary response affects all components equally, decreasing excitability of all coupled motor representations. Our data indicate that a unitary response was cancelled through suppression of both FDI motor representations.

Delayed responses on Partial trials can be conceptualized as follows. Movement components are "uncoupled" after termination of the unitary response (MacDonald et al. 2012). Uncoupling leads to separation of components, thus allowing the initiation (or selective reinitiation) of only the left response (Fig 4C), albeit delayed relative to target. The delayed response occurs at a higher gain than on execution trials (Coxon et al. 2007; Ko and Miller 2011; MacDonald et al. 2012). The higher gain may arise from a steeper rise in facilitatory input to overcome inhibition that resulted from cancellation of the original response.

On unsuccessful GS trials a bimanual response was made in error. Even on these occasions left FDI MEP amplitude decreased 175 ms after the stop signal (Fig 3D). This indicates that the inhibitory process was activated, but unable to sufficiently suppress the preprogrammed response. The temporal pattern of CME for unsuccessful GS trials (Fig 3D) was "shifted to the left" of Go trials, indicating that the excitability of involved motor representations was at a higher level and the excitatory process was further progressed when the stop signal was processed. Akin to the horse-race model, the excitatory process, likely belonging to the earlier part of the response distribution, 'won the race' and the bimanual response was generated (De Jong et al. 1990; Logan and Cowan 1984). Note however that the temporal consistency of CME suppression suggests independence between the excitatory and inhibitory processes, fulfilling

another crucial assumption of the horse-race model. Therefore the bimanual response was generated because the excitatory process was initiated earlier, whereas the latency of the inhibitory process, in response to the stop signal, remained the same. In summary, the pattern of CME modulation on successful and unsuccessful GS trials adheres to the principles of the horse-race model. Furthermore, it appears that a decrease in CME to some threshold relative to baseline is necessary to terminate the preprogrammed response in advance of successful selective response reinitiation.

The activation threshold model (ATM) can be used to explain CME modulation during the selective reinitiation process. During simple action execution muscle activity is not initiated until facilitatory inputs onto M1 exceed resting (tonic) inhibitory inputs (Fig 4A & B) (Dacks et al. 2012; Duque et al. 2010; Jaffard et al. 2008). This idea is consistent with existing "hold your horses" models of stop signal reaction time tasks (Ballanger et al. 2009). During partial response cancellation however, the activation threshold is elevated due to non-selective processing of the stop signal. The ATM accounts for the trend for decreased MEP amplitude during initial anticipation of the response on GS trials relative to Go (Fig 3A -125 and -100 ms; $P = 0.052$). With an equivalent initial rise in facilitatory drive and a simultaneous increase in inhibition, the rate of CME increase must be less. This is supported by the 50% lower rate of CME increase on GS trials compared to GG trials (Fig 3C), although this trend was not significant ($P = 0.09$). After uncoupling, a greater facilitatory drive is generated in the responding muscle to surpass the elevated activation threshold and initiate the reprogrammed response (Fig 4C). Once facilitatory inputs overcome inhibitory inputs, the response is necessarily at a higher gain, as can be seen in the rate of EMG onset and the example EMG traces (compare Fig 4A and C), and as shown previously (Coxon et al. 2007; MacDonald et al. 2012).

If foreknowledge about cancellation was provided, the ATM would predict the same inhibitory response for the responding component, from reactive processing of the stop signal, and an earlier change to facilitatory drive from prior knowledge of which component to reinitiate. An equivalent inhibitory increase but an earlier facilitatory response would lead to a shorter LT delay in Partial trials. This is speculative and remains to be tested in the context of the ARI task in a future study. Importantly however, the present and previous results indicate an elevated threshold is obligatory for reactive processing of a stop-signal.

Experiment 2

During motor preparation the amplitude of MEPs from TMS over involved motor representations may partly reflect GABAergic inhibition, which tonically suppresses inappropriate or premature movements (Dacks et al. 2012; Duque et al. 2010; Jaffard et al. 2008). Tonic GABAergic inhibition potentially includes cortical (Duque et al. 2010; Jaffard et al. 2008), spinal (Duque et al. 2010) and subcortical (Ballanger et al. 2009) inhibitory circuits. Paired-pulse TMS can be used to investigate local M1 intracortical inhibition, by pairing a subthreshold conditioning stimulus with a subsequent suprathreshold test stimulus (Coxon et al. 2006; Fisher et al. 2002; Kujirai et al. 1993; Peurala et al. 2008; Roshan et al. 2003), and can examine the contribution of M1 intracortical circuits to inhibition during motor preparation (Coxon et al. 2006). *Experiment 2* examined whether sICI within M1 was responsible for the elevated threshold within our model during Partial trials. We investigated whether modulation of sICI would coincide with modulation of CME from the first experiment.

Experiment 2 Methods

Protocol

The task and procedure was identical to *experiment 1* with the following exceptions:

All three stop conditions (SS, GS, SG) were of interest and equiprobable. There were 817 trials in total, 565 Go (70%) and 252 Stop trials (30%). Go and Stop trials were pseudo-randomized across 19 blocks of 43 trials.

For paired-pulse TMS, an inter-stimulus interval of 2 ms was chosen for investigating sICI (Peurala et al 2008) to examine $GABA_A$-mediated intracortical inhibitory processes within M1 (Di Lazzaro et al. 2000; Ziemann et al. 1996). Active motor threshold (AMT) was determined while the participant maintained an isometric left FDI contraction at about 5% of maximal voluntary contraction. TS and conditioning stimulus (CS) intensity were determined during practice of Go trials at -600 ms, prior to M1 movement preparation associated with switch release (Coxon et al. 2006). TS intensity was set to consistently evoke a MEP of about 1.5 mV with only minimal interference of task performance. CS intensity was determined by starting at 65% AMT and increasing in 1% MSO increments until the conditioned (C) MEP amplitude was 50% of non-conditioned (NC) MEP (CS_{50}) (Coxon et al. 2006; Fisher et al. 2002; Stinear and Byblow 2003).

The sICI protocol necessitated a more narrow range of stimulation times to ensure a tolerable experiment duration. TMS was delivered early or late, at -75 ms and -25 ms on Partial trials, -25 ms and +25 ms on SS, and -600 ms and -125 ms on GG trials (Fig 2B). Stimulation on Go trials at -600 ms ensured a baseline measure prior to trial related modulation of CME. Stimulation at -125 ms enabled the comparison of CME to -25 ms on GS trials, following

findings from *experiment 1*. Stimulation on all Stop trials was 175 ms and 225 ms post stop signal, to examine sICI at the time of MEP suppression and subsequent increase. Twenty single- and paired-pulse TMS trials were collected in each condition in pseudo-random order. All three stop trial conditions included stimulated trials.

Dependent measures

Lift times (LTs) were determined for successful Go and Partial trials. Average LTs were calculated after removing outliers (± 3 SD) (1.2 ± 0.2% and 0.2 ± 0.1%, respectively). LT from successful Partial trials corresponds to the responding digit. All LTs are reported in milliseconds relative to the target. Stop signal reaction time (SSRT) was determined for each stop condition using the integration method as described for *experiment 1*.

MEP amplitude for both C and NC trials, percent inhibition (%INH) and pre-trigger rmsEMG were determined. %INH was calculated as [(NC MEP – C MEP) / NC MEP] * 100. NC MEP amplitudes were compared within and between GG and Partial trials using planned comparisons, following results from *experiment 1*. Primary measures of interest were the differences in %INH among the three types of Stop trials. Pre-trigger rmsEMG was calculated within a 50 ms window prior to TMS and trials were discarded if rmsEMG was above 14μV. Trials were visually inspected and discarded if activity was present between the stimulus and MEP onset.

Statistical analysis

Dependent measures were subjected to RM ANOVAs, as in *experiment 1*, with the same criteria for statistical significance. LT and predetermined indicator stop times were analyzed as in *experiment 1*. All results are shown as group means ± standard error.

NC MEP amplitude and pre-trigger rmsEMG were examined in 4 Trial Type (GG, SG, GS, SS) x 2 Stimulation Time (early, late) RM ANOVAs. The sICI protocol was checked by examining %INH on Go trials (-600 ms) against 0 using a one-sample *t* test. %INH on Stop trials was examined in a 3 Stop Trial Type (SG, GS, SS) x 2 Stimulation Time (early, late) RM ANOVA. For Go trials, %INH was examined using a two-tailed paired *t* test. Linear regression was performed to determine if the change in %INH between GG and GS trials (-125 ms on GG vs -25 ms on GS) was associated with LT delay. SSRTs were analyzed using a one-way RM ANOVA with Stop Condition (SG, GS, SS) as factors.

Experiment 2 Results

Behavioral Data: Lift times and SSRT

LTs are shown in Table 2. For Go trials, LTs occurred on average 14 ± 2 ms after the target, indicating successful performance as reported previously and in *experiment 1*. There was a main effect of Trial Type ($F_{1,12}$ = 321.6, P < 0.001), with LTs delayed on Partial trials to 100 ± 5 ms after the target. There were no other main effects or interactions (all P > 0.130). Go LTs were not significantly different between stimulated (at -125 ms) and unstimulated trials (t = 1.8, P = 0.099), indicating that TMS did not have an appreciable affect on behaviour.

For SSRT there was a main effect of Stop Condition ($F_{2,24}$ = 27.3, P < 0.001). The SSRT for SS trials (222 ± 4 ms) was faster than that for SG (254 ± 6 ms; t_{12} = -7.6, P < 0.001) and GS trials (252 ± 5 ms; t_{12} = -5.9, P < 0.001), which did not differ from each other (t_{12} = 0.5, P = 0.644). Success on GS trials was greater than 50% (65.6 ± 5.0%; t_{12} = 3.1, P = 0.009) and significantly higher than in *experiment 1* (t_{12} = 3.9, P = 0.002). Success on SG (60.6 ± 6.1%) and

SS trials (42.7 ± 4.4%) did not differ significantly from 50% successful inhibition (t_{12} = 1.7, P = 0.108 and t_{12} = -1.7, P = 0.124, respectively).

Neurophysiological Data: MEP amplitude, sICI and pre-trigger rmsEMG

Due to an insufficient number of MEPs after rejecting trials with pretrigger rmsEMG above 14 μV, three participants were removed from the neurophysiological data for *experiment 2*, leaving 10 participants in the analysis. AMT was 38 ± 3% MSO, TS intensity was 55 ± 4% MSO, and average CS_{50} was 29 ± 2% MSO (76.0 ± 2.3% of AMT). The conditioning protocol successfully produced sICI using TS and CS intensities set during practice blocks. Average NC MEP amplitude on Go trials (-600 ms) was 1.48 ± 0.20 mV. Average %INH during Go trials decreased compared to practice blocks, but was still significantly larger than zero (28.4 ± 7.8%; t_9 = 3.6, P = 0.005), as observed previously (Coxon et al. 2006).

For %INH on Stop trials there was a main effect of Stimulation Time ($F_{1,9}$ = 9.1, P = 0.015) but no effect of Stop Trial Type ($F_{2,18}$ = 0.3, P = 0.847) or Stop Trial Type x Stimulation Time interaction ($F_{2,18}$ = 1.9, P = 0.173). %INH was on average greater at the later (33.0 ± 4.5 %) compared to early (28.2 ± 4.7 %) stimulation time on Stop trials. On Go trials, there was no group level significant difference between %INH at early (-600 ms; 28.4 ± 7.8 %) and late (-125 ms; 37.0 ± 4.6 %) stimulation times (t_9 = 1.0, P = 0.355). This non-significant difference arose from participants with lower sICI at -600 ms increasing %INH during task Go trials whereas participants with higher sICI at -600 ms decreased %INH during Go trials (r = 0.85, P = 0.002; Fig 5). The change in sICI was correlated with baseline levels of sICI at -600 ms. The opposing modulation of sICI during Go trials resulted in the non-significant group effect. A paired-sample t test (one-tailed) testing for greater %INH on GS trials at -25 ms compared to GG trials at -125

ms was not significant (30.9 ± 5.4 % on GS vs 37.0 ± 4.6% on GG; $t_9 = 1.1$, $P = 0.151$). There was no correlation linking change in %INH between GG and GS trials and LT delay ($r = 0.20$, $P = 0.587$).

For NC MEP amplitude there was a Trial Type x Stimulation Time interaction ($F_{3,27} = 6.0$, $P = 0.003$, Fig 6), a main effect of Stimulation Time ($F_{1,9} = 17.0$, $P = 0.003$), and no main effect of Trial Type ($F_{3,27} = 1.3$, $P = 0.284$). On Go trials NC MEP amplitude increased from -600 ms (1.48 ± 0.20 mV) to -125 ms (2.62 ± 0.39 mV; $t_9 = 3.6$, $P = 0.006$), indicating that CME increased on GG trials as demonstrated in *experiment 1*. On GS trials NC MEP amplitude increased from -75 ms (2.17 ± 0.30 mV) to -25 ms (2.75 ± 0.40 mV; $t_9 = 3.0$, $P = 0.014$), mirroring the increase in CME between these stimulation times in *experiment 1*. On SG trials NC MEP amplitude also increased from -75 ms (2.01 ± 0.23 mV) to -25 ms (2.51 ± 0.39 mV; $t_9 = 2.4$, $P = 0.042$). On SS trials NC MEP amplitude did not differ between stimulation times ($t_9 = 1.2$, $P = 0.247$). There was a significant decrease in NC MEP amplitude at -75 ms on GS trials compared to -125 ms on GG trials ($t_9 = 2.0$, $P = 0.041$), mirroring results of *experiment 1*. NC MEP amplitude also decreased at -75 ms on SG trials compared to -125 ms on GG trials ($t_9 = 2.1$, $P = 0.030$). Based on results of *experiment 1*, a planned comparison tested for a difference in NC MEP amplitude between -125 ms on Go trials and -25 ms on GS trials. No significant difference was found ($t_9 = 0.8$, $P = 0.452$), as expected.

Mean pre-trigger rmsEMG level was 8 ± 1 μV indicating that the FDI remained at rest throughout testing. There were no main effects or interactions for pre-trigger rmsEMG (all $P > 0.099$).

Experiment 2 Discussion

Experiment 2 was designed to investigate the inhibitory component of the ATM. In support of the model, sICI showed an overall increase over the course of stop trials. However, contrary to our second hypothesis, there was no modulation of M1 sICI during GS trials that could account for the observed CME modulation. CME suppression 175 ms after the stop cue on GS trials of *experiment 1* does not appear to rely purely on M1 intracortical inhibitory mechanisms. We did not observe a significant increase in sICI at this time point on GS trials. Given this disparity between CME and sICI data on GS trials, it is unlikely that the $GABA_A$-mediated intracortical inhibitory processes within M1 (Di Lazzaro et al. 2000; Ziemann et al. 1996) probed at an ISI of 2 ms can fully account for attenuated left FDI MEP amplitude after the right finger was cued to stop. Our results suggest M1 sICI is unlikely to be the primary mechanism contributing to the decrease in excitability on Partial trials and the increased activation threshold within the ATM.

Experiment 2 was successful at validating the main results from *experiment 1* and extending the model. NC MEP amplitude increased during Go trials of *experiment 2* (Fig 6), further confirming that CME reliably increases in a temporally appropriate manner during movement anticipation in the ARI task (Coxon et al. 2006). NC MEP amplitude was suppressed at -75 ms on GS trials relative to -125 ms on GG trials, mirroring CME suppression in *experiment 1*. NC MEP amplitude was also suppressed at -75 ms on SG trials, indicating this same dip in CME is seen whether the left side is cancelled or executed in a Partial trial. The decrease in NC MEP amplitude on both GS and SG trials (Fig 6) informed the ATM by indicating an equivalent increase in inhibition for both digits (Fig 4C & D) following processing of the stop cue. The subsequent equivalent increase in CME for cancelled and executed digits from -75 ms to -25 ms (Fig 6) would indicate full uncoupling between response representations has not yet occurred at

these time points. We propose uncoupling on Partial trials is achieved between -25 ms and 0 ms prior to facilitation of the reprogrammed, single component response ('U', Fig 4C & D).

M1 sICI at 2 ms ISI is unlikely to be the primary mechanism contributing to the decrease in excitability on Partial trials and the increase in the activation threshold. sICI demonstrated an overall increase over the course of stop trials as our model would predict, indicating cancellation of a prepared bimanual response recruits sICI in this context (Coxon et al. 2006). However the delayed increase at 225 ms would indicate it is not the inhibitory mechanism responsible for CME suppression 175 ms post stop signal on GS trials. For a comparable level of corticomotor pathway excitability (-125 ms on GG versus -25 ms on GS trials), sICI was not comparably higher on GS trials. Furthermore, there was no correlation between the difference in sICI between GG and GS trials and the extent of LT delay. While M1 sICI appears to be modulated during stop trials of a bimanual ARI task, it is unlikely to be the sole inhibitory mechanism producing the dynamic modulation of CME on GS trials or the increased threshold within our model.

Non-significant results are difficult to interpret and there are a couple of considerations for this study. Firstly, MEPs are point-wise measures of CME and can be influenced by multiple co-occurring and/or temporally overlapping processes (Duque et al. 2010). For example, sICI and interhemispheric inhibition (IHI) may be occurring simultaneously during this bimanual task. SICI is significantly reduced in the presence of IHI (Daskalakis et al. 2002). It is possible that IHI masked the true involvement of sICI during Go and Partial trials. As our study did not include any direct measures of IHI we can only speculate as to its role on sICI measures. Secondly, the inherent dynamic excitability of involved motor representations prior to an anticipated response resulted in significant differences in NC MEP amplitude during Go and

Partial trials. It can be exceedingly difficult to match NC MEP amplitudes during an active task. Unfortunately a change in NC MEP amplitude complicates the comparison of sICI across and between trials (Daskalakis et al. 2002; Sanger et al. 2001). Nevertheless, it is important to note that TS intensities consistently produced average NC MEP amplitudes between 1.5 and 2.8 mV, within the optimal range for sICI (Sanger et al. 2001).

If sICI is not the primary mechanism contributing to the raised activation threshold within the model, other likely mechanisms include cortico-subcortical loops through the basal ganglia or cortico-cortical afferents (Alexander and Crutcher 1990; Ballanger et al. 2009; Danion and Latash 2011; Di Lazzaro et al. 2008; Jahfari et al. 2011; Mattia et al. 2012). The involvement of cortico-subcortical loops during Partial trials for the ARI task would align with two recent studies (Coxon et al. 2012; Majid et al. 2013). Further research is warranted into the inhibitory mechanisms involved in this bimanual task.

General Discussion

Participants performed the task correctly, assuring validity of the study. Firstly, Go LTs confirmed that participants did not delay their response in anticipation of a stop cue. The traditional stop-signal task can allow adjustments to response strategies (i.e. response slowing) to balance the requirements of the execution and inhibition conditions (Lappin and Eriksen 1966; Verbruggen and Logan 2009). However, due to task design (stop signal occurring *before* the target), an ARI task ensures go-response preparation in the presence of stop cues. The current study is therefore reliably investigating CME modulation during partial cancellation of an *initiated* bimanual response. Secondly, partial trial LTs were significantly delayed compared with complete movement execution, as seen previously. Finally, LTs were comparable between

experiments and with previous studies using this task (Coxon et al. 2007; MacDonald et al. 2012), so TMS did not affect behavioral performance. Therefore, the data reflect the unpredicted (reactive) cancellation of an initiated response.

Conclusion

These studies provide novel insight into RI. Partial response cancellation requires complex temporal modulation of CME in a pattern consistent with the anticipation, suppression and subsequent selective reinitiation of the response. The proposed activation threshold model can account for CME modulation leading to delayed reinitiation of the reprogrammed response at a higher gain. Elucidating the mechanisms responsible for RI and CME modulation during such a cognitively demanding task is challenging and may involve a combination of cortical and subcortical processes. Whatever the underlying mechanism, it appears that neuroanatomical constraints prevent purely selective inhibition in a reactive context.

Author contributions

H.M. collected the data. H.M., J.C. and W.B conceived and designed the experiment. HM wrote the first draft of the manuscript. All authors participated in the analysis and interpretation of the data and critical editing of the manuscript. All authors approved the final version of the manuscript.

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Figure Legends

Figure 1. Visual display. Top left: the start of each trial when trial type is ambiguous. Top right: successful Go (GG) trial when both bars were stopped at the target by the participant. Bottom left: successful Stop Both (SS) trial when both bars automatically stopped before reaching the target (-200 ms) and the participant correctly inhibited their response. Bottom right: successful Partial trial (Go Left - Stop Right, GS) when the right hand response was correctly inhibited but the left response missed the target and was delayed. S and G labels were not displayed to participants. Visual feedback ("success" or "missed") was displayed after each trial.

Figure 2. Schematic of *experiment 1* (A) and *2* (B) design showing trial types of interest. Horizontal solid lines represent time relative to trial onset (-800 ms). The vertical dashed line represents the target (0 ms). Stop times on stop trials are represented by the short vertical lines. Horizontal dashed lines on GS trials indicate that the left digit is still required to respond. Black vertical arrows indicate the pseudorandom times at which single-pulse TMS was delivered over right M1 (25 ms intervals, e*xperiment 1*). Grey vertical arrows show time when paired-pulse (sICI) and single-pulse TMS was delivered over right M1 (*experiment 2*). These timings were derived from the results of *experiment 1*. All numbers indicate time in milliseconds prior to target.

Figure 3. Modulation of left FDI corticomotor excitability (CME) in *experiment 1.* (*A*) Left FDI MEP amplitudes during Go trials (GG) and Partial trials (GS) (N = 15). (*B*) Individual participant data showing the temporal evolution of CME following the Partial stop cue (GS). This demonstrates that the dip in CME on GS trials was highly consistent (N = 13: 2 participants had a missing data point in this range). (*C*) Rate of CME increase leading up to the response for Go and GS trials (N = 13 as for B). Note that the slope for GS is half that of GG. (*D*) Re-

illustration of panel *A* including MEP amplitudes during unsuccessful GS trials for comparison. Significant differences are not identified. MEP: motor evoked potential; GG: Go trials; GS: Go Left – Stop Right trials; rmsEMG: root mean square electromyography. Stop cue given at -250 ms on GS trial. Hashes represent significant increases relative to baseline during GG trials: # $P < 0.05$; ## $P < 0.01$; daggers denote trends: † $P = 0.052$; asterisks represent significant differences during GS trials: * $P < 0.05$; ** $P < 0.01$. All symbols are means ± SE.

Figure 4. An activation threshold model (ATM) can account for corticomotor excitability modulation preceding movement initiation on Go trials (*A, B*) and the delayed reinitiation at a higher gain on GS trials (*C*). The ATM represents co-existing facilitatory and inhibitory processes that compete upstream of the final common motor pathway preceding muscle activity. The y axis is unitless and reflects amplitude. Dotted vertical lines identify when the facilitation exceeds the activation threshold, corresponding to the generation of muscle activity. Lightning bolts represent the timing of single-pulse TMS. The single arrow represents timing of stop signal (*C, D*), causing a step input to inhibitory levels (*I*), raising the activation threshold. A new ramp facilitatory input (*F*) causes deviation of the facilitatory slope in (*C*), representing the facilitation and initiation of the reprogrammed response (comprised of one component) after uncoupling of the unitary response (*U*). Left digit is modelled using result data (*A, C*), right digit is hypothesized (*B, D*). EMG: electromyography; LT: lift time. Rectified EMG traces from individual participant representing a GG (*A*) and GS (*C*) trial in *experiment 1*.

Figure 5. Linear regression between %INH at -600 ms and change in %INH ($r = 0.85$, $P = 0.002$) on Go trials in *experiment 2*. Participants with higher %INH at -600 ms demonstrated a decrease in %INH during Go trials, whereas those with lower baseline %INH demonstrated an increase in %INH during Go trials. %INH: percent inhibition.

Figure 6. Modulation of corticomotor excitability in *experiment 2*. Left FDI non-conditioned MEP amplitudes and pre-trigger rmsEMG shown at -600 ms and -125 ms stimulation on GG trials (filled circles), -75 ms and -25 ms stimulation on SG (open circles) and GS trials (filled triangles), -25 ms and +25 ms stimulation on SS trials (open triangles). MEP: motor evoked potential; NC: non-conditioned; rmsEMG: root mean square electromyography; GG: Go trials; SG: Stop Left – Go Right trials; GS: Go Left – Stop Right trials; SS: Stop Both trials. Symbols are means ± SE (N = 13). * $P < 0.05$ between stimulation times for GG, SG and GS trials.

Table Legends

Table 1. GG: Go trial; GS: Go Left – Stop Right trial; SG: Stop Left – Go Right trial; LT: lift time; SD: standard deviation; SE: standard error. Lift times are represented relative to target at 800 ms.

Table 2. GG: Go trial; GS: Go Left – Stop Right trial; SG: Stop Left – Go Right trial; LT: lift time; SD: standard deviation; SE: standard error. Lift times are represented relative to target at 800 ms.

Table 1: Lift times for Go and Partial trials for each participant in *experiment 1*.

Subject	GG trial: Left digit LT (ms)	GG trial: Right digit LT (ms)	GS trial: Left digit LT (ms)	SG trial: Right digit LT (ms)
1	10	3	71	81
2	0	28	79	155
3	1	12	69	76
4	-4	5	73	109
5	22	35	112	67
6	7	2	101	118
7	5	38	78	117
8	3	20	79	NA
9	15	15	93	72
10	9	10	137	NA
11	20	28	90	122
12	10	14	105	119
13	8	11	65	NA
14	22	17	115	121
15	19	20	102	102
Average	10	17	91	105
SD	8	11	21	26
SE	2	3	5	8

Table 2: Lift times for Go and Partial trials for each participant in *experiment 2*.

Subject	GG trial: Left digit LT (ms)	GG trial: Right digit LT (ms)	GS trial: Left digit LT (ms)	SG trial: Right digit LT (ms)
1	5	12	71	108
2	2	6	80	82
3	24	22	146	101
4	24	-1	113	79
5	12	22	115	85
6	6	3	95	128
7	18	12	103	74
8	18	12	91	75
9	29	9	120	111
10	25	16	120	108
11	20	13	81	74
12	21	13	90	88
13	13	16	134	141
Average	17	12	105	96
SD	8	7	22	22
SE	2	2	6	6