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Uncoupling Response Inhibition

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H.M. collected the data. All authors conceived and designed the experiment. All authors participated in the analysis and interpretation of the data and writing of the manuscript. All authors approved the final version of the manuscript.

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Abstract

The ability to prevent unwanted movement is fundamental to human behaviour and often impaired in neurodegenerative conditions. When healthy adults must prevent a subset of prepared actions, their execution of the remaining response is markedly delayed. We hypothesized that the delay may be sensitive to the degree of similarity between the prevented and continued actions. Fifteen healthy right handed participants performed an anticipatory response inhibition task that required bilateral index finger extension or thumb abduction with homogeneous digit pairings, or a heterogeneous pairing of a combination of the two movements. We expected that the uncoupling of responses required for selective movement prevention would be more difficult with homogeneous pairings (same digit, homologous muscles) than heterogeneous pairings (different digits, non-homologous muscles). Measures of response times (response time delay and asynchrony between digits during action execution), stopping performance and electromyography from EIP (index finger extension) and APB (thumb abduction) were analyzed. Interestingly, successful performance in the selective condition occurred via suppression of the entire prepared response and subsequent selective re-initiation of the remaining component. The delayed re-initiation of motor output was sensitive to the degree of similarity between responses, occurring later but at a faster rate with homogeneous digits. There were persistent after-effects from the selective condition on the motor system which indicated greater levels of inhibition and a higher gain were necessary to successfully perform selective trials with homogeneous pairings. Overall the results support a model of inhibition of a unitary response and selective re-initiation, rather than selective inhibition.

Keywords: selective inhibition, response coupling

Introduction

Response inhibition requires prevention of unwanted movement and is fundamental to human behaviour. It is challenging because it requires higher order control, and is often impaired in neurodegenerative conditions (Gauggel et al. 2004; Stinear et al. 2009). Response inhibition engages a right-lateralized brain network comprised of the inferior frontal cortex (IFC), supplementary motor areas (SMA), nuclei of the basal ganglia, thalamic regions and primary motor cortex (M1) (Aron et al. 2003; Aron and Poldrack 2006; Coxon et al. 2006; 2009; Garavan et al. 1999; Liddle et al. 2001; Mostofsky et al. 2003; Rubia et al. 2003; Stinear et al. 2009). The specific regions activated depend on the goal of the inhibition: inhibition of all movement or inhibition of only a subset of movement components (Cai et al. 2011; Coxon et al. 2009).

Response inhibition is traditionally investigated using a Stop Signal or Go/No-Go paradigm (or variations of these paradigms), both in humans and animals (Aron et al. 2003; Aron and Poldrack 2006; Aron and Verbruggen 2008; Eagle and Robbins 2003; Kenner et al. 2010; Leocani et al. 2000; Mars et al. 2009; Sharp et al. 2010). Although the Stop Signal paradigm offers advantages with respect to well defined go and stop cues, this paradigm has suspected limitations (Verbruggen and Logan 2009). One cannot be certain that a response has been planned or initiated at the time of the stop signal. This is an important consideration when calculating the latency of the stop process (stop signal reaction time, SSRT), which is used as an index of inhibitory control. Conversely, an anticipatory response inhibition (ARI) task (Slater-Hammel 1960) better ensures go response preparation in the presence of stop cues. Coxon et al. (2007; 2009) and Stinear et al. (2009) used the ARI task to investigate the selectivity of inhibitory control by requiring some, but not all, prepared movements to be inhibited in response to a selective stop cue. This requirement produced markedly delayed execution of the remaining

go response. Coxon and colleagues speculated that this delay was the result of rapid non-selective suppression of all prepared movements and subsequent selective re-initiation of the required response. These movement re-selection and initiation processes are thought to be occurring within the SMA and M1 (Coxon et al. 2009; Rubia et al. 2003).

An alternative way to conceptualize the process of selective movement prevention is with the suppression of a single unitary response, which is comprised of all prepared movement components 'coupled' together. The suppression would therefore affect all subcomponents of the single response simultaneously. The response would then need to be separated into its subcomponents before selective re-initiation of only the required movement could occur. The separation would be achieved through uncoupling all the response components. If this model is correct, the uncoupling and re-initiation processes should be sensitive (under time pressure) to the strength of coupling between subcomponents in the prepared movement.

The aim of the present study was two-fold: firstly, to investigate the aforementioned re-selection and initiation processes presumed to occur during selective tasks; and secondly, to investigate whether the delays in responding that occur on selective trials reflect the degree of coupling between independent components of the previously prepared movement. This was done by altering hand and arm posture during a bimanual ARI task employed previously (Coxon et al. 2006; 2007; 2009; Zandbelt and Vink 2010). The alteration of posture was intended to produce a strongly coupled homogeneous pairing and a weakly coupled heterogeneous pairing. We hypothesized that the requirement for selective response prevention would cause a delay in the remaining response, compared to standard go trials (Coxon et al. 2007). Secondly, we hypothesized that the delay would be greater (with a different underlying EMG profile) in homogeneous pairings. We further hypothesized that the carry-over effects of uncoupling during

selective trials would be more prominent in the non-dominant hand, indicative of more stringent coupling of the non-dominant to the dominant hand than vice versa (Byblow et al. 2000; Carson 1993).

Methods

Participants

Fifteen healthy adults with no neurological impairment were included in the study (mean age 25 years, range 20 – 32 years, 9 male). All participants were right handed (mean laterality quotient 0.94, range 0.79 – 1.0) 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.

Behavioural Task

The bimanual ARI task is based on the paradigm by Slater-Hammel (1960), adapted previously for examining selective response inhibition (Coxon et al. 2007). Participants sat 1 m in front of a computer display while performing the task. The display consisted of two vertically orientated indicators, 18 cm tall and 2 cm wide, separated by 2 cm (Figure 1). The left indicator corresponded to the left hand digit and the right indicator to the right hand digit. The task was controlled using custom software (MatLab R2011a) interfaced with two custom made switches. Each trial commenced after a variable delay when both switches were depressed. Both indicators moved upwards from the bottom at the same rate, reaching the target after 800 ms.

The majority of trials (66 %, main experiment) involved releasing both switches in time to stop both indicators at the target (Go trials). To emphasize that trials were to be performed as accurately as possible, visual feedback was displayed at the completion of each trial, stating whether the indicator(s) had been stopped sufficiently close to the target (within 30 ms) (See Figure 1). Occasionally one or both indicators stopped automatically before reaching the target. In this case, participants were required to not lift the corresponding digit(s) (Stop trials). There were three types of Stop trials: Stop Both, when both indicators stopped automatically and Stop Left and Stop Right (selective trials), when only the left or right indicator stopped, respectively. Selective trials still required the participant to stop the other indicator as accurately as possible at the target, by lifting the corresponding digit. Feedback also indicated whether inhibition of one or both responses was successful.

The indicator for each Stop trial type was initially set to stop automatically at 600 ms and the indicator stop time changed dynamically throughout the task. Following successful inhibition, the stop time was delayed by 25 ms on the subsequent Stop trial (increasing difficulty); following unsuccessful inhibition, the stop time was set 25 ms earlier. This staircase procedure ensured convergence to a stop time that resulted in a 50 % probability of successful inhibition for each type of Stop trial. The task consisted of 8 blocks, each comprising 30 trials. The first two blocks involved only Go trials. Of the remaining 180 trials (6 blocks), 120 were Go trials and 60 were Stop trials (20 trials per Stop type). Go and Stop trials were pseudo-randomized across the 6 blocks. Each participant completed the task four times in different postures. Each posture required either bilateral index finger extension or thumb abduction (homogeneous pairings), or a combination of the two (heterogeneous pairings).

Recording procedure

Electromyography (EMG) data were recorded from bilateral extensor indicis proprius (EIP) and abductor pollicus brevis (APB) muscles. Electrodes were placed in a belly tendon montage and ground electrodes were placed over the lateral surface of the wrist (for APB) and the lateral surface of the olecranon of the elbow (for EIP). EMG signals were amplified (CED 1902, Cambridge, United Kingdom), bandwidth filtered (20 - 1000 Hz) and sampled at 2 kHz (CED 1401, Cambridge, United Kingdom). Data were saved for later offline analysis using Signal (CED, Cambridge, United Kingdom) and custom software (MatLab R2011a).

Dependent measures

Average lift time (LT) was determined for Go and selective trials. LT from successful selective trials corresponds to the responding digit. Average LT was calculated after removing LTs more than 3 SD from the mean. Lift time asynchrony (LTA) was calculated on Go trials following Go trials, and following successful Stop trials. LTA was calculated from (left digit LT) – (right digit LT) and reported in milliseconds.

For Stop trials, stop signal reaction time (SSRT) and staircased indicator stop time (producing 50 % probability of success) were determined for each trial type. Staircased indicator stop time refers to the time the indicator was programmed to stop relative to the trial onset due to the staircase procedure. SSRT was calculated using the mean method (Logan and Cowan 1984) as the staircase procedure ensured a success rate of 50 %.

Stop trials exhibited an initial EMG burst in both muscles (partial bursts) followed by a delayed main EMG burst in only the responding muscle. Partial bursts are reported as a

percentage of total successful Stop trials for each stop type. Partial bursts were documented as the percentage of successful selective trials, Stop Both trials, and when they occurred only in the non-responding muscle in selective trials. Onset time and peak rate of onset for the main EMG burst causing the lift (lifting burst) was determined. Peak rate of EMG onset was also determined for Go trials, calculated using a dual-pass 20 Hz Butterworth filter prior to differentiation (Coxon et al. 2007). EMG burst onset was defined as a rise of 3 SD above baseline causing the lift response (Hodges and Bui 1996). Offset times (drop below 3 SD of baseline) of both partial EMG bursts were also calculated. Electromechanical delay (EMD) was determined for Go and selective trials. EMD was calculated as the time (ms) between EMG burst onset and LT (EMD = LT – EMG onset).

Statistical analysis

All dependent measures were subjected to repeated measures (RM) analysis of variance (ANOVA) with post hoc comparisons when necessary. A 4-way RM ANOVA tested for differences in mean LT, EMD and peak rate of EMG onset between Go and selective trials, with factors Side (Left, Right), Digit (Thumb, Index), Pairing (Same, Different) and Trial Type (Go, Selective).

Go trials preceded by a successful Stop trial were sorted according to Stop trial type. The average LT for the left and right digit and the LTA were calculated. LTA and average LTs were also determined for Go trials preceded by Go trials (not Stop trials) for comparison. Differences in average LTA were analyzed with a 3-way RM ANOVA, factors Digit, Pairing and Preceding Trial Type (Go, Stop Left, Stop Right, Stop Both). The LTs were analyzed with a 4-way RM

ANOVA, factors Side, Digit, Pairing and Preceding Trial Type. LTs were also analyzed using a 4-way RM ANOVA with Stop Both trials removed.

A 3-way RM ANOVA with factors Digit, Pairing and Trial Type (Stop Left, Stop Right, Stop Both) tested for differences in mean staircased indicator stop time, SSRT and percentage partial bursts. A 3-way RM ANOVA tested for differences in average percentage of dual burst trials as well as initial burst offset and main EMG burst onset time in dual burst trials. Factors were Digit, Pairing and Trial Type (Stop Left, Stop Right).

For non-spherical data, the conservative Greenhouse-Geisser P value was reported. Criterion for statistical significance was $\alpha = 0.05$. Post hoc Bonferroni corrected paired *t* tests were used to test main effects or interactions. All results are shown as group means ± standard error (SE).

Results

Stop signal reaction time

There was a main effect of Trial Type ($F_{2,14} = 9.3$, $P = 0.003$). The SSRT for Stop Both trials (208.1 ± 3.7 ms) was faster than Stop Left (242.3 ± 8.7 ms, $P < 0.001$) and Stop Right (250.2 ± 9.5 ms, $P < 0.001$) trials, which did not differ from each other ($P = 0.556$). This effect was precipitated by an effect of Trial Type ($F_{2,14} = 11.8$, $P = 0.001$) on the time at which the staircase procedure stopped the indicator on Stop trials to achieve a 50 % success rate. The staircase procedure stopped the indicator later for Stop Both trials (603 ± 5 ms) than Stop Left

208 (567 ± 9 ms, $P < 0.001$) and Stop Right (562 ± 9 ms, $P < 0.001$) trials, which did not differ from
209 each other ($P = 0.690$). There were no other main effects or interactions.

210

211 *Lift times for Go and selective trials*

212 LTs are shown in Figure 2. For Go trials, LTs were 810.6 ± 1.8 ms and similar to those reported
213 previously (Coxon et al. 2006; 2007). LT during the selective condition was delayed (901.0 ± 4.9
214 ms) compared to Go trials (main effect of Trial Type ($F_{1,14} = 465.9$, $P < 0.001$) (Figure 2). There
215 was a main effect of Side ($F_{1,14} = 6.3$, $P = 0.025$) but no effect of Digit ($F_{1,14} < 1$) or Pairing
216 ($F_{1,14} = 1.5$, $P = 0.243$). For Go and selective trials combined, LTs for the left digit (859.3 ± 2.9
217 ms) were slower than the right (852.3 ± 3.8 ms). There were no other main effects or
218 interactions.

219

220 *Lift times for Go trials preceded by Go vs successful Stop trials*

221 There was a Side x Trial Type interaction ($F_{3,14} = 24.6$, $P < 0.001$) which was preserved when
222 Stop Both trials were removed ($F_{2,14} = 33.3$, $P < 0.001$). The following results are from the
223 analysis with Go and selective trials only. There was no effect of Digit ($F_{1,14} = 1.3$, $P = 0.277$) or
224 Pairing ($F_{1,14} < 1$). Post hoc tests revealed a faster average Go LT with the left side immediately
225 after a Stop Right trial (806.2 ± 3.5 ms) compared to after a Go trial (813.5 ± 2.1 ms, $P = 0.022$)
226 (Figure 3A). There were no differences between Go LTs with the right side. There were no other
227 main effects or interactions. Figure 3B and C show the Side x Trial Type interaction for
228 homogeneous and heterogeneous pairings respectively.

229

Lift time asynchrony between digits on Go trials preceded by Go vs successful Stop trials

There was a main effect of Trial Type ($F_{3,14}$ = 24.6, P < 0.001) and a Digit x Pairing interaction ($F_{1,14}$ = 5.2, P = 0.039). There were no other effects or interactions. LTA on Go trials was larger when preceded by Stop Left trials (11.1 ± 3.0 ms), than by Go trials (3.4 ± 2.7 ms, P < 0.001), indicating the left LT lagged the right LT to a greater extent when the left digit was previously inhibited (Figure 4). Conversely, LTA on Go trials was less when preceded by Stop Right trials (-2.4 ± 3.0 ms), than by Go trials (P < 0.001). There was no difference in LTA following Stop Both compared to Go trials (P = 0.349). The Digit x Pairing interaction arose because LTA was larger with the heterogeneous pairing when the left digit was the thumb (7.9 ± 3.1 ms) rather than the index finger (-1.1 ± 3.7 ms, P = 0.047), but there was no difference between digits for homogeneous pairings (P = 0.204).

EMG onset time, rate and EMD during successful selective and Go trials

For the lifting EMG burst onset time, there was a main effect of Pairing ($F_{1,14}$ = 6.0, P = 0.028), shown in Figure 5A. EMG burst onsets were later with homogeneous pairings (833.0 ± 5.3 ms) than heterogeneous pairings (821.7 ± 6.3 ms). There were no other main effects or interactions.

For EMD there was only a main effect of Pairing ($F_{1,14}$ = 5.5, P = 0.035), which was shorter with homogeneous (74.0 ± 2.4 ms) than heterogeneous (77.1 ± 2.8 ms) pairings (Figure 5B).

The rate of EMG burst onset showed a main effect of Digit ($F_{1,14}$ = 5.0, P = 0.042), Pairing ($F_{1,14}$ = 5.3, P = 0.038) and Trial Type ($F_{1,14}$ = 8.6, P = 0.011), as well as a Digit x Pairing interaction ($F_{1,14}$ = 5.0, P = 0.042) but no effect of Side ($F_{1,14}$ = 4.2, P = 0.059). Peak

rate of onset was larger during selective trials (5.9 ± 0.5 mV/s) than Go trials (5.5 ± 0.5 mV/s, P = 0.011) (Figure 5C). Peak rate of onset in the APB (thumb) was larger during homogeneous (7.5 ± 0.9 mV/s) than heterogeneous pairings (6.2 ± 0.8 mV/s, P = 0.031) but pairing had no effect on EIP (index finger) (Figure 5D). There were no other main effects or interactions.

Percentage of partial EMG bursts on Stop trials

Partial bursts occurred in the inhibited muscle(s) during successful Stop Both (Figure 6A) and selective (Figure 6B) trials. There was a main effect of Trial Type ($F_{(2,14)}$ = 15.9, P < 0.001) and post hoc tests revealed Stop Both (35.1 ± 2.1 %) had a higher percentage of partial bursts than Stop Left (22.9 ± 2.8 %, P < 0.001) and Stop Right (27.3 ± 2.1 %, P < 0.001), which did not differ from each other (P = 0.111). There was a Digit x Pairing x Trial Type interaction ($F_{2,14}$ = 4.6, P = 0.028) that did not decompose meaningfully. There were no other main effects or interactions.

Partial EMG bursts on selective trials

Some successful selective trials showed two important characteristics: 1) a partial burst in *both* muscles as well as 2) a lifting EMG burst in only the responding muscle (Figure 6B). These trials were expressed as a percentage of the total number of successful selective trials. These trials occurred with both digit pairings and both types of selective trials. There was a main effect of Trial Type ($F_{1,14}$ = 8.1, P = 0.013) but no effect of Pairing ($F_{1,14}$ < 1) or Digit ($F_{1,14}$ = 1.2, P = 0.291). This revealed a higher percentage of these trials during the Stop Right (26.2 ± 4.3 %) than Stop Left (18.6 ± 3.3 %) condition. There were no other main effects or interactions. For the

offset time of the partial bursts, there was a Digit x Trial Type interaction that did not decompose meaningfully. There was no effect of Pairing ($F_{1,14} = 3.6$, $P = 0.077$) or any other main effects or interactions.

Discussion

The novel finding in support of our main hypothesis was that selective trials involved movement re-initiation processes that were sensitive to response coupling. As predicted, pairings of same digits were more strongly coupled than pairings of different digits, and the effects of uncoupling the digit pairs during selective trials were more prominent in the non-dominant than the dominant hand. The persistent effects of the selective trials on the motor system were also dependent on coupling and hand dominance, indicating that successful performance on selective trials temporarily altered the gain of involved motor representations. These novel findings indicate that stopping the prepared, coupled response was a unitary phenomenon, followed by uncoupling of the response to allow selective initiation of one component. As such, the task may be better described as a selective *re-initiation* task than a selective *stopping* task. Given that the task caused pairing-dependent changes in motor output, it may be sensitive to the onset of basal ganglia dysfunction which impairs task-dependent modulation of motor set.

Firstly, it is important to note that participants performed the task correctly. During Go trials participants did not delay their response to allow possible detection of a stop cue, as can be the case with Stop Signal tasks (Verbruggen and Logan 2009). Go LTs were on average within 11 ms of the target (810.6 ± 1.8 ms). These results show that the task was reliably investigating the ability to suppress a pre-planned motor response. The staircase procedure resulted in later

indicator stop times and shorter SSRTs during Stop Both trials than during selective trials, as expected (Coxon et al. 2007).

Lift times were delayed when one part of the movement was prevented, compared to when the complete prepared movement was executed, as previously observed (Aron and Verbruggen 2008; Cai et al. 2011; Claffey et al. 2010; Coxon et al. 2007; 2009; Dove et al. 2000). In the present study there was a substantial delay in the lift time of the responding digit during selective trials (average of 90.4 ms) (Figure 2). It has been speculated that the delayed reaction time is due to rapid, non-selective suppression of all prepared movements (Aron and Verbruggen 2008; Coxon et al. 2007; Kenner et al. 2010) via a non-selective neural pathway (Coxon et al. 2006; Leocani et al. 2000). A candidate neuro-anatomical substrate is the 'hyperdirect' pathway between the inferior frontal gyrus and subthalamic nucleus (Aron and Poldrack 2006; Rubia et al. 2003). Our EMG data clearly illustrate a rapid suppression of prepared movement during selective trials, where the partial EMG bursts were rapidly suppressed in both digits (Figure 6B). We propose that this reflects the suppression of a single prepared movement, which would have been performed by a pair of digits, rather than the non-selective suppression of two separately prepared movements. This proposition is supported by the synchronised offset of the partial EMG bursts during selective trials. Importantly, the partial EMG burst was rapidly suppressed in both muscles at the same time regardless of the whether digit pairings were homogeneous or heterogeneous. Therefore suppression of the prepared movement is a unitary phenomenon, insensitive to the strength of coupling, posture or hand dominance. This indicates that regardless of pairing or posture, planned movements were integrated together into a unitary response during Go trials (and at the beginning of Stop trials when trial type was unknown), indicative of immediate "conceptual binding" within the motor

system (Wenderoth et al. 2009). It therefore logically follows that suppression of this single, coupled response would affect all of its components equally, even though the intention may be to selectively suppress one component of the response only.

Once a prepared response is suppressed on a selective trial, the desired component is selectively re-initiated by engaging execution pathways, and the time required for this process accounts for the delay in lift time (Coxon et al. 2009; Kenner et al. 2010). The present data highlight the role of uncoupling of movement representations in this process. To successfully re-initiate the desired component of the prepared movement, synchronised neural activity between coupled cortical movement representations must be sufficiently uncoupled. After uncoupling, each response component can then be separately suppressed or executed. The execution of the desired response was delayed to a greater extent in homogeneous compared to heterogeneous pairings (Figure 5A). This indicates that uncoupling was more difficult and took longer to achieve with homogeneous digit pairings, as expected. It is possible that more inhibition was required to achieve uncoupling of homogeneous pairings, and that this in turn was responsible for the longer delay in subsequent selective responses. However, the longer delay was offset by a higher gain, shown by a shorter EMD (Figure 5B) and faster rate of EMG onset (Figure 5D) with homogeneous pairings. Therefore when the prepared movement components are strongly coupled, an increase of both inhibition and gain seem necessary to successfully uncouple the prepared movement and re-initiate only the desired component.

What are the consequences of selective response re-initiation on the motor system? Coxon et al. (2007) found that uncoupling of the digits on successful selective trials had carry-over effects on subsequent Go trial performance, and the present study confirms and extends these findings (Figure 4). For example, after a Stop Left trial, the left LT was delayed relative to

342 the right on a subsequent Go trial. Whereas after a Stop Right trial, the right LT was delayed
343 relative to the left on a subsequent Go trial, as also observed by Coxon et al. (2007). The novel
344 finding here was that after a Stop Right trial, the left digit was lifted sooner, which may indicate
345 persistent increased gain from selective re-initiation of the responding left digit on the previous
346 trial. This carry-over effect was specific to the non-dominant hand, and aligns with previous
347 findings that the non-dominant hand is more strongly coupled to the dominant hand than vice
348 versa during bimanual tasks (Byblow et al. 2000; Carson 1993). However, this interpretation
349 must be considered with caution as any effect due to hand dominance cannot be ascertained
350 definitively from only right-handed participants.

351 The carry-over effects observed in the non-dominant hand were also influenced by digit
352 pairings. Only homogeneous pairings exhibited the speeding up of left digit LT following Stop
353 Right trials. Furthermore, only homogeneous pairings showed a slower left digit LT following
354 Stop Left trials compared to after Go trials, possibly due to persistent inhibition (Coxon et al.
355 2007; Kennerley et al. 2002). Neurophysiological investigations would be required for
356 confirmation. Taken together, the carry-over effects observed in the non-dominant hand may
357 reflect asymmetric coupling between the hands on the uncoupling and selective re-initiation of
358 finger movements. Importantly, we found no evidence of uncoupling after successful Stop Both
359 trials. Therefore, only *selective re-initiation* temporarily altered the gain of the motor
360 representations.

361 Previous studies have shown that impaired response suppression is associated with basal
362 ganglia dysfunction (Gauggel et al. 2004; Stinear and Byblow 2004). The present results indicate
363 that a selective response task may provide further insight into basal ganglia function, and may
364 assist in the prognosis of basal ganglia dysfunction. For example, damage of gain setting nuclei

is believed to accompany early changes in Parkinson's disease (Braak et al. 2004). Therefore, parameters derived from this type of task may provide sensitive biomarkers of Parkinson's disease and warrant further investigation.

In summary, this study has demonstrated that selective movement prevention occurs through rapid suppression of the prepared movement and subsequent re-initiation of the desired component of the response. This results in a movement delay and is more difficult to achieve when the prepared response is comprised of strongly coupled components. The rapid suppression of the prepared response was not affected by the strength of coupling between digits. However, the re-initiation of the desired movement component was delayed and occurred at a higher rate when the prepared response involved same pairings of digits. This is the first study to show that greater levels of inhibition and a higher gain are necessary to successfully perform selective re-initiation in strongly coupled postures. The carry-over effects observed in the lift times of the left hand with homogeneous pairings further support this idea. Further research is needed to elucidate the neurophysiological mechanisms underlying the observed effects.

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Disclosures

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

Author contributions

H.M. collected the data. All authors conceived and designed the experiment. All authors participated in the analysis and interpretation of the data and writing of the manuscript. All authors approved the final version of the manuscript.

References

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, and Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience* 6: 115-116, 2003.

Aron AR, and Poldrack RA. Cortical and subcortical contributions to stop signal response inhibition: Role of the subthalamic nucleus. *Journal of Neuroscience* 26: 2424-2433, 2006.

Aron AR, and Verbruggen F. Stop the presses: Dissociating a selective from a global mechanism for stopping: Research article. *Psychological Science* 19: 1146-1153, 2008.

Braak H, Ghebremedhin E, Rub U, Bratzke H, and Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res* 318: 121-134, 2004.

Byblow WD, Lewis GN, Stinear JW, Austin NJ, and Lynch M. The subdominant hand increases the efficacy of voluntary alterations in bimanual coordination. *Experimental Brain Research* 131: 366-374, 2000.

Cai W, Oldenkamp CL, and Aron AR. A proactive mechanism for selective suppression of response tendencies. *Journal of Neuroscience* 31: 5965-5969, 2011.

Carson RG. Manual asymmetries: Old problems and new directions. *Human Movement Science* 12: 479-506, 1993.

Claffey MP, Sheldon S, Stinear CM, Verbruggen F, and Aron AR. Having a goal to stop action is associated with advance control of specific motor representations. *Neuropsychologia* 48: 541-548, 2010.
Coxon JP, Stinear CM, and Byblow WD. Intracortical inhibition during volitional inhibition of prepared action. *Journal of Neurophysiology* 95: 3371-3383, 2006.
Coxon JP, Stinear CM, and Byblow WD. Selective inhibition of movement. *Journal of Neurophysiology* 97: 2480-2489, 2007.
Coxon JP, Stinear CM, and Byblow WD. Stop and go: The neural basis of selective movement prevention. *Journal of Cognitive Neuroscience* 21: 1193-1203, 2009.
Dove A, Pollmann S, Schubert T, Wiggins CJ, and Yves Von Cramon D. Prefrontal cortex activation in task switching: An event-related fMRI study. *Cognitive Brain Research* 9: 103-109, 2000.
Eagle DM, and Robbins TW. Lesions of the medial prefrontal cortex or nucleus accumbens core do not impair inhibitory control in rats performing a stop-signal reaction time task. *Behavioural Brain Research* 146: 131-144, 2003.
Garavan H, Ross TJ, and Stein EA. Right hemispheric dominance of inhibitory control: an event-related functional MRI study. *Proc Natl Acad Sci U S A* 96: 8301-8306, 1999.
Gauggel S, Rieger M, and Feghoff TA. Inhibition of ongoing responses in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* 75: 539-544, 2004.
Hodges PW, and Bui BH. A comparison of computer-based methods for the determination of onset of muscle contraction using electromyography. *Electroencephalography and Clinical Neurophysiology - Electromyography and Motor Control* 101: 511-519, 1996.
Kenner NM, Mumford JA, Hommer RE, Skup M, Leibenluft E, and Poldrack RA. Inhibitory motor control in response stopping and response switching. *Journal of Neuroscience* 30: 8512-8518, 2010.
Kennerley SW, Diedrichsen J, Hazeltine E, Semjen A, and Ivry RB. Callosotomy patients exhibit temporal uncoupling during continuous bimanual movements. *Nature Neuroscience* 5: 376-381, 2002.
Leocani L, Cohen LG, Wassermann EM, Ikoma K, and Hallett M. Human corticospinal excitability evaluated with transcranial magnetic stimulation during different reaction time paradigms. *Brain* 123: 1161-1173, 2000.
Liddle PF, Kiehl KA, and Smith AM. Event-related fMRI study of response inhibition. *Hum Brain Mapp* 12: 100-109, 2001.
Logan GD, and Cowan WB. On the ability to inhibit thought and action: A theory of an act of control. *Psychological Review* 91: 295-327, 1984.
Mars RB, Klein MC, Neubert FX, Olivier E, Buch ER, Boorman ED, and Rushworth MFS. Short-latency influence of medial frontal cortex on primary motor cortex during action selection under conflict. *Journal of Neuroscience* 29: 6926-6931, 2009.
Mostofsky SH, Schafer JGB, Abrams MT, Goldberg MC, Flower AA, Boyce A, Courtney SM, Calhoun VD, Kraut MA, Denckla MB, and Pekar JJ. fMRI evidence that the neural basis of response inhibition is task-dependent. *Cognitive Brain Research* 17: 419-430, 2003.
Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 9: 97-113, 1971.
Rubia K, Smith AB, Brammer MJ, and Taylor E. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *NeuroImage* 20: 351-358, 2003.

460 **Sharp DJ, Bonnelle V, De Boissezon X, Beckmann CF, James SG, Patel MC, and Mehta**
461 **MA**. Distinct frontal systems for response inhibition, attentional capture, and error processing.
462 *Proceedings of the National Academy of Sciences of the United States of America* 107: 6106-
463 6111, 2010.
464 **Slater-Hammel A**. Reliability, accuracy and refractoriness of a transit reation. *The Research*
465 *Quarterly* 31: 217-218, 1960.
466 **Stinear CM, and Byblow WD**. Impaired inhibition of a pre-planned response in focal hand
467 dystonia. *Experimental Brain Research* 158: 207-212, 2004.
468 **Stinear CM, Coxon JP, and Byblow WD**. Primary motor cortex and movement prevention:
469 Where Stop meets Go. *Neuroscience and Biobehavioral Reviews* 33: 662-673, 2009.
470 **Verbruggen F, and Logan GD**. Proactive Adjustments of Response Strategies in the Stop-
471 Signal Paradigm. *Journal of Experimental Psychology: Human Perception and Performance* 35:
472 835-854, 2009.
473 **Wenderoth N, Van Dooren M, Vandebroek A, De Vos J, Vangheluwe S, Stinear CM,**
474 **Byblow WD, and Swinnen SP**. Conceptual binding: Integrated visual cues reduce processing
475 costs in bimanual movements. *Journal of Neurophysiology* 102: 302-311, 2009.
476 **Zandbelt BB, and Vink M.** On the role of the striatum in response inhibition. PLoS One
477 5:e13848, 2010.
478

479 **Figure captions**

480 **Figure 1.** Visual display at the start of a trial (top left) when trial type is ambiguous; successful
481 Go trial (top right) when the participant has stopped both indicators at the target; successful Stop
482 Both trial (bottom left) when the participant kept both digits on the switches when the two
483 indicators automatically stopped early (600 ms); typical successful selective trial (Stop Left)
484 when the left response was correctly inhibited but the right response was delayed (bottom right).
485 Other selective condition (Stop Right) is not shown.

486

487 **Figure 2.** Group LT for Go and selective trials collapsed across side, digit and pairing. For
488 selective trials, LT is from the responding digit following inhibition and selective re-initiation.
489 Asterisks indicate significant differences for paired *t* tests: *** $P < 0.001$. Error bars indicate 1
490 SE.

491

Figure 3. Group LT for the left and right digit on Go trials preceded by Go and successful selective trials. Collapsed across digit and pairing (A) and separated into homogeneous (B) and heterogeneous pairings (C). Black bars, Go is preceding trial type; white bars, Stop Left is preceding trial; grey bars, Stop Right is preceding trial. Horizontal dashed line indicates target line at 800 ms. Asterisk indicates significant difference from post hoc paired *t* test: * $p < 0.05$. Error bars indicate 1 SE.

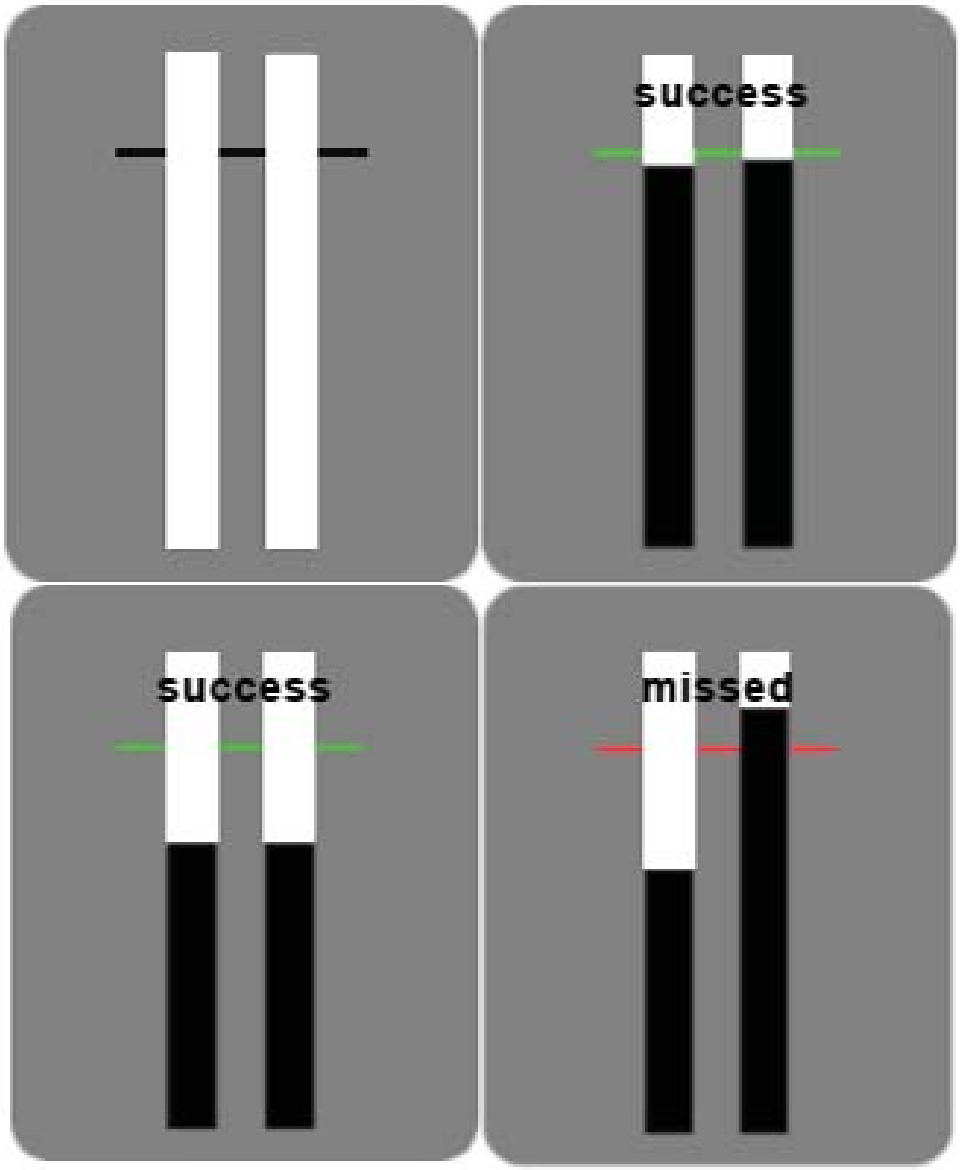
Figure 4. Group Go trial lift time asynchrony (LTA) following Go and Stop trials. Positive LTA indicates right digit lifted before the left. Asterisks indicate results of paired *t* tests: *** $P < 0.001$. Error bars indicate 1 SE.

Figure 5. Group results for lifting EMG burst onset time (A), electromechanical delay (B) and peak rate of lifting EMG burst onset across trial types (C) and digits (D) for Go and selective trials. Electromechanical delay = lift time – lifting EMG burst onset time. In graph D: black bars, homogeneous pairing; white bars, heterogeneous pairing. Asterisks indicate significant results from post hoc *t* tests: * $P < 0.05$. Error bars indicate 1 SE.

Figure 6. EMG traces from an individual participant representing a successful Stop Both (A) and Stop Left (B) trial with a homogeneous pairing. Dashed vertical line indicates target line. B: Middle: Responding muscle. Bottom: Non-responding muscle. Dashed green line, bilateral

512 response initiation; dashed red line, inhibition following stop signal; solid green line, selective
513 re-initiation of the responding muscle; APB, abductor pollicis brevis.

514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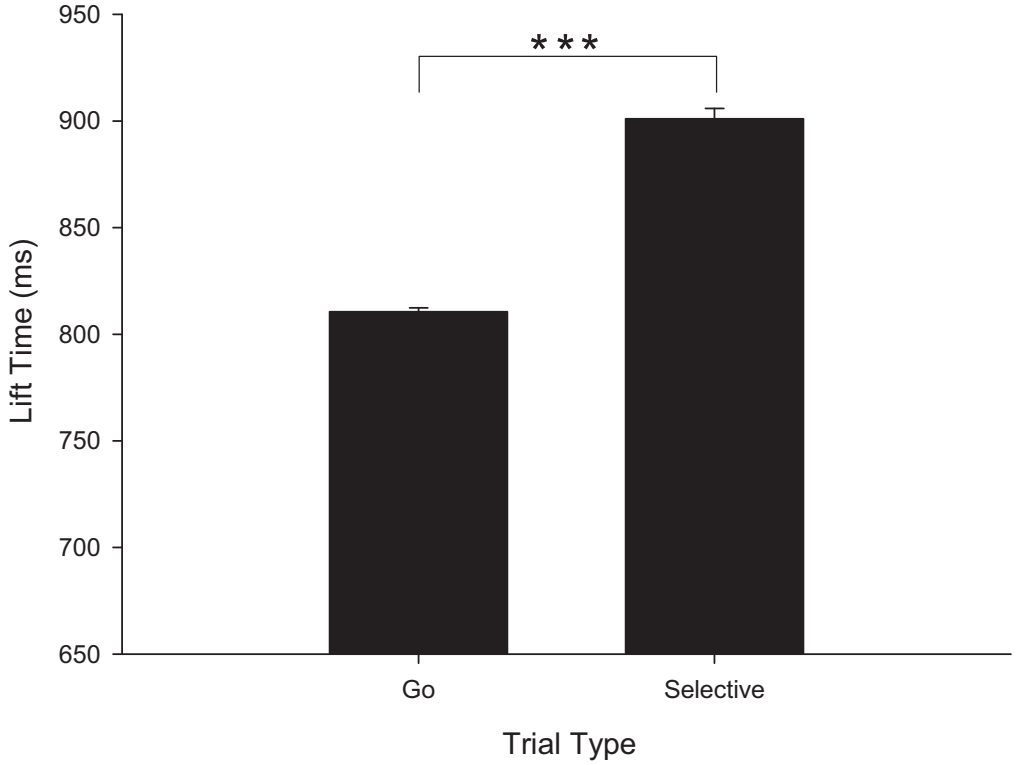
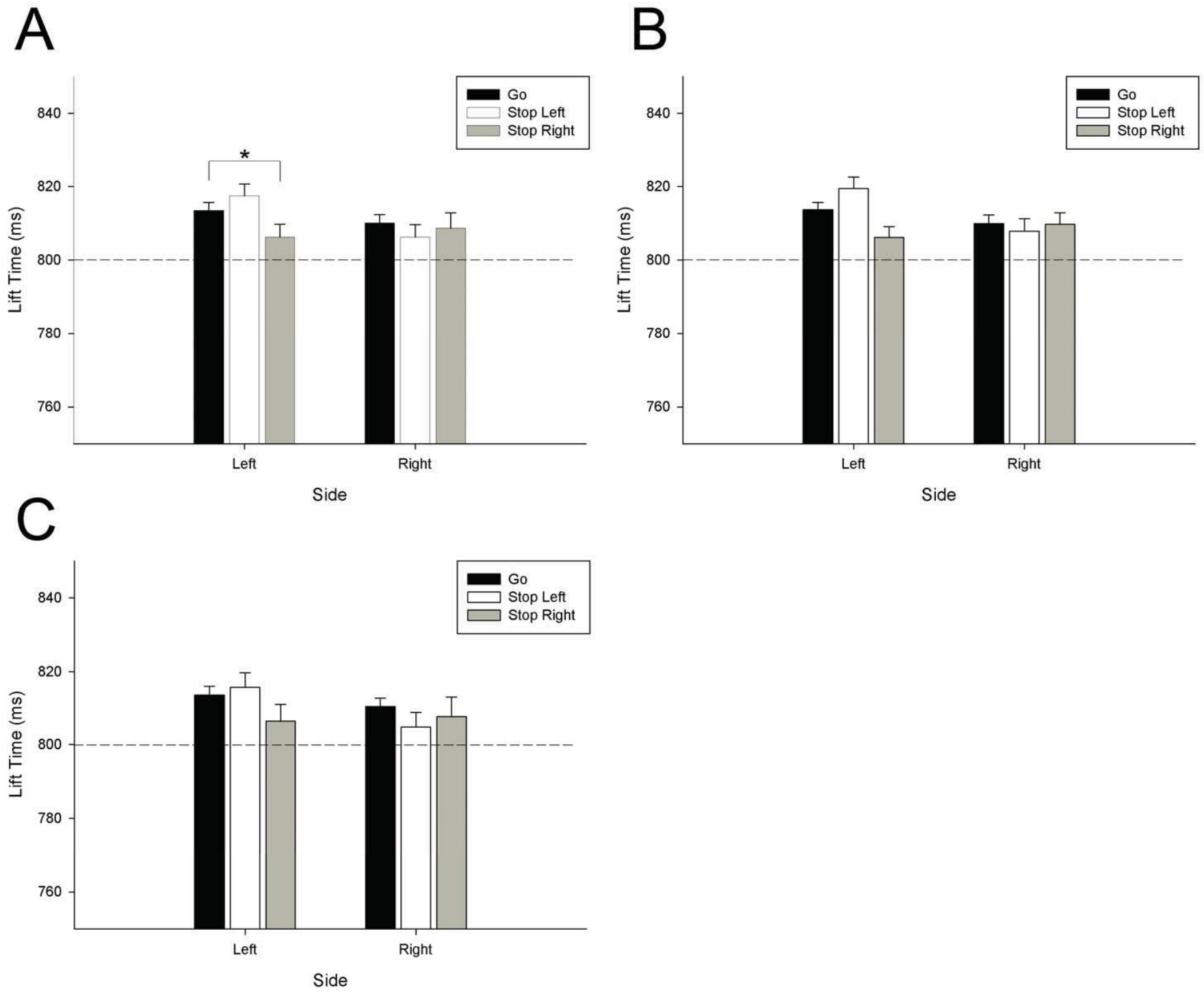
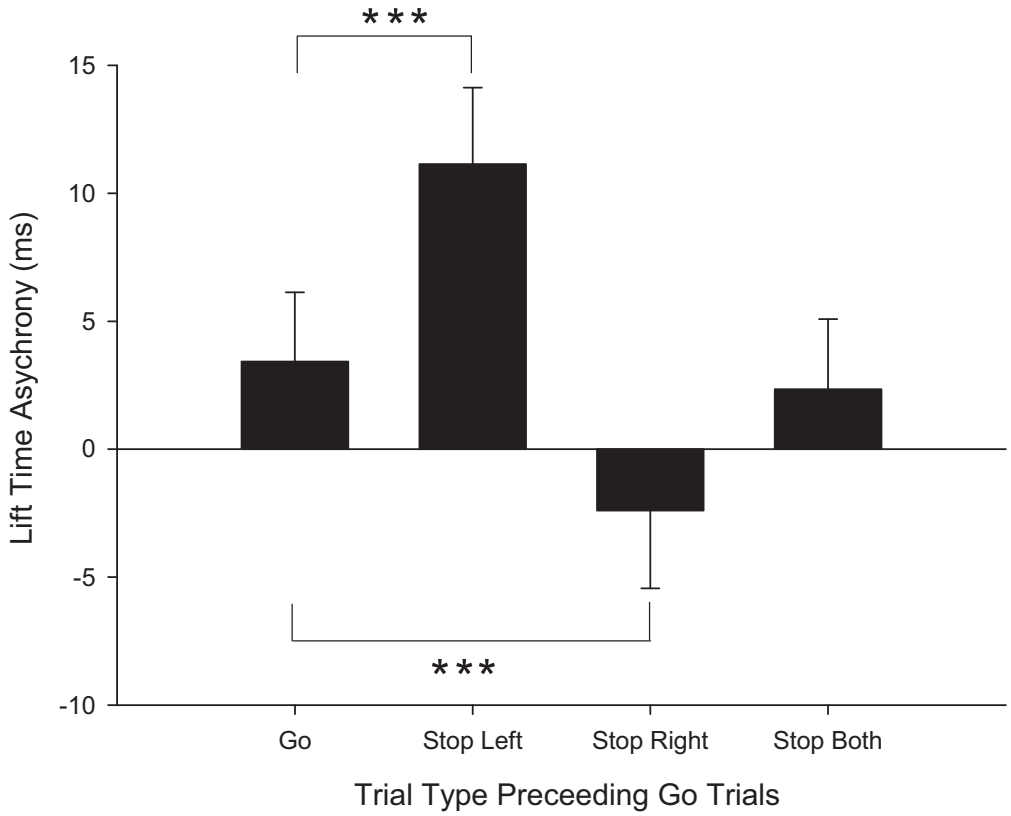
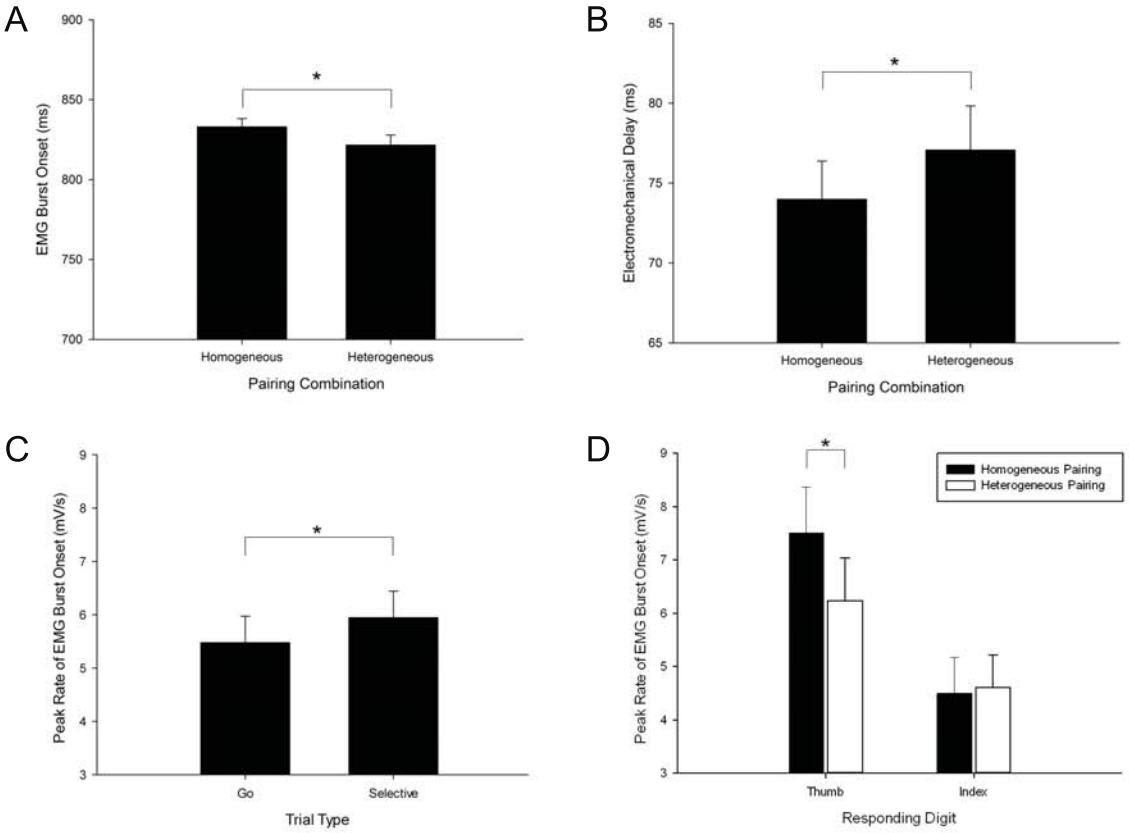
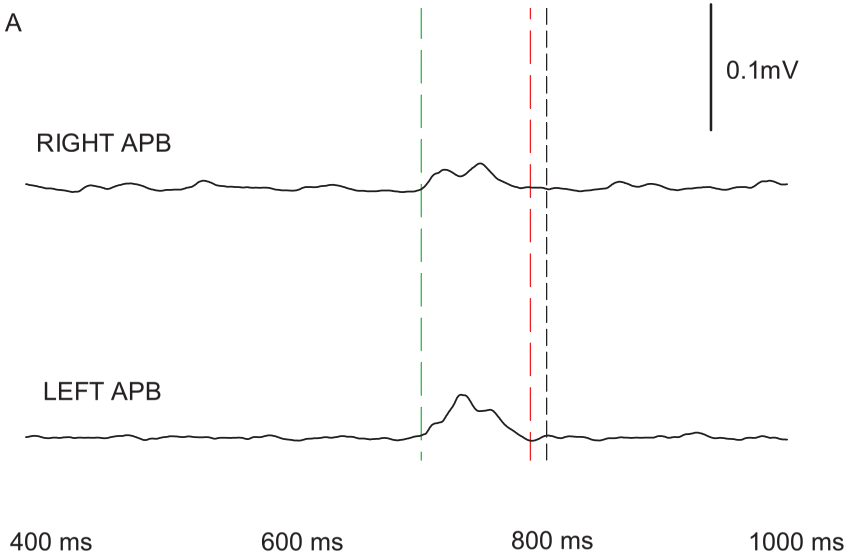
success
missed

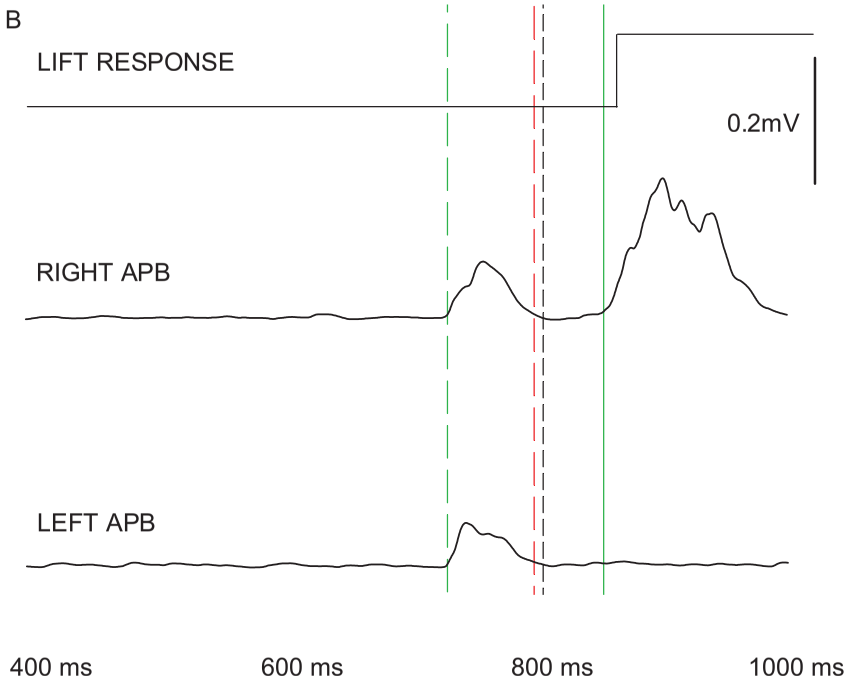

950
900
850
800
750
700
650
Lift Time (ms)
***
Go
Selective
Trial Type


A
B
C
Go
Stop Left
Stop Right
Lift Time (ms)
840
820
800
780
760
*
Left
Right
Side


***
15
10
5
0
-5
-10
***
Lift Time Asychrony (ms)
Go
Stop Left
Stop Right
Stop Both
Trial Type Preceeding Go Trials


A
900
850
800
750
700
EMG Burst Onset (ms)
*
Homogeneous
Heterogeneous
Pairing Combination
B
85
80
75
70
65
Electromechanical Delay (ms)
*
Homogeneous
Heterogeneous
Pairing Combination
C
9
8
7
6
5
4
3
Peak Rate of EMG Burst Onset (mV/s)
*
Go
Selective
Trial Type
D
9
8
7
6
5
4
3
Peak Rate of EMG Burst Onset (mV/s)
*
Homogeneous Pairing
Heterogeneous Pairing
Thumb
Index
Responding Digit


A
0.1mV
RIGHT APB
LEFT APB
400 ms
600 ms
800 ms
1000 ms


B
LIFT RESPONSE
0.2mV
RIGHT APB
LEFT APB
400 ms
600 ms
800 ms
1000 ms