Training voluntary motor suppression with real-time feedback of motor evoked potentials

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Training people to voluntarily suppress motor representations could improve response control. We evaluated a novel training procedure of real-time feedback of motor evoked potentials (MEPs) generated by transcranial magnetic stimulation (TMS) over motor cortex. On each trial, a cue instructed participants to use a mental strategy to ‘suppress’ a particular finger representation, without overt movement. A single pulse of TMS was delivered over motor cortex, and an MEP-derived measure of hand motor excitability was delivered visually to the participant within 500ms. In Experiment 1, we showed that participants learned to reduce the excitability of a particular finger beneath baseline (selective motor suppression) within 30 minutes of practice. In Experiment 2, we performed a double-blind study with two training groups (one with veridical feedback, one with matched sham feedback) to show that selective motor suppression depends on the veridical feedback itself. Experiment 3 further demonstrated the importance of veridical feedback by showing that selective motor suppression did not arise from mere mental imagery, even when incentivized with reward. Thus, participants can use real-time feedback of TMS-induced MEPs to discover an effective mental strategy for selective motor suppression. This high temporal-resolution trial-by-trial feedback training method could be used to help people better control response tendencies and may serve as a potential therapy for motor disorders such as Tourette’s and dystonia.
INTRODUCTION

Inhibitory response control (hereafter, Inhibitory Control, IC) refers to the neural processes by which individuals suppress movement. IC is thought to be implemented by top-down (prefrontal) control over response channels in basal ganglia and/or M1 (reviewed by Aron et al. 2014; Bari and Robbins 2013; Coxon et al. 2009; Spierer et al. 2013).

Different forms of IC might be employed depending on the context (Aron 2011; Spierer et al. 2013). For instance, one can rapidly stop an action when a sudden event occurs, which is a reactive form of IC modeled by Stop-Signal or Go/NoGo tasks (Verbruggen and Logan 2009). One can also employ IC proactively to dampen the motor system in preparation for having to stop. For example, in one kind of proactive suppression paradigm, participants are given a cue to suppress muscles of a particular hand, and they must then implement this suppression in advance, so that, if they are subsequently required to stop action they can do so in a targeted way (Cai et al. 2011; Chikazoe et al. 2009; Jahfari et al. 2012; Majid et al. 2013; Smittenaar et al. 2013).

Much research has shown that impairments in IC partly underlie impulse control disorders such as Attention Deficit/Hyperactivity Disorder and Tourette’s syndrome (Chamberlain and Sahakian 2007; Chambers et al. 2009; Channon et al. 2009; Lijffijt et al. 2005; Shahana and Gilbert 2013). Consequently, it is important to discover behavioral regimens that improve IC (reviewed by Enriquez-Geppert et al. 2013; Spierer et al. 2013).

Training studies of IC have mostly focused on having participants repeatedly practice the reactive stopping of action; however, these have had mixed success (e.g. Berkman et al. 2014; Chevalier et al. 2014b; Cohen and Poldrack 2008; Enge et al. 2014; Logan and Burkell 1986; Schapkin et al. 2007; and reviewed by Spierer et al. 2013). Interestingly, in one study that showed faster stopping speeds with training, IC improvements seemed to be related to greater emphasis on the brain circuitry for preparing to suppress (Berkman et al. 2014). This suggests that training proactive suppression of the motor system is a good avenue for improving IC. There are also other considerations in favor of trying to train proactive IC. First, it might be more amenable to training than the reactive system, which is very quick, and perhaps largely down to stimulus detection and then white matter pathways. Second, it is probable that fewer situations in real life require rapid reactive IC; instead one often has to prepare to suppress a response in advance; and this requires translating goals into action influences, i.e. ‘implementation intentions’ (Burkard et al. 2013) which are probably more amenable to training.
Here we tested a novel method of training proactive IC. On each trial we instructed the participant to try to suppress a right hand muscle. Then, on the same trial, we delivered a single pulse of TMS, recorded the MEP, and immediately returned the MEP to the participant as visual feedback. The participant’s task was to try to discover an effective mental strategy to suppress the muscle. Experiment 1 investigated whether this feedback method allowed participants to mentally ‘drive down’ a particular muscle’s excitability beneath baseline. Experiments 2 examined whether veridical feedback is key, by performing a rigorous double-blind study comparing real and sham feedback groups. Experiment 3 addressed an alternative possibility for the effects, that veridical feedback is not important and that selective motor suppression can instead be achieved through mere mental imagery.
EXPERIMENT 1

METHODS

Participants
Fourteen healthy right-handed participants (4 males, 10 females, mean age: 20.9±4.1 years) provided consent in accordance with Institutional Review Board guidelines at UCSD, completed a TMS safety questionnaire (Rossi et al. 2009) and were paid $15/hr.

Behavioral Task and Mental Procedures
Participants sat in front of a 19-inch monitor with the right hand resting on a table. Electromyography (EMG) was recorded using a pair of 10mm silver electrodes for two separate muscles: 1) the first dorsal interosseous (FDI) of the index finger and 2) the abductor digiti minimi (ADM) of the pinky (Figure 1). Ground electrodes were placed on the radial and ulnar wrist protuberances for the FDI and ADM, respectively. Single-pulse TMS was delivered over contralateral M1 to produce MEPs in both muscles simultaneously.

Each participant performed 10 blocks of 36 trials each. The first 12 trials of each block were baseline trials for the MEP normalization procedure (see below). For these 12 trials, participants saw the “Null” cue for 500ms, indicating they should rest. A blank screen then followed for an additional 1s before TMS was delivered and the resulting MEPs were recorded. The screen then remained blank for another 2.5s before the start of the next trial. After these 12 Null trials, the mean MEP amplitude for each muscle was calculated to serve as a resting baseline.

The remaining 24 trials of each block began with a 500ms cue that either instructed participants to “Suppress Index” or “Suppress Pinky” (12 each, randomly presented). Participants were instructed to experiment with different mental strategies to reduce the excitability of the muscle recorded from the cued finger, using the real-time feedback (see results for a description of post-hoc subjective reports). After the “Suppress” cue disappeared, the screen turned blank for 1s before TMS was delivered and MEPs were obtained. The screen remained blank for another 500ms before feedback was presented for 1s. Participants saw a feedback bar for the index on the left and another for the pinky on the right. A red bar indicated that the finger was cued for suppression, and a blue bar indicated it was not. The bar height was calculated as: \( \log(\text{trial MEP}) - \log(\text{mean Null MEP}) \). Thus, a
downward pointing bar indicated MEP reduction relative to the mean Null baseline. A “Good Job!” feedback message was only delivered if the cued (red) bar was downward pointing and more negative than the uncued (blue) bar. If not, a “Try Again” message was delivered. After feedback, the screen turned blank for 1s before the next trial.

On all trials, pre-trigger EMG was obtained for each muscle for 100ms before TMS. If the root-mean-square for either trace exceeded 10µV, a 1s “No Tensing!” warning was delivered as feedback to prevent participants from prematurely activating any muscle. These trials were excluded from subsequent analysis.

**Real-time TMS procedure details**

EMG for each muscle was amplified using a Grass QP511 Quad AC Amplifier System (Grass Technologies, West Warwick, RI). A 30Hz to 1kHz band-pass filter and a 60Hz notch filter were applied. The amplifier output was then split (using T-shaped coaxial junctions), with one signal directed to an EMG recording computer (via a CED Micro 1401 mk II acquisition system, sampled at 2 kHz) and the other to the participant’s presentation computer (via analogue inputs to a USB-1208FS data acquisition device, Measurement Computing Corporation, Norton, MA). On the presentation computer, the signal was read into MATLAB using the Psychtoolbox function *DaqAInScan.m* (Kleiner et al. 2007). The parameters for this function specified i) the two muscles’ input leads and ii) a sampling rate of 2000/s.

TMS was delivered with a MagStim 200-2 system (Magstim, Whitland, UK) and a figure-of-eight coil (7cm diameter). The coil was initially placed 2 inches left and 1 inch anterior to the vertex to find the cortical representation of the resting right hand. The coil was incrementally repositioned and the stimulus intensity was increased until an MEP was obtained in both the right FDI and ADM. The resting motor threshold was the lowest stimulation level required to elicit MEPs of at least 0.05 mV in at least 5 of 10 trials in both recorded muscles. The experimental stimulation intensity was 110% of resting motor threshold rounded to the nearest percentage point, averaging 49.3±8.7% of maximum stimulator output across participants.

**TMS analysis**

Peak-to-peak MEP amplitude was calculated with custom MATLAB software. Trials were excluded when the root-mean-square of 100 ms of pre-TMS EMG trace exceeded
10µV (8.7±8.9 trials per subject). The distribution of MEP amplitudes following each cue (“Suppress Index,” “Suppress Pinky,” and “Null”) for the FDI (index) and ADM (pinky) were then respectively trimmed (to approximate normality of the distribution) by removing the upper and lower 10% of values (Wilcox 2001) and then averaged. MEP modulation of each muscle on a “Suppress cue” was calculated as the percentage change compared to the mean “Null” MEP, i.e. (Suppress cue MEP – Null MEP)*100/(Null MEP).

Four TMS measures were calculated: 1) FDI modulation on “Suppress Index” trials (Cued Index Modulation), 2) ADM modulation on “Suppress Pinky” trials (Cued Pinky Modulation), 3) FDI modulation on “Suppress Pinky” trials (Uncued Index Modulation), and 4) ADM modulation on “Suppress Index” trials (Uncued Pinky Modulation). ANOVA was run with three factors, Session Half [Early vs. Late], Recorded Muscle [Index vs. Pinky], and Cued State [whether the muscle was cued for suppression or not]. Similar analysis was done on the root-mean-square of EMG for 100ms prior to TMS.

RESULTS

For the MEP analysis, the 10 blocks of the experiment were divided into two halves (five blocks each), and repeated-measures ANOVA was done with three factors (Session Half [Early vs. Late] X Recorded Muscle [Index vs. Pinky] X Cued State [The muscle was cued for suppression or not]). There was a significant effect for Cued State ($F_{1,13}=7.711$, $d=0.81$, $p=.016$), no effect of Session Half ($F_{1,13}=1.434$, $d=0.12$, n.s.), no effect for Recorded Muscle ($F_{1,13}<1$, $d=0.37$), no Cued State X Recorded Muscle interaction ($F_{1,13}=2.767$, $d=0.08$, n.s.), no Session Half X Recorded Muscle interaction ($F_{1,13}<1$, $d=0.01$), and no three-way interaction ($F_{1,13}<1$, $d=0.09$). The Cued State X Session Half interaction trended towards significance ($F_{1,13}=3.969$, $d=0.25$, $p=.068$), suggesting a training effect in the ability to modulate MEPs to a cued stimulus (Figure 2A, Table 1).

To examine pre-TMS excitability, the same ANOVA was run for the pre-TMS EMG. There was a significant effect of Session Half ($F_{1,13}=6.690$, $d=0.50$, $p=.011$) – with EMG being greater for the first half than second half – no effect of Cue ($F_{1,13}=2.090$, $d=0.27$, n.s.), no effect of Recorded Muscle ($F_{1,13}<1$, $d=0.09$), and no interactions (all $F_{1,13}<1$). This raised the possibility that differences in pre-TMS EMG may account for some of the above MEP effects.
To further characterize the data, we conducted post-hoc tests on Cued vs. Uncued trials in the first and second halves of training separately. Since there were no effects of Recorded Muscle, the data from both muscles were pooled. In the first half (Early Training), there was no significant modulation of the Cued or Uncued conditions (Cued Modulation: -3.5±48.5%, one-sample \( t_{13}<1, d=0.07 \); Uncued Modulation: 42.3±113.1%, one-sample \( t_{13}=1.40, d=0.37, \) n.s.) and no significant difference (paired \( t_{13}=1.961, d=0.52, \) n.s.). By contrast, pre-TMS EMG did show significant activity in both the Cued (one-sample \( t_{13}=2.332, d=0.62, p=.036 \)) and Uncued (\( t_{13}=2.936, d=0.78, p=.012 \)) conditions and a condition difference (Uncued greater than Cued, paired \( t_{13}=3.074, d=0.82, p=.009 \)). In the second half (Late Training), MEPs were significantly below baseline in the Cued condition for 10 out of 14 participants (-28.4±29.9%, one-sample \( t_{13}=3.563, d=0.95, p=.003 \)) but not the Uncued condition (50.7±106.2%, one-sample \( t_{13}=1.785, d=0.48, \) n.s.), with a significant difference between conditions (paired \( t_{13}=3.244, d=0.87, p=.006 \)). There was no significant pre-TMS EMG activity for Cued (one-sample \( t_{13}<1 \)) or Uncued (one-sample \( t_{13}=1.837, \) n.s.) conditions and no condition difference (paired \( t_{13}=1.143, \) n.s.).

In summary, participants could indeed selectively reduce the excitability of a muscle, as manifest in the significant main effect of Cue. Moreover, this effect was particularly apparent in the last half of the experiment (as would be expected of a training effect), and importantly, this was unconfounded by pre-TMS EMG activation.

When queried about effective mental suppression strategies, participants reported imagining the particular muscle “going numb” or “going on ice” or “thinking away” from the cued muscle to an alternative muscle (e.g. thinking about moving the pinky when told to “suppress index”).

While the results of this study were striking, the question arises whether the proactive selective suppression was specifically due to the veridical feedback procedure. In Experiment 2 we performed a double blind study comparing groups with veridical and sham feedback.

**EXPERIMENT 2**

**METHODS**

*Participants*
Thirty healthy right-handed participants were randomly assigned to either a “real-feedback group” or “sham-feedback” group (see below for gender and age distributions). Consent ing, screening and payment were the same as above.

**Behavioral Task and Mental Procedures**

A written list of strategies was provided from the outset, derived from the anecdotal responses from Experiment 1:

1. Divert your attention away from the cued finger by thinking about moving the other.
2. Divert your attention to another part of the body.
3. Think about tensing the cued finger so it remains still.
4. Think about that muscle going numb or going on ice.
5. Think about suddenly stopping a movement of the cued finger.
6. Use any other strategy you come up with.

Participants then engaged in 10-12 blocks (depending on fatigue or time limitations) of the suppression task, identical in presentation and timing to Experiment 1. A key difference, however, was that the unknowing participant was randomly assigned to either a “real-feedback” group, for whom the feedback accurately reflected hand MEPs on a particular trial (as in Experiment 1), or a “sham-feedback” group. Feedback for each participant in the “sham-feedback” group was matched to a previous participant in the “real-feedback” group, such that each group experienced the same frequency of positive (“Good Job”) and negative (“Try Again”) feedback. The experimenter was also blind to group assignment except for the first participant (who must necessarily be in the “real-feedback” group) and the last participant (who must necessarily be in the “sham-feedback” group). A mixed model ANOVA was run with the factors Cued state [whether a muscle was cued for suppression or not] and Group. We treated the two groups as independent rather than paired samples when doing t-tests.

After task completion, all participants were asked what strategies they had used and whether they felt they improved in their suppression ability.

**TMS procedure details and analysis**
The real-time TMS procedure was identical to Experiment 1. Since there was now no
difference between index and pinky in suppression of MEPs, we pooled these into two
conditions “Cued Modulation” (FDI modulation on “Suppress Index” trials and ADM
modulation on “Suppress Pinky” trials) and “Uncued Modulation” (FDI modulation on
“Suppress Pinky” trials and ADM modulation on “Suppress Index” trials). Trials were
excluded if the pre-TMS EMG trace exceeded 10µV (10.6±11.6 trials per subject).

Standard box-plot analysis of the group data revealed two extreme values in the real
feedback group. Since this may have affected the behavior of the two matched sham-
feedback participants, these sham-feedback participants were also excluded. This left
twenty-six participants in the analysis (real feedback group: n=13, 6 males, 7 females, mean
age = 20.9±2.4 years; sham-feedback group: n=13, 6 males, 7 females, mean age =
20.7±2.3 years, no statistical difference in age). The experimental stimulation intensity was
also comparable between groups (Real: 48.3±9.5% vs. Sham: 49.8±8.5%, t<1).

RESULTS

We now asked if it was specifically the feedback that enabled participants to develop
a mental strategy for motor suppression. A mixed-model ANOVA with Group (Real- vs.
Sham-Feedback) X Cued state (Cued vs. Uncued) revealed a significant Group X Cued
State interaction ($F_{1,24}=4.394$, $d=0.86$, p=.047) (**Figure 2B, Table 2**). There was also a
significant effect of Group ($F_{1,24}=11.313$, $d=1.37$, p=.003), but no effect of Cued State
($F_{1,24}<1$, $d=0.04$). There were no significant effects or interactions when the above mixed-
model ANOVA was applied to the pre-TMS EMG (all $F_{1,24}<1$), showing that preparatory
activation cannot account for the above results.

To follow up the Group X Cued State interaction, MEP analyses were done
separately for each group. In the Real-feedback group, participants significantly reduced the
Cued, but not the Uncued, finger below baseline (Cued Modulation: -21.3±26.9%, $t_{12}=2.860$,
$d=0.79$, p=.014; Uncued Modulation: -2.3±29.2%, $d=0.11$, $t_{12}<1$; Cued vs. Uncued,
$t_{12}=2.563$, $d=0.48$, p=.025). Importantly, there was no significant difference in pre-TMS EMG
activity between the Cued and Uncued condition in the Real-Feedback group ($t_{12}=1.042$,
**n.s.**). By contrast, MEP analysis showed that the Sham-feedback group did not reduce but
rather activated both the Cued and Uncued fingers (Sham-Feedback Cued Modulation:
53.4±70.5%, \( t_{12}=2.388, d=0.76, p=.032; \) Uncued Modulation: 32.3±52.1%, \( t_{12}=2.233, d=0.67, p=.045; \) Cued vs. Uncued, \( t_{12}=1.199, d=0.32, \) n.s.

When directly comparing the Real- and Sham-Feedback groups, there was a difference in both Cued (\( t_{24}=3.574, d=1.40, p=.002 \)) and Uncued finger modulation (\( t_{24}=2.089, d=0.76, p=.047 \)). Again, there were no differences between groups between pre-TMS EMG in either the Cued (\( t_{24}=1.185, \) n.s.) or Uncued (\( t_{24}<1 \)) conditions.

In summary, the Real-Feedback group was able to reduce MEPs below baseline in the cued condition (an effect seen in 11 out of 13 participants), whereas this was not the case for the Sham-Feedback group (where only 4 of 13 participants showed the below-baseline effect).

In the Real-Feedback group, nine of the thirteen participants reported trying to suppress by diverting attention away from the cued finger to another finger of the hand. The other four reported a mix of imagining the cued finger going on ice, commanding the cued finger to stop, tensing the cued finger, or daydreaming. Six felt they improved, six were not sure, and one felt there was no improvement. In the Sham-Feedback group, six of the thirteen participants reported trying to suppress by diverting attention away from the cued finger to another finger of the hand; three participants reported trying to tense the cued finger, two reported directly commanding the finger to stop, and two reported other strategies. Eight felt they improved, three were not sure, and two thought there was no improvement.

The results of the Real-Feedback group in this study were striking in replicating those of Experiment 1. However, an alternative possibility is that the proactive selective suppression is not due to veridical TMS feedback so much as the subject practicing mental imagery. For example, an earlier study showed that participants could dampen the excitability in the hand using motor imagery (Sohn et al. 2003). On this account, MEPs are reduced in the Real-Feedback group in Experiment 2 because of motor imagery, while in the Sham-Feedback group the presentation of yoked feedback is confusing to the subject, leading to activation rather than suppression. In Experiment 3 we therefore examined whether cued suppression could arise from mere mental imagery in the absence of any feedback.
**Participants**

Eighteen healthy right-handed participants took part. Consent and screening were the same as above.

**Behavioral Task and Mental Procedures**

Our prediction in this study was a null effect: i.e. that mental imagery alone would not be effective for proactive selective suppression, even when incentivized by money. Accordingly, it was important that the experimenter was blind to the study’s purpose. We trained a research assistant (CL) for this purpose, and she acquired all the data. Participants were given the same written list of strategies as in Experiment 2 and then engaged in 12 blocks of the suppression task, as before. Now, however, trial-by-trial feedback was not provided. Instead, $0.05 was accumulated for each trial corresponding to a “Good Job!” trial in the feedback paradigm (i.e. cued finger excitability reduced below baseline and more negative than uncued finger excitability reduction). Participants were informed of total reward earned at the end of every four blocks. A repeated-measures t-test compared Cued state [whether a muscle was cued for suppression or not]. After task completion, all participants were asked what strategies they had used and whether they felt they improved in their suppression ability.

**TMS procedure details and analysis**

As in Experiment 2, trials were pooled into “Cued” and “Uncued” Modulation conditions. Trials were excluded if the pre-TMS EMG trace exceeded 10µV (5.0 ± 9.5 trials per subject). Standard box-plot analysis of the group data revealed four participants with extreme values. This left 14 participants in the analysis (3 males, 11 females, mean age = 19.4±1.2 years). The experimental stimulation intensity was 54.2±10.4%.

**RESULTS**

We now asked whether cued suppression could arise from mere mental imagery in the absence of any feedback (cf. Sohn et al. 2003). Participants underwent the same procedure but, instead of trial-by-trial feedback, accumulated $0.05 for each trial corresponding to a “Good Job!” The total reward was displayed at the end of each four-block
Consistent with our hypothesis that veridical trial-by-trial feedback is needed, there was no significant reduction of Cued finger excitability below baseline (Cued Modulation: -4.7±36.5%, $t_{13}<1$, $d=0.13$) nor was the Uncued finger excitability significantly different from baseline (Uncued Modulation: 21.7±60.2%, $t_{13}=1.352$, $d=0.36$, n.s.). The null result for Cued finger suppression was unlikely due to weak power: we estimated that 375 participants would be needed to have 80% power to show a significant below-baseline Cued finger modulation reduction.

There was a trend towards selective control (Cued vs. Uncued, $t_{13}=2.104$, $d=0.56$, $p=.06$) (Figure 2C, Table 2); however, rather than reflecting selective suppression (as for Expts 1 and 2) this may have reflected the trend towards greater pre-TMS EMG in the Uncued condition compared to the Cued condition ($t_{13}=1.824$, $d=0.49$, $p=.09$).

When directly comparing the current subjects with the Real-Feedback group in Experiment 2, there was indeed a difference for the Cued condition with moderate effect size although this was not significant ($t_{25}=1.335$, $d=0.52$, n.s.), reflecting relatively poor power for a between-group comparison. There was no significant Uncued finger modulation from baseline ($t_{25}<1$, $d=0.23$). There were no differences between groups between pre-TMS EMG in either the Cued ($t_{25}<1$) or Uncued ($t_{25}<1$) conditions.

In summary, when the participants underwent the very same procedure as in Experiments 1 and 2 but now without trial-by-trial feedback, they could not learn to suppress a particular response, even though they were motivated by monetary reward to do their best.

Thirteen of the fourteen participants reported trying to suppress by diverting attention away from the cued finger to another finger of the hand. The remaining participant reported attempting non-specific relaxation techniques. Eight felt they improved through the training paradigm (perhaps on account of financial compensation).

Thus, this Experiment showed that that mere motor imagery was not sufficient to lead to cued suppression, even when incentivized by monetary reward.

**DISCUSSION**

We tested whether real-time feedback of TMS-derived MEPs allows participants to discover a mental strategy that is effective for suppressing a particular muscle. Experiment 1
showed that by the latter half of the training period, participants could effectively reduce the motor excitability of a particular hand muscle below a resting baseline when cued to ‘suppress’ that muscle. Since this reduction occurred only in the cued muscle in the absence of pre-TMS EMG activity, this reduction in excitability likely reflects a voluntary ‘suppression’ of a particular finger representation. Experiment 2 replicated the suppression effect in a group that received veridical feedback while showing that this was not the case for a yoked sham-feedback group. Notably, the choice of control (sham) group in this double-blind study is highly rigorous, as these participants received feedback that matched the real-feedback experimental group, thus experiencing the same degree of positive and negative feedback in the same temporal progression. Experiment 3 went further by showing that mere motor imagery was not sufficient to lead to cued suppression, even when incentivized by monetary reward. Taken together the control experiments thus establish that veridical feedback, and not sham-feedback or mere motor imagery, is necessary for cued motor suppression within the time constraints of one hour of training.

Not Mere Motor Imagery

The absence of motor suppression in Experiment 3 is at odds with the motor imagery study of Sohn, et al. (2003). They demonstrated reduced hand muscle excitability when participants were instructed to engage in mental relaxation techniques in the absence of visual feedback. Yet a key difference in paradigms was that in ours, participants were required to engage in selective motor control (suppression of a specific cued finger rather than the hand in general), which prevented them from possibly relying on a strategy of non-specifically increasing motor excitability on baseline trials (and thus leading to an apparent reduction of excitability on non-baseline trials). We suppose that selective response suppression is more complicated mechanistically than generalized relaxation and may thus require training with veridical feedback. It is also noteworthy that Sohn et al. (2003) used TMS stimulation at 140% RMT during their mental-relaxation paradigm (much larger than the 110% RMT used here) which surely causes the fingers to ‘jump’; therefore, participants could use the perceived level of that sensation as a method for actual trial-by-trial feedback. In that sense, their result may not have been based on pure motor imagery. By contrast, although participants in the present study experienced a small twitch, the sham-feedback and no-feedback controls of Experiments 2 and 3 demonstrate clearly that participants were unable to use the perceived sensation of this twitch as a form of trial-by-trial feedback.
Mental Strategies and Mechanism of Suppression

By what mental strategy did our participants achieve cued motor suppression? In the veridical feedback group of Experiment 2, most eventually settled upon thinking away from the cued muscle. Since such motor imagery would activate the M1 representations of alternative muscles (Sharma et al. 2006), one mechanistic possibility is that this activation in turn inhibits the M1 representation of the cued finger through a form of motor surround inhibition (Hallett 2003; Sohn and Hallett 2004).

Surround inhibition is a well-documented organizational principle of the sensory system (Hubel and Wiesel 1968) and was originally thought to be a function of cortico-cortical inhibition local to the cortex (Gilbert and Wiesel 1983). Analogously, cortico-cortical inhibition has also been suggested in the motor cortex (Hanajima et al. 1996; Kujirai et al. 1993) and could underlie the suppression seen here. Further work in sensory systems, however, has suggested that the actual locus of surround inhibition may be in lower level thalamic structures that in turn reduce excitatory drive to cortical sensory regions (Ozeki et al. 2004; Smith 2006). Similarly, surround inhibition of the motor cortex has been thought to be a function of the influence of inhibitory basal ganglia pathways, such as the Indirect Pathway, in reducing thalamocortical drive to the cortex (Mink 2003). Further neuroimaging studies may serve to better elucidate the locus of this training effect.

There are however some concerns with this ‘motor surround’ explanation. Although this account predicts activation of the alternate finger, e.g. the index when suppressing the pinky, this was not clear from the data (i.e. Figure 2 shows no significant elevation from baseline in the Real-Feedback Uncued condition). However, we only recorded MEPs from the index and pinky, and it is possible that excitability in other motor effectors was elevated. Interestingly, participants in Experiment 3 also mostly reported relying on thinking away from the cued muscle yet did not show reliable motor suppression. It is thus possible that the above verbalized strategy does not correspond to the underlying physiological mechanism.

Instead of using a motor surround inhibition mechanism, which relies first on activating an alternative motor effector to suppress another, participants might instead have directly targeted suppression at the cued effector. Such a mechanism could depend on cortico-striatal signaling to bring about top-down (prefrontally-driven) suppression of particular basal ganglia ‘motor channels’ via the classical Indirect Pathway, leading to downstream
suppression of the M1; such top-down control has been suggested by recent studies using

Study Novelty and Future Directions

Our method contrasts with earlier studies that have attempted to train IC using paradigms
where people must rapidly stop in response to an external signal. One such study showed a
modest 20ms improvement of stopping speed over the course of ten sessions of Stop-
Signal task training (Berkman et al. 2014), while another showed that practicing motoric
stopping (as well as detecting occasional signals and responding to them) also led to faster
stopping speed when compared to a control group (Chevalier et al. 2014a). However, other
stop-signal training studies report null findings (Cohen and Poldrack 2008; Enge et al. 2014;
Logan and Burkell 1986; and reviewed by Spierer et al. 2013). It is possible that these
effects are inconsistent (and only modest when they occur) because these studies engage a
“reactive” form of IC, where sudden stopping in response to an external signal is already too
rapid to allow for much improvement with training (Spierer et al. 2013). Moreover, even if
that system can be trained, the behavioral benefit of training may not be generalizable to
real-world situations that require IC in the absence of clear external signals to stop. Rather,
these real-world situations may benefit from training a more “proactive” form of IC (as we
use here), where one suppresses the motor system before any need arises. Such proactive
IC training may be more feasible because participants must consciously apply mental
strategies (also known as ‘implementation intentions,’ see Burkard et al. 2013) before overt
behavior, in a way that is not under speed pressure.

Further work is necessary to establish the functional benefit of training using this
paradigm. This could be attempted, for instance, by coupling the selective training of motor
suppression described here with behavioral tasks of selective stopping for which advanced
motor suppression of a particular effector might facilitate subsequent complex responses to
a stop-signal (for a task example, see Cai et al. 2011; Majid et al. 2013). More ambitiously,
training motor suppression of a particular movement (such as index finger grasping) in the
context of a provocative stimulus (a cigarette, for instance) might lead to reduced urges for
that stimulus (cf. Freeman et al. 2014).

The motor suppression trained in this present study also differs from phenomena
observed in other TMS studies that have previously shown suppression of a muscle when
cued to possibly stop later in a trial or when preparing to select a response (Cai et al. 2011;
Duque and Ivry 2009; Labruna et al. 2014; Majid et al. 2013). Whereas those effects arose in highly specific task contexts, participants in this study achieved motor suppression using a verbalizable mental strategy without overt behavior. This raises the interesting prospect that the mental suppression strategies could be flexibly translated to other motor effectors such as the leg or face. A limitation of the current study is that it did not test this generalizability of mental strategy, but if this held true, it would have high clinical relevance for Tourette’s disorder, for instance, where targeted suppression may be of benefit against motor tics that affect and migrate between a number of regions (Shahana and Gilbert 2013). Another potential clinical application is with regards to focal hand dystonia where impairments of motor inhibition are known (Shahana and Gilbert 2013; Stinear and Byblow 2004). Here, suppression or activation training could be used to help patients better individuate particular movements.

In summary we developed a new methodology of trial-by-trial real-time feedback of MEPs, and we show that this is effective in helping participants discover a mental strategy for selective motor suppression.

**ACKNOWLEDGMENTS**

We thank Jan Wessel for help with the real-time feedback method, Melissa Aguilar for data acquisition, Mark Appelbaum for statistical advice, David Linderman for participant recruitment, Scott Freeman and Melissa Burney for helpful comments, and the NIH (Grant DA 026452 and F31 NS077560) for financial support.
## Tables

### Table 1: Experiment 1 Raw Data (µV)

<table>
<thead>
<tr>
<th></th>
<th>First 5 blocks (early training)</th>
<th>Last 5 blocks (late training)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raw MEP amplitude</td>
<td>Pre-TMS EMG</td>
</tr>
<tr>
<td>Index null baseline</td>
<td>532±295</td>
<td>1.7±1.2</td>
</tr>
<tr>
<td>Index when cued</td>
<td>432±352</td>
<td>2.1±1.3</td>
</tr>
<tr>
<td>Index when not cued</td>
<td>610±456</td>
<td>2.4±1.6</td>
</tr>
<tr>
<td>Pinky null baseline</td>
<td>266±187</td>
<td>1.5±0.6</td>
</tr>
<tr>
<td>Pinky when cued</td>
<td>284±253</td>
<td>1.9±0.9</td>
</tr>
<tr>
<td>Pinky when not cued</td>
<td>333±247</td>
<td>2.0±0.8</td>
</tr>
</tbody>
</table>

Raw MEP amplitude is mean amplitude of the motor evoked potentials for a given condition. Pre-TMS EMG is the root-mean-square average of the electromyographic trace for 100ms preceding TMS delivery.

### Table 2: Experiment 2 and 3 Raw Data (µV)

<table>
<thead>
<tr>
<th></th>
<th>Real-feedback group (Exp. 2, n=13)</th>
<th>Sham-feedback group (Exp. 2, n=13)</th>
<th>No-feedback group (Exp. 3, n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raw MEP amplitude</td>
<td>Pre-TMS EMG</td>
<td>Raw MEP amplitude</td>
</tr>
<tr>
<td>Index null baseline</td>
<td>657±174</td>
<td>1.8±1.2</td>
<td>676±295</td>
</tr>
<tr>
<td>Index when cued</td>
<td>459±266</td>
<td>1.8±1.0</td>
<td>758±541</td>
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<tr>
<td>Index when not cued</td>
<td>618±276</td>
<td>1.8±1.0</td>
<td>694±396</td>
</tr>
<tr>
<td>Pinky null baseline</td>
<td>266±221</td>
<td>2.0±1.2</td>
<td>240±147</td>
</tr>
<tr>
<td>Pinky when cued</td>
<td>198±106</td>
<td>2.2±1.3</td>
<td>397±229</td>
</tr>
<tr>
<td>Pinky when not cued</td>
<td>246±136</td>
<td>2.2±1.3</td>
<td>352±273</td>
</tr>
</tbody>
</table>

Refer to Table 1 for legend.
Figure Captions

Figure 1: Feedback-driven task. A. Null trials at start of each block. B. Suppression trials followed Null trials. MEP amplitudes compared to baseline were fed back visually on each trial. A red bar corresponded to the muscle cued for suppression. Participants saw “Good Job!” if 1) the cued MEP was reduced compared to baseline (i.e. the red bar was pointing downward) and 2) the cued MEP was reduced compared to the uncued MEP (i.e. the red bar was more negative than the blue bar). Otherwise, participants were told to “Try Again.” C. Placement of FDI (index) and ADM (pinky) electrodes. D. Qualitative shape of MEP in both FDI (index) and ADM (pinky). Lightning bolt indicates time of stimulation with associated artifact. MEP amplitudes measured in microvolts from peak to trough.

Figure 2: MEP results. A. Experiment 1. There was a main effect of Cue, particularly seen in the later blocks. B. Experiment 2 with Real- vs. Sham-Feedback groups. The real feedback group suppressed the cued finger (as for Experiment 1), whereas the sham-feedback paradoxically activated both cued and uncued fingers. C. Experiment 3. Participants showed no significant suppression of the cued finger. “Percent Modulation” represents the percentage change of the mean MEP amplitude on “Suppress” trials compared to that on “Null” trials: (“Suppress” cue MEP – “Null” MEP)/“Null” MEP *100%. Asterisks indicate a significant change from the zero-baseline (p<.05). Error bars represent one standard error of the mean.
References


ANOVA results:
Cue effect: p = 0.016

* Group X Cue interaction: p = 0.047
Group effect: p = 0.003

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Cue effect: p = 0.016

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